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Contents

Original Articles

Indole-Based Compounds as Promising Inhibitors of SARS-CoV-2

Anqi Sun

The College of Post and Telecommunication, Wuhan Institute of Technology, Wuhan 430073, People's Republic of China.

Abstract: This review focused on the recent development of indole-based compounds as anti- SARS-CoV-2 agents with focus on the following objectives: 1) present the design strategy of indole-based compounds as promising inhibitors; 2) focus on recent developments of indole-based compounds and their anti-severe acute respiratory syndrome coronavirus 2 and anti-severe acute respiratory syndrome coronavirus activities; 3) summarize molecular docking and the structure–activity relationship, in hopes to inspire the development of new and more creative approaches; and 4) offer perspectives on how indole scaffolds might be exploited in the future.

Keywords: Indole; Protease; Inhibitor; SARS-CoV-2

1. Introduction

Indole is an important structural motif in drug discovery and is described as a "privileged scaffold," a term first introduced by Evans *et al*. to define scaffolds capable of serving as a ligand for a diverse array of receptors. Furthermore, indole derivatives can mimic the structures of peptides and bind reversibly to protease, providing tremendous opportunities to discover novel drugs with different modes of action. Indole scaffold is widely used in the design and synthesis of antiviral drugs and shows high biological activities; it can be used as a framework to design SARS-CoV-2 inhibitors. Therefore, indole-based scaffolds have been extensively used in drug discovery and have resulted in the development of related drugs [1].

2. Design strategy of indole-based compounds as inhibitors of SARS-CoV-2

The drug design strategy included screening for indole-based bioactive compounds with reported antiviral activities. First, their chemical structures and activities were investigated. Subsequently, the structure-based approach for repurposing these compounds against SARS-CoV-2 co-crystallized proteins was addressed. The departure point started with docking indole-based molecules with Mpro, RdRp, and spike proteins. Then, full binding modes and poses were discussed for the highest-scoring compounds. Finally, the structure–activity relationship was derived to find the link between the chemical structure of the indole-based molecule and its cytotoxic activity. These bioactive compounds were made publicly accessible to facilitate further studies and optimization by the scientific community [2].

3. Indole-based compounds as promising inhibitors of SARS-CoV-2

3.1 Indole-based compounds as Mpro inhibitors

The active sites of Mpro are highly conserved among all coronavirus Mpros and are usually composed of the following

four sites: S1′, S1, S2, and S4. Dai group [3] have designed and synthesized inhibitors targeting SARS-CoV-2 Mpro by analyzing the substrate-binding pocket of SARS-CoV Mpro (Fig. 1). An indole group was introduced into P3 to form new hydrogen bonds with S4 and improve drug-like properties. Compounds **1** and **2** exhibited high SARS-CoV-2 Mpro inhibition activity, reaching 100% for **1** and 96% for **2** at 1 μM, respectively. The X-ray crystal structures of SARS-CoV-2 Mpro in complex with **1** and **2** showed that the aldehyde groups of **1** and **2** are covalently bound to cysteine 145 of Mpro. Both compounds showed good pharmacokinetic properties *in vivo*, suggesting that these compounds are promising drug candidates.

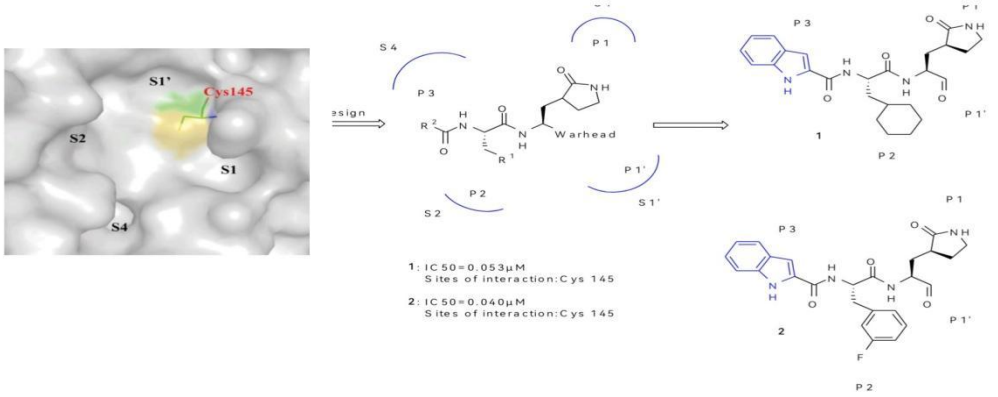


Fig. 1. The design strategy of SARS-CoV-2 main protease (Mpro) inhibitors a6nd the chemical structures of **1** and **2**.

A set of indole-based compounds (**3a–3o**) was synthesized and tested by Singhal *et al.* (Fig. 2) [4]. **3o** had higher antibacterial action at 50 μg/mL, verifying that the inhibitory effect increased with an increasing number of carbon atoms on the linker chain. The protease from SARS-CoV has a protein data bank code 1UK4, whereas SARS-CoV-2 has protein data bank code 6LU7. The key residues in this protease substrate-binding pocket are Thr45, Met49, Phe140, Asn142, Cys145…His41 dyad, Met165, His172, Glu166, Asp187, Arg188, and Gln189. **3o** was most effective with 6LU7. Three conventional H-bonds occurred between NH of the benzimidazole rings and indole carbonyl of **3o;** PHE140, ASN142, CYS145 of the enzyme proved its efficacy as potential DNA binders and anti-SARS-CoV-2 agents.

R n	2	3	4	5	6
H	a	d	g	j	m
Cl	b	e	h	k	n
Br	c	f	i	l	o

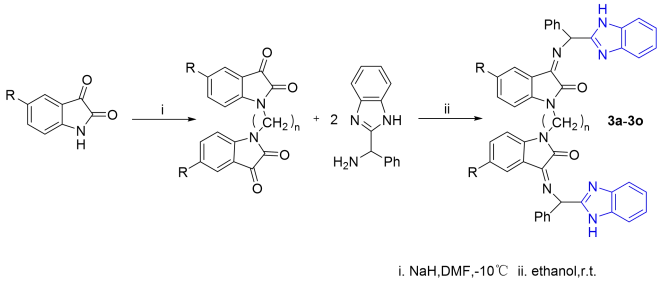
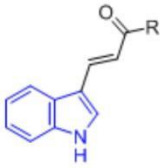


Fig. 2. The synthetic protocol for **3a–3o**.

3.2 Indole-based compounds as RdRp inhibitors

The SARS-CoV-2 replication mechanism is chiefly led by RdRp, which is a complex of nsp12, nsp8, and nsp7. RdRp is largely carried over by SARS-CoV and provides certain targets of opportunity for the selected indole-based compounds. The key catalytic residue sequence of Ser759, Asp760, and Asp761 is the binding site of RNA on the palm region, partly assisted by Asp618, which is a divalent cation-binding residue; these are essential to replication. In addition, residues Lys545 and Arg555 stabilize the incoming orientation of RNA, whereas Lys500 and Ser501 mobilize to accommodate its approach. In addition to these residues, 29–50 on β-hairpin of nsp12 are responsible for RdRp structural stabilization by interacting with other nsp12 domains.

Vijayakumar group studied a set of indole-based compounds 4a–4x (Fig. 3) [5]. They all obeyed Veber's rules and showed excellent DLM properties. Postdocking analysis shows that library members **4d**, **4h**, **4l**, **4p**, **4q**, **4t**, **4v,** and **4w** interact with β-hairpin residues. The results suggested that the indole-based compounds fight SARS-CoV-2.



4a R=4-F-C_6H_5 4b.R=4-CF_3-C_6H_5 4c.R=3-CF_3-C_6H_5 4d.R=4-Cl-C_6H_5
4e.R=2,4-Cl-C_6H_5 4f.R=4-Br-C_6H_5 4g.R=4-NO_2-C_6H_5 4h.R=4-OH-C_6H_5
4i.R=3-NH_2-C_6H_5 4j.R=4-CH_3-C_6H_5 4k.R=3-OCH_3-C_6H_5 4l.R=3,4-OCH_3-C_6H_5
4m.R=4-pyridyl 4n.R=3-pyridyl 4o.R=2-pyridyl
4p.R=4-OH-4-C_6H_5-piperazine
4q.R=1-C_6H_5-imidazole 4r. R=3-furyl 4s. R=2-pyroyl 4t. R=2-thiophenyl

4a–4x

Fig. 3. Synthetic indole-based compounds.

4. Conclusion and prospects

In this study, first, a panel of indole compounds based on the previously known structures was synthesized, and their inhibitory activity against SARS-CoV-2 was demonstrated. Then, using molecular docking, the binding of the indole-based compounds was assessed against their proteins, namely, RdRp, Mpro, and spike protein. If the compounds showed better binding affinity and overall dynamic stability, further *in vitro* and *in vivo* studies were conducted and the structure–activity relationships of such compounds were derived to discover a link between chemical structures and their corresponding activities.

So far, the research and development of new drugs usually require many human, material, and financial resources and time. Considering the urgent need for drugs in the current COVID-19 epidemic, the strategy of "new use of old drugs" can save resources and time. Then, through structure–activity relationship research, structural optimization, and drug-ready evaluation, we can discover lead compounds, candidate drugs, and clinically effective drugs that can enrich the "repository" of anti-SARS-CoV-2 drugs.

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Symptom Correlation Analysis of Upper Respiratory Tract Infections in Children at Primary Community Health Service Centers

Jing Xu

Chengdu Jinniu District Simaqiao Caojia Lane Community Health Service Center, Chengdu 610021, China.

Abstract: Objective: To investigate the time-to-cure correlation of upper respiratory tract infections in children in primary community health service centers, and to provide high-quality medical technology for primary health care. Methods: A total of 70 children from January 2020 to January 2021 were admitted to the hospital and treated for 3 weeks to compare the treatment effects. Results: The recurrent causes of recurrent upper respiratory tract infections in children were viral infections, immune abnormalities, malnutrition, bronchial asthma, chronic diseases, iron deficiency anemia, the main causes were viral infections, and there were statistical differences in the number of incidences, course and interval of onset in the control group. Conclusion: The nature of treatment in grassroots community health service centers can be analyzed in a timely and effective manner and is worth promoting.

Keywords: Upper Respiratory Tract; Lower Respiratory Tract; Primary Community

Introduction

Respiratory syncytial virus (RSV) is the most important pathogen of lower respiratory tract infections in infants and young children worldwide[1], and RSV infection can cause bronchiolitis, pneumonia, and even respiratory failure. At the same time, the combination of upper respiratory tract infections is easy to cause serious complications of children's respiratory tract, while the treatment timing, cure effect and timeliness can be effectively observed, the lack of resources in the primary medical community has also led to a shortage of medical technology and materials, unable to keep up, and the epidemic season of RSV has also undergone major changes after the epidemic. RSV detection rates are higher in the winter and lower in the summer, but after the COVID-19 outbreak, RSV detection rates have declined sharply worldwide, with the maximum decline rate being 70% to 90% due to measures such as wearing masks, hand hygiene, and social distancing [2]. At the same time, factors such as immune abnormalities, malnutrition, bronchial asthma, chronic diseases, and iron deficiency anemia have also improved the satisfaction of patients seeking medical treatment, and the curative nature of grass-roots community health service centers can be effectively analyzed and worth promoting.

1. Information and Methods

Our hospital selected 140 children from January 2020 to January 2021, 70 cases, respectively, the treatment intervention for 3 weeks, the treatment effect analysis, the control group of 34 boys and 36 girls; Age 1-10 years, mean age (8.29 ± 1.24 years). Statistical analysis of variance.

1.1 Inclusion and exclusion criteria

Selection Criteria:

Fever is mild or non-feverish. The symptoms caused by nasal congestion and nasal congestion are more prominent, the common cold. Nasal congestion, nasal discharge, sneezing, sore throat, dysphagia, fever, cough , cervical lymphadenopathy, crying and restlessness, breathing open, difficulty sucking, refusing to breastfeed, sometimes accompanied by vomiting and diarrhea Systemic toxicity symptoms are more serious, and suddenly high fever at the beginning of the fever is 39.5-40 °C, lasting 1-2 days, some people suffer from high fever and convulsions; Symptoms such as nasal congestion, runny nose, cough or sore throat are generally severe; (3) Often accompanied by digestive tract symptoms such as refusal to eat, vomiting, diarrhea or constipation; There is a high fever, accompanied by chills, headache, sour taste throughout the body, loss of appetite and other upper respiratory symptoms are generally obvious

Method:

Treatment observation group: such as crying and restlessness, breathing with open mouth, difficulty sucking, lactation refusal, etc., sometimes accompanied by vomiting and diarrhea, and severe symptoms of systemic toxicity, 1 Medication 1 1. Antibiotic therapy: the common cold does not require antibiotics, there is evidence of bacterial infections such as elevated white blood cells, pus moss in the pharynx, yellow sputum cough and runny nose, oral penicillin, first-generation cephalosporins, macrolides or quinolones are available, and it is rare to select sensitive antibiotics depending on the pathogen.

1.2 Antiviral drug therapy

For patients without fever, normal immune function, and the onset of the disease does not exceed 2 days, there is generally no need to apply antiviral drugs. For immunocompromised patients, early routine use of ribavirin and oseltamivir has a strong inhibitory effect on influenza viruses and respiratory syncytial viruses. 2. Traditional Chinese medicine treatment: By giving traditional Chinese medicine with antipyretic and detoxifying or antiviral effects, it can identify upper respiratory tract infections and help improve symptoms, such as Xiaochai Hu Chong Agent, Ban Lan Root Agent, etc., which are widely used.

2. Other treatments

Symptomatic treatment can be taken in patients with upper respiratory tract infections: 1. Fever: For patients with high fever, physical cooling can be used, cold compresses can be performed, ice packs can be placed in the armpits, groin and head, or oral acetaminophen or ibuprofen. 2. Sore throat: various throat tablets can be taken orally to relieve symptoms. 3. Cough: For people with obvious cough symptoms, dextromethorphan, valeric acid bacteriocin, hydroxymethyl group and so on can be given Antitussive.

3. Laboratory tests

3.1 Blood routine

The total number of peripheral blood leukocytes in patients infected with the virus is not high or low, neutropenia, lymphatic.

The proportion of cells is relatively increased, and some children may have a decrease in the total number of white blood cells and lymphocytes.

Peripheral blood white blood cells and neutrophils can be increased in bacterial infected.

Pathogenic examination.

4. Principles of treatment.

Because most colds are caused by viral infections, they are self-limiting and for most people.

There is no specific drug for the virus, so symptomatic treatment is the mainstay. Only a small percentage are present when bacterial infection is present.

Consider antibiotics before use. The basic principles of treatment are as follows:

If the symptoms are mild, no drug treatment is needed, and the symptoms obviously affect daily life before taking medicine.

Symptomatic treatment is the mainstay.

Pay attention to rest and replenish liquids appropriately.

Avoid secondary bacterial infections, etc.

5. General treatment

Appropriate bed rest, drink more water, eat lightly, and maintain nasal, pharyngeal and oral hygiene;

If drug treatment is required, oral route is preferred to avoid blind intravenous infusion.

If there is headache and fever, you can choose antipyretic analgesics or proprietary Chinese medicines. Antipyretic drugs include paracetyl

Aminophenol, ibuprofen and the like. Nasal drops can be applied topically.

Observe the indicators

3 weeks watch form 1

Fever	Cough	Chills, headache,	sour taste throughout the body,	loss of appetite	Enlarged lymph nodes in the neck
Number of cases (n)	36	33	20	18	15	10	8
Percentage (%)	25.71	23.57	14.29	12.86	10.71	7.14	5.71

Discussion

The analysis of the symptoms related to the cure time of children's upper respiratory tract infection by the grass-roots community health service center and the relevant guidelines for acute upper respiratory tract infection in children are the basic basis for clinical prevention and treatment, but for this common clinical disease, there are provisions for the use of antibiotic drugs for children's acute upper respiratory tract sensitivity, but there are still relatively common antibiotic abuse problems in the clinic. [3] The literature shows that antibiotics have good efficacy and application prospects in the treatment of acute upper respiratory tract infections in children, while immune abnormalities, malnutrition, bronchial asthma, chronic diseases, iron deficiency anemia, etc. increase the satisfaction of patients seeking medical treatment and upper respiratory tract patients. Symptomatic therapy may be given to patients with high fever, body cold, cold compresses, ice packs in the armpits, groin, and head, or oral acetaminophen or ibuprofen. Sore throat can be taken orally to relieve symptoms, cough and cough symptoms are more obvious, can be given dextromethorphan, valerate, hydroxymethanesulfonic acid and other cough medicines. The nature of treatment in grass-roots community health service centers can be analyzed in a timely and effective manner and is worthy of promotion.

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Effect of Rehabilitation Training on Limb Function and Self-Care Ability of Patients with Parkinson's Disease

Yue Liu, Peng Tang* Corresponding author：Peng Tang
The third department of Neurology, the Shaanxi Provincial People's Hospital, Xian 710068, China.

Abstract: Objective: This study mainly analyzes the effect of rehabilitation training on limb function and self-care ability of Parkinson's disease patients. Methods: 50 patients with Parkinson's disease who were diagnosed and treated in a Shaanxi Provincial People's Hospital in China from February 2, 2018 to July 2, 2021 were tested. These patients were divided into two groups randomly with 25 patients in each group. The control group should adopt routine treatment and nursing intervention, and the experimental group should take the control group as the benchmark and apply rehabilitation exercise training, The limb function and self-care ability of patients in the experimental group were compared with control group before and after the intervention. Results: after the intervention, the patients in the control group, whether Berg balance scale or UPDRS - III score, will be lower than the patients in the observation group. And after the intervention, the Barthel score of both groups will be better than that before the intervention ($P < 0.01$). Conclusion: rehabilitation training has a great impact on the limb function and self-care ability of patients with Parkinson's disease. Through the form of rehabilitation exercise training, we can further improve the limb function of current patients, make the self-care ability of patients become higher, and delay the development of the disease.

Keywords: Rehabilitation Training; Parkinson's Disease Patients; Limb Function; Self-Care Ability; Influence

Introduction

Parkinson's disease is a kind of neurodegenerative disease that is more common in clinical elderly patients in China at this stage. It will include many kinds of symptoms such as postural gait abnormalities and bradykinesia, and non-motor symptoms will include many contents such as mental disorders and sleep disorders. This disease is mainly caused by the damage of dopamine neurodegeneration in the substantia nigra of the brain, which is lack of dopamine medium support in the brain, as a result, choline and dopamine are out of balance, and the clinical treatment method used for the treatment of Parkinson's disease is not more accurate, so lifelong medication maintenance will be adopted for diagnosis and treatment. Most patients will have limb motor dysfunction, which will have a direct impact on the patients' ability to take care of themselves, so it is necessary to implement efficient and reasonable training methods to further delay the development of the disease course, formulate more targeted training contents and methods according to the patient's condition, pay attention to cultivating and improving the patients' limb motor ability, and vigorously carry out the training of self-care ability.[1]

1. Data and methods

1.1 Clinical data

50 patients with Parkinson's disease admitted to a Shaanxi Provincial People's Hospital in China from February 2, 2018 to July 2, 2021 were taken as the research objects of the experiment. These patients and their families signed relevant experimental agreements and voluntarily participated in the clinical study. All patients met the diagnostic criteria of

Parkinson's disease and received regular drug treatment for Parkinson's disease. Excluding patients with incomplete clinical data or who have received rehabilitation diagnosis and treatment in the past three months, there were 25 patients in the experimental group and the control group. Among them, there were 12 male patients and 13 female patients in the control group; The youngest is 55 years old, and the oldest is 78 years old; Hoehn Yahr grade I 6 cases, grade II 8 cases, grade III 6 cases, grade IV 5 cases; The minimum length of education is 8 years and the maximum is 12 years; There were 16 patients with hypertension, 9 patients with diabetes, 14 male patients and 11 female patients in the experimental group; The youngest is 52 years old, and the oldest is 77 years old; Hoehn Yahr grade I in 5 cases, grade II in 9 cases, grade III in 5 cases, and grade IV in 6 cases; The minimum length of education is 7 years and the maximum is 11 years; There were 15 cases of hypertension and 10 cases of diabetes. There was no significant difference in the general data between the two experimental groups ($P > 0.05$).[2]

1.2 Method

1.2.1 Control group

Routine nursing intervention was carried out based on routine treatment. First of all, in terms of medication guidance, we should communicate with patients so that they can follow the doctor's advice, take drugs on time, clarify the time and type of drug taking, and record the patient's remission information after taking drugs. Secondly, in terms of psychological knowledge, communicate with patients to appease their emotions in real time, so that patients can actively cooperate with relevant diagnosis and treatment work. Thirdly, it is the safety protection intervention measures, which should help patients choose to wear appropriate clothes, ensure the cleanliness of the ward, and protect the bedside guardrail, so as to prevent patients from falling and other problems. Finally, it is the guidance of routine rehabilitation training, so that patients can actively participate in rehabilitation training activities. When walking, they should keep in step with the upper step, control the speed of stepping, and carry out a series of facial expression training such as laughing and frowning.[3]

1.2.2 Experimental group

Based on the control group, rehabilitation exercise training is applied. During the hospitalization of patients, medical staff should lead patients and their families to learn relevant exercise methods, master the essentials of rehabilitation exercise training, and formulate a more targeted training plan for the patient's condition. Under normal circumstances, their training time should be controlled at 3-5 times a week, the length of each training should be controlled at 30-45 minutes, and they should continue to train for three months without interruption. After discharge, they should be guided to continue to exercise and develop good exercise habits, from the original 3-5 times to 2-3 times a week, and the training time should be controlled at 60 minutes. First of all, in the stage of physical and mental relaxation exercise, patients can take the form of sitting or supine position to practice abdominal breathing, put their hands on the abdomen or chest, so as to better help them perceive the changes of chest and abdomen fluctuations. They should first breathe naturally through the nose, close their lips in the process of breathing, slowly exhaust all the lung gas, and then slowly inhale through the nose, and adjust the time of exhalation and inhalation to 2:1, Let the patient repeat the above process for three times. Secondly, when carrying out facial rehabilitation training, let them frown first, focus on the middle of the two eyebrows, and then let the patient carry out panic and other actions after the concentrated exercise, do a good job of eye muscle exercise, open and close eyes, smile training, show teeth, whistle training, etc. Thirdly, the limb rehabilitation training is to guide the patient to carry out the traction exercise after lifting the shoulder. After completing the training task, the medical staff will help the patient relax and massage the muscles, guide the patient to move the head up and down, first raise the head, then lower the head, and let the patient try to move the head left and right, and then swing the head. In terms of gait practice, guide patients to stand still, practice walking slowly, and communicate with patients, so that they can swing their upper limbs as much as possible while walking, and practice repeatedly. In terms of posture and gait practice, let patients stand up and sit down first, and practice alternately

in this way.[4]

2. Results

The results of this study showed that after the intervention, the updrs- III score and BBS score of the observation group were better than those of the control group ($P < 0.01$); After the intervention, Barthel score of the two groups was higher than that before the intervention ($P < 0.01$), and that of the observation group was higher than that of the control group ($P < 0.05$).

3. Discussion

With the aggravation of population aging in China, the incidence rate of Parkinson's disease patients has increased significantly. Most patients with Parkinson's disease have static tremor, myotonia and gait abnormalities, followed by motor dysfunction. According to statistics, Parkinson's disease has become the third major neurological disease affecting the quality of life of the elderly in China, which has a serious impact on daily life. Nondrug treatment methods, such as rehabilitation exercise training, have achieved satisfactory application results in patients with Parkinson's disease, which can improve the patient's joint function, correct the poor motor state, and posture, and improve the patient's limb function. The theory of modern rehabilitation training therapy believes that passive stimulation is constantly implemented in the early stage of illness, and stimulating information is continuously input into brain cells by stimulating the afferent impulse of receptors in the body, so as to promote the germination and extension of neuronal axons in the brain of patients with Parkinson's disease, continue to form new protrusions, intensify repeated training stimulation, promote the brain to accept sensory stimulation, and promote the reorganization of the central nervous system.[5]

4. Conclusion

In recent years, due to the increasingly serious problem of population aging in China, the incidence rate of Parkinson's patients is also increasing. Most Parkinson's patients will have symptoms such as gait abnormalities and tremor. And through statistical analysis of data, we can understand that Parkinson's disease has become an important nervous system disease that affects the quality of life of the elderly in China and will have an adverse impact on their daily life. To improve this clinical symptom, the medical community will promote the medical model and pay attention to drug treatment. This method will ignore other factors that affect the quality of life of patients, which makes the effect of diagnosis and treatment not particularly good. We should pay attention to non-drug treatment methods, such as rehabilitation exercise training, and use this diagnosis and treatment intervention method to improve the joint function of patients and correct their wrong exercise posture.

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Study on the Effect of Fuzi Rhubarb Xanxin Decoction Combined with Qinghua Decoction on Periodontitis

Derjeu Chen, Chenghung Lai*
Department of Veterinary Medicine, National Chung Hsing University, Taichung 402204, China.

Abstract: Many reasons may lead to the occurrence of periodontitis disease in the human body, especially the people who often get overheated. If they do not pay much attention to oral hygiene, and even like to eat some spicy and stimulating food, the probability of periodontitis will increase. Fuzi Rhubarb Xanxin decoction is a traditional Chinese medicine prescription, because the prescription is warm and dissipates cold, so it has the effect of relieving pain. In the treatment of patients with periodontitis, the application of Fuzi Rhubarb Xanxin decoction can improve the disease through recuperation.Qinghua decoction mainly had clear heat, detoxification, analgesic effect, so as to improve the effect of the further consolidated. In this paper, the causes of periodontitis and the application of Fuzi Rhubarb Xasimin decoction were analyzed to explore the role of Fuzi Rhubarb Xasimin decoction in the treatment of periodontitis.

Keywords: Fuzi Rhubarb Xasimin Decoction; Qinghua Decoction; Periodontitis; Traditional Chinese Medicine Treatment

Introduction

Periodontitis is the main manifestation of tooth and gingiva pain. Mostly because of plain oral unclean or over eating paste liang thick taste, stomach fuzi accumulation heat, stomach fire on the flush, or wind fire evil poison invasion, injury and teeth, or kidney Yin loss, deficiency fire on the inflammation, burning gum caused. There are two reasons for the formation of periodontitis: (1) because of the fire, the Yangming Fu fire and the evil of wind and heat, wind and fire on the tooth pain. The cold and pain of the affected tooth should abate. Treatment should be thin wind, fire, detoxification. Add and subtract treatment with Qingwei powder, Yunvjian, etc. (2) Because of the cold, the evil guest of wind and cold in the tooth, tooth pain, tooth heat pain reduction. It should dissipate cold and relieve pain. Ephedra aconite asarum soup can be selected. Based on the application effect of Fuzi Rhubarb Xiaxin decoction, the effect of treating periodontitis was analyzed.

1. Overview of periodontitis

1.1 Epidemiology

1.1.1 Incidence

Periodontitis, also known as destructive periodontal disease, is a chronic inflammation caused by the invasion of periodontal tissue by bacteria in the patient's dental plaque. If not treated in time, periodontal support tissues such as cementum, alveolar bone, periodontal membrane and gingiva will be destroyed, forming a periodontal pocket, which is a small pocket formed by widening the gap between the tooth and gingiva, causing the tooth to lose adhesion and absorb alveolar bone. With the gradual aggravation of the patient's condition, it will cause the patient's teeth to loosen, make the gingival retreat and even lead to the loss of tooth function.

Periodontitis is a common oral disease in People's Daily life. According to the Fourth Chinese Oral Health Epidemiology Report published in 2017, the detection rate of deep periodontal pocket (≥24mm) and attachment loss (≥24mm) in 15-year-olds was 6.5% and 0.5%, respectively. The detection rate of gingival bleeding, deep periodontal pocket (≥26mm) and attachment loss (≥24mm) was 87.4%, 6.9% and 33.2% in 35-44 year olds. The detection rate of deep periodontal pocket (≥26mm) and attachment loss (≥24mm) was 15.1% and 69.9% in 55-64 year olds.

1.1.2 Incidence trend

The prevalence of periodontitis increased with age. The prevalence of periodontitis increased significantly after 35 years of age, peaked at 50~60 years of age, and then decreased. With the strengthening of oral hygiene awareness, the prevalence of mild to moderate periodontitis will gradually decrease. Adults over 35 years old have a high incidence of periodontitis. The incidence of periodontitis is slightly higher in men than in women. Smokers have a higher incidence than non-smokers.

1.2 Disease Types

1.2.1 Chronic periodontitis

The most common type of periodontitis, which accounts for about 95% of all periodontitis patients, occurs most often in adults, but children may also be affected. This disease is often caused by the accumulation of dental plaque, the course of disease is slow and gradually aggravated, untreated may lead to gum and alveolar bone destruction and even tooth loss.

1.2.2 Invasive periodontitis

It usually occurs in adolescents, and the destruction of periodontal support tissue is rapid and severe, with familial aggregation. If left untreated, it can lead to rapid tooth loss.

1.3 The cause

1.3.1 Local factors

Dental plaque, which is mainly composed of bacteria adhering to the tooth surface, intercellular material, exfoliated epithelial cells and food residues, is the most important local cause of periodontitis.

Calculus is calcified plaque and sediment deposited on the surface of teeth, which cannot be removed by brushing. The main damage to periodontal tissue of calculus comes from the accumulation of plaque on its surface. Calculus is an important factor in the development of periodontitis.

Traumatic occlusal injury occurs in periodontal tissue due to excessive bite force or abnormal direction, including early contact during occlusal, night molar, etc. As a synergistic factor in the destruction process, it can aggravate the progression of periodontitis.

Food impaction mainly refers to the insertion of food into the interdental space of two adjacent teeth. It is one of the common causes of local periodontal inflammation, and can also aggravate the existing pathological changes of periodontal tissue.

2. The effect of Fuzi Rhubarb xanxin decoction combined with Qinghua decoction on periodontitis

2.1 Aconiti Rhubarb and Xasimin Decoction treatment plan

Prescription: Aconite 15g, asarum 10g, Angelica dahurica 12g, Fangfeng 12g, rhubarb 4g, dried ginger 12g, processed licorice 15g. Fry ACONITE, dried GINGER and broiled Licorice for 40 minutes, then add the remaining herbs and cook for 40 minutes, open the lid and cook. Cook the second time for 50 minutes. Mix the juice between the two times and take it in five doses.

2.2 Qinghua decoction treatment plan

Prescription of Qinghua Soup: 10 g of Beauveria bassiana, 6 g each of Cicada decidua, honeysuckle, Zeilan, Scutellaria baicalensis, 3 g each of Coptis coptidis, fried Gardenia jasminoides, forsythiae forsythiae, gentian, Radix scrophora, Platycodon grandiflorum, 2 g each of tangerine peel, and 1.5 g each of white aconite and licorice. After decocting to 300 mL in water, they were orally divided into 2 times, 1 dose per day. The time interval between the two doses was 0.5 h and lasted for 14 days.

2.3 Effect of Fuzi Rhubarb xanxin decoction combined with Qinghua decoction on periodontitis

On the concept of TCM, tooth periarthritis and belongs to the "tooth non-traumatic" xuan "teeth" teeth "shake", etc., the original account in huangdi neijing, and points out that the main reason there are roughly several diet dishonor, spleen and stomach injuries, eagerness and hot fire. Eating for a long time thick taste, greasy food, alcohol, resulting in moist attack, the tooth bed is not clear, prone to inflammation. Kidney essence depletion, Yin deficiency fire flourishing. While the kidney is the main bone, the tooth is bone, kidney qi is missing, the tooth is dry. Qi and blood are not enough. Fine can not reach the gingiva, and cause the gingival flesh hypotrophic. According to this, in the clinical practice of traditional Chinese medicine often from tonifying kidney and consolidating qi, clearing heat and resolving table, to deal with periodontitis . The main ingredients of Aconite Rhubarb and asarum decoction consist of aconite, rhubarb and asarum, which can tonify kidney and warm Yang, dispel fire, clear heat and detoxify. Li Yang et al. used Rhubarb Fuzi Xiaxin decoction to diagnose and treat patients with chronic renal failure, and believed that the renal function of patients was significantly enhanced after cure[1]. Qinghua Decoction is often used in the diagnosis and treatment of inflammatory diseases because of its functions of detoxification and fire removal, qi sterilization and so on. Yu Haiping et al. applied Qinghua decoction in the diagnosis and treatment of spleen deficiency and damp-heat syndrome, which proved that the content of inflammatory factors in patients was significantly reduced after cure, and the overall curative effect reached 94.29%[2]. Rhubarb asarum decoction combined with lateral root of aconite thanh hoa soup after treatment, the proof of aconite rhubarb soup with thanh hoa asarum soup for periodontitis has various function, can significantly improve symptoms, and illustrates the monkshood rhubarb soup with thanh hoa asarum soup treatment, the improvement of disease symptoms in patients with integral group effect is obvious, can significantly improve the periodontal status, control periodontal status improve higher than the control group, showed Aconite rhubarb Xasingfen decoction combined with Qinghua decoction can improve the periodontal status of patients especially obviously[3]. In addition, the study shows that the combination of Fuzi rhubarb xanxin decoction and Qinghua decoction has an obvious effect on relieving headache .

White batryticated silkworm functions of analgesia of thanh hoa soup cicada scattered in addition to the hot wind, honey dogwood antipyretic, evacuate blast temperature, the effect of promoting blood circulation to remove blood stasis, red ginger, purging fire down poison, dry radix scutellariae antipyretic, fry ginger Bang autumn zephyrlily ping lishi, soil forsythia antipyretic, anti-inflammatory, fights, radix geutianae flat autumn zephyrlily dry wet, figwort decrease internal heat, antipyretic, orange flower clear heat nourish, pain, will new dried tangerine or orange peel to fill gas, rhizoma typhonii analgesic antipyretic, gansu Grass heat-clearing and detoxification drugs, adjusting all drugs, the whole prescription played the Qingshu Jiebiao, heat dissipation and pain relief. Periodontitis with rhubarb asarum soup of lateral root in coordination with the Qinghua soup treatment, two kinds of liquid form together play a synergistic effect, the former mainly in kidney and explored ways to tooth periarthritis for curative effect, while the latter mainly had clear heat, detoxification, analgesic effect, so as to improve the effect of the further consolidated, and can make the tooth periarthritis patients symptoms fundamentally change, thereby reducing the Traditional Chinese medicine syndrome integral, and to the periodontal condition to be obviously improved, so that the patient's pain effectively alleviated.

Conclusion

Fuzi Rhubarb xanxin decoction combined with Qinghua decoction has significant effect in the treatment of periodontitis, which can effectively improve the symptoms and periodontal status of patients, and reduce the pain score. Large sample data analysis, long-term follow-up, animal model construction and other studies need to be carried out in the subsequent work to further explore the clinical value of Fuzi rhubarb xanxin decoction combined with Qinghua decoction in the treatment of periodontitis.

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Monitoring the Immune Response to Coronaviruses in SARS-CoV-2 Exposed and Vaccinated Individuals

Mingdi Wu[1,a*], Brian J Willett [2,b], Maria Manali[3,c], Irfanulhaq Ahmadzai[4,d], Xiaoyu Dong[5,e]

1. College of Medical, Veterinary & Life Sciences, University of Glasgow, Glasgow G128QQ, United Kingdom.

2. MRC-University of Glasgow Centre for Virus Research, Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, United Kingdom.

3. MRC-University of Glasgow Centre for Virus Research, University of Glasgow, Glasgow G12 8QQ, United Kingdom.

4. College of Medical, Veterinary & Life Sciences, University of Glasgow, Glasgow G12 8QQ, United Kingdom.

5. College of Veterinary Medicine, Northwest A&F University, Shanxi 712100, China.

Abstract: Identifying factors associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure and immunity is critical for quantifying mass immunity and preventing future pandemics. The current SARS-CoV-2 vaccine was losing efficacy in the face of new variants, and it is urgent to seek a broad coronavirus vaccine. We conducted a cross-sectional serosurvey of patients in Scotland from September 2021 to April 2022. The indirect enzyme-linked immunosorbent assay (ELISA) against 2135 patient serum samples showed monthly infection and vaccination rates from 24.71%-72.00% and 28.00%-61.50%. We showed that people over 65 receive higher priority vaccination, and 65–74-year-old female patients exhibited higher vaccination rates and lower probability of infection. In addition, we investigated cross-reactive antibodies of SARS-CoV-2 negative, infected, and vaccinated samples against the seasonal human coronavirus (sHCoV) spike (S) protein by ELISA. We found a 1.2-1.4-fold increase in antibody reactivity among sHCoV-229E, NL63, and OC43 against vaccinated donors compared to negative donors. These findings provided insights into exposure patterns in Scotland and support the feasibility of developing a broad coronavirus vaccine.

Keywords: SARS-CoV-2; sHCoVs; ELISA; Seroprevalence; Cross Protection

1. Author Summary

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has experienced a global pandemic in the past two years. Identifying factors associated with SARS-CoV-2 infection and vaccination is essential for controlling transmission and preventing possible future pandemics. With the continuous mutation of SARS-CoV-2 and the perennial prevalence of seasonal human coronavirus (sHCoV), it is also important to develop a vaccine that can deal with various coronaviruses. Our study conducted a cross-sectional survey of patient sera in Scotland from September 2021 to April 2022 using an enzyme-linked immunosorbent assay (ELISA). Monthly infection and vaccination rates were calculated from 24.71%-72.00% and 28.00%-61.50%. We showed that people over 65 receive higher priority vaccination, and 65–74-year-old female patients exhibited a higher vaccination rate and lower probability of infection. In addition, We

performed sHCoV-spike (S)-protein-ELISA against SARS-CoV-2 negative, infected, and vaccinated samples. Vaccinated samples exhibited significant antibody reactivity to sHCoV-229E, NL63, and OC43. This study could provide insights into the Scotland epidemic prevention strategy and confirm the feasibility of developing a broad coronavirus vaccine.

2. Introduction

The current Coronavirus disease 2019 (COVID-19) pandemic caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in China and various European countries in late 2019 and 2021[1]. The infection rate of Delta and Omicron variants in Scotland has seen a significant peak in August/September 2021. SARS-CoV-2 seroprevalence in populations over 60 has exceeded 90%, and vaccination programs have been expanded to cover 12-to-17-year-old people[2]. Comparably, there are four common seasonal human coronaviruses (sHCoVs) (α-sHCoV229E, sHCoV-NL63, and β-sHCoV-HKU1, OC43) that have spread globally, accounting for about 30% of common cold cases in humans[3]. There was a study that reported that the seroprevalence of adults for sHCoV-229E, sHCoV-NL63, and sHCoV-OC43 was more than 90% and that for sHCoV-HKU1 was nearly 60% [4]. This indicated that most of the millions of individuals who may be infected with sHCoVs may have received the SARS-CoV-2 vaccine.

Spike (S) protein is the most crucial surface membrane protein of SARS-CoV-2, an important site for host neutralizing antibodies, and a key target for vaccine design. The S protein enables virus entry into human cells, consisting of S1 and S2 protein subunits, of which S1 promotes the ability of the virus to bind with host cell receptors and contains an essential C-terminal receptor binding domain [5]. Nucleocapsid (N) protein holds the RNA genome, regulates the life cycle of the virus, is highly immunogenic, and is one of the conditions for confirming infected patients [6]. SARS-CoV-2 and SARS-CoV belong to the same family. The S proteins of both have approximately 75% amino acid sequence identity, whereas the S protein of SARS-CoV-2 exhibits a lower identity with sHCoVs of only 23%-29% [7]. Despite the fact that this sequence identity was thought to be minimal from the standpoint of vaccination-mediated cross-reactive antibodies, some studies have reported cross immune-reactivity between COVID-19 sera and other sHCoVs [8]. Serological assays are necessary to detect serum antibody levels and cross-reactivity with viral pathogens [9]. SARS-CoV-2 exhibits clinical symptoms in up to 7 days, and some people are asymptomatic, whereas the sHCoVs typically develop clinical symptoms within 3 days [10, 11]. In addition, serological assays can investigate s immunoglobulin (IgG) antibodies against SARS-CoV-2 and sHCoVs and recognize viral exposures, including asymptomatic infection. Antibody levels in this study were measured by an indirect enzyme-linked immunosorbent assay (ELISA) with SARS-CoV-2 S1 protein and nucleocapsid (N)protein and sHCoVs spike (S) protein.

Therefore, in this report, we sought to build models linking serum sample information (e.g., date of sampling, sex, and age) to exposure and vaccination to SARS-CoV-2 to investigate the vaccination and infection situation in the late 2021 and 2022 by SARS-CoV-2-S1-subdomain ELISA and SARS-CoV-2-N-protein ELISA assays. In addition, we tried to identify broad sHCoVs antibody responses resulting from SARS-CoV-2 exposure and vaccinated individuals. We used sHCoVs S protein as the ELISA assay's main target of cross-reactive antibodies.

2.1 Aim of study

Herein, we aimed to study hypothesizing that vaccination rates and exposure prevalence may differ by age, sex, and region in late 2021 and 2022 and whether SARS-CoV-2 vaccines exhibit broad immunity against sHCoVs. We showed that the infected population of SARS-CoV-2 is mainly distributed among the elderly over 65 years old. Whether the increase in the vaccination rate can reduce the exposure prevalence of this part of the population requires further analysis. In addition, although the S protein of SARS-CoV-2 has a low amino acid sequence identity with that of sHCoVs, whether the SARS-CoV-2 vaccine could generate cross-immune protection with sHCoVs also requires further analysis. The efficacy of

the SARS-CoV-2 vaccine against sHCoVs is needed to be analyzed to guide the development of a broad coronavirus vaccine.

3. Materials & Methods

3.1 Serum samples

The NHS Greater Glasgow and Clyde (NHSGGC) Biorepository provided ethical support for this study and random residual biochemical serum samples from healthcare facilities from September 2021 to April 2022 (n=2135). The relevant metadata includes only the time of sample collection, gender, age, region, and time of vaccination and infection. Samples are numbered, and the patient's name and private information are kept confidential. All serum samples were cryopreserved at -20°C and inactivated in a constant temperature water bath at 56°C for 30 minutes before testing.

3.2 ELISA assay

SARS-CoV-2-S1 and N antigens and S antigens of sHCoV-229E, HKU1, NL63, and OC43 were made according to other instructions [12]. Antigen constructs were tagged with twin Strep. All proteins were transiently expressed in Expi293F cells maintained in FreeStyle medium ((Thermo Fisher Scientific). After seven days post-transfection, By centrifuging the supernatant for 30 minutes at 4000 rpm, the protein was extracted from the mixture. Twin Strep-tagged proteins were collected by filtration on a Steritop filter unit (IBA LifeSciences). Further purification was performed using size exclusion chromatography on Superdex 200 (GE Healthcare). Ultrafiltration was used to concentrate antigen to 5 mg/mL, then frozen quickly and stored at –80°C for later use.

IgG antibody detection against sHCoVs S antigen and SARS-CoV-2 S and N antigens were carried out as previously described. [13]. First, 96-well plates (Immulon 2HB 3455) were coated with 50 μL antigens at 1:100 diluted in 1 X phosphate-buffered saline (PBS), incubating overnight at 4 °C. After being washed 3 times with wash buffer (10 X PBS/0.05% Tween-20) by using the microplate washer (thermoscientific 5165050), antigens were blocked with 200 μL diluent buffer making of wash buffer with 10% casein (Vector labs. SP-5020) and serum samples were 1:100 diluted in the diluent buffer. Incubate for 1 hour at room temperature before the second wash (consistent with the above washing method). Rabbit anti-human lgG(H+L) horseradish peroxidase (HRP) conjugate (A80-118P, Bethyl labs) was diluted at 1:3000 in the diluent buffer, then added 50 μL per well and incubated for 1 hour. After the third wash, 50 μL per well of 3,3′,5,5′-tetramethylbenzidine (Sigma-Aldrich (Merck)) was added and allowed to develop in the dark for 10 minutes.

The reaction was stopped by adding 50 μL of 1-mol/L H2SO4. Read at 450nm absorbance on a plate reader immediately (Labsystems Multiskan Ascent). Since there was no negative control sample for sHCoVs, no negative and positive controls are set on each sHCoVs antigen plate, leaving one well as a blank control. One known positive and negative control was placed on each SARS-CoV-2 antigen plate. The raw optical density (OD) values were adjusted using the following formula.

$$\frac{\text{sample absorbance} - \text{negative ccontrol mean}}{\text{negative control mean}}$$

Receiver operating characteristic (ROC) analysis was performed to choose the positive and negative cutoff values from corrected absorbance values for positive and negative samples tested in the assay.

A positive control is a sample that is not exposed to the experimental treatment but is exposed to a known effect-producing treatment. As positive controls, 100 samples in total were used. All samples in this ELISA assay were tested against SARS-CoV-2-S1 and nucleocapsid (N) antigens. ROC analysis was used in the 9.4.0 version of GraphPad Prism (GraphPad). Determining whether a sample was infected or vaccinated was calculated by applying the respective cutoff

values for S1 and N antigens derived from the ROC analysis. Namely, if a sample was positive for both antigens (adjusted OD of S1 protein >7.761 & adjusted OD of N protein <3.666), it was considered as positive. Conversely, it was uninfected if a sample was positive for S1 antigen (adjusted OD of S1 protein >7.761) but negative for N antigen (adjusted OD of N protein <3.666), it was considered as negative.

3.3 Sensitivity and specificity

True positives, true negatives, false positives, and false negatives were determined using negative and positive cutoff to calculate specificity and sensitivity. There were 704 RT-PCR-confirmed SARS-CoV-2 infections. A total of 16 samples were classified as false positives. A sensitivity for SARS-CoV-2 was 98%. To confirm the specificity of the SARS-CoV-2 ELISA assays, a total of 59 SARS-CoV-2 RT-PCR negatives, of which 2 were positive by ELISA. Specificity for SARS-CoV-2 was 97%.

3.4 Statistical Analysis

The infection and vaccination rates of different gender groups and age groups and each month were shown using histograms and scatterplots. Differences in unadjusted optical density values of ELISA-determined SARS-CoV-2 exposed, negative, and vaccinated samples of the four sHCoVs were investigated using the Wilcoxon paired signed-rank test. We performed a straightforward calculation to establish the sample size for test sHCoVs. The seropositive prevalence (p) of the samples tested in this study was 91.78%, leaving the confidence level as 95%. The sample size was 116 by substituting into the equation $n=\frac{1.96^2 p（1-p）}{d^2}$ (d is precision as 0.05). All analysis and data visualisation was done by R software [14], version 4.2.1. The dplyr and ggplot2 packages were used to run the models [15].

4. Result

4.1 SARS-CoV-2

The S1 subdomain of the SARS-CoV-2 and N protein was detected by IgG antibodies in 2 ELISA assays in 2135 residual biochemical serum samples from NHSGGC patients [13]. The sample spans 8 months, starting September 22nd, 2021, and ending April 21st, 2022. Covering all NHSGGC regions and all age groups but not collecting children under the age of 15, the pediatric patient sample was not representative enough to reflect the SARS-CoV-2 infection rate, and the incidence of clinical symptoms in children was low. Because parents can avoid taking their children to medical facilities to protect them from the virus and potentially reduce the risk of COVID-19 [16].

The overall adjusted infection prevalence was 32.22% (95% CI, 30.24%-34.21%) (Figure 1A). Infection rates in men and women patients were approximately the same and consistent with the overall infection rate, as well as vaccination rates in men and women were consistent with overall (59.02%, 95% CI, 56.93%-61.10%) (Figure 1B). In the 15-44-year-old group, both men and women, the infection rate was highest (Figure 1A). It may be because this age group includes young people aged 15-18, resulting in a lower vaccination rate (50.38%, 95% CI, 46.07%-54.71%) (Figure 1B). In contrast, the 65-74 and 75+ age groups have the highest vaccination rates (66.35%, 95%CI, 61.82%-70.87% and 66.67%, 95%CI, 62.41%-70.92%) and the lowest infection rates (26.25%, 95%CI, 22.04%-30.47% and 23.35%, 95%CI, 19.95%-27.18%). Antibodies generally increased earlier in the older group than in the younger group. This reflected the prioritization of age in existing vaccination schedules [17]. For the age group 65-74 years, the infection rate was higher in men (32.18%, 95%CI, 25.73%-46.83%) (Figure 1A), possibly due to gender bias in treatment with SARS-CoV-2 [18], since the account of women being vaccinated (72.35%, 95% CI, 66.40%-78.30%) was higher than men (59.90%, 95% CI, 53.14%-66.66%) (Figure 1B).

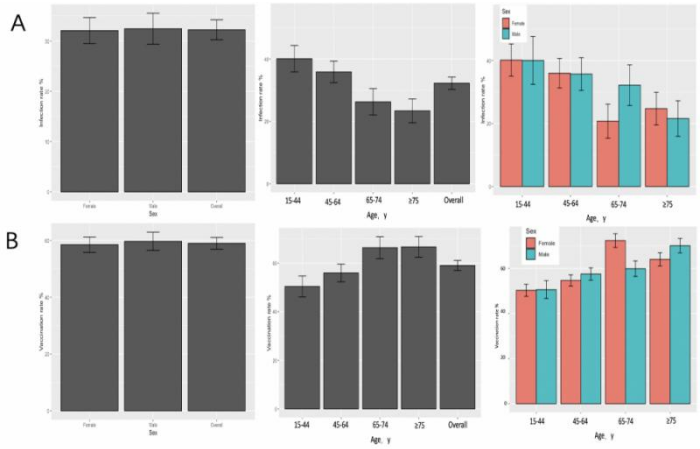

Figure 1. Glasgow, Scotland, UK, adjusted SARS-CoV-2 infection and vaccination rates in patient populations. A、B、Infection rate (A), vaccination rate (B), and 95% confidence intervals are shown across age groups and sexes.

During these 8 months, the monthly vaccination rate was roughly in line with the overall vaccination rate (59.02%, 95% CI, 56.93%-61.10%) (Figure 2A), except for January and April. There was a significant drop to 28.00% (95% CI, 19.02%-36.98%) (Figure 2A) in January, perhaps because January 2022 was the time when the rapid spread of Omicron BA.1 began, and there was no corresponding vaccine yet [2]. In April 2022, the vaccination rate decreased to 50.84% (95% CI, 43.51%- 58.16%) (Figure 2A), perhaps because reinfection by Omicron BA.2 resulted in reinfection in some vaccinated populations in the ELISA assays [19]. Meanwhile, the infection rate has continued to rise for these eight months and peaked in January (72.00%, 95%CI, 54.40%-89.60%) (Figure 2B). This was not the same as the reported weekly decline in infection rates, where more patients with secondary infections may be counted every month in this study. SARS-CoV-2 may adapt more efficiently to human transmission due to an update in immune evasion of SARS-CoV-2 [20, 21]. However, the sample size in January was too small, only 25, which may be one of the reasons for the vast difference in January.

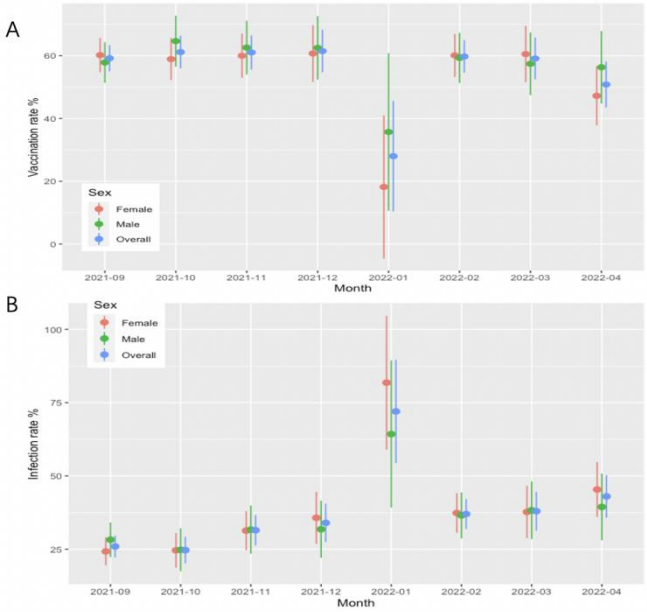

Figure 2. Glasgow, Scotland, UK, adjusted monthly SARS-CoV-2 infection and vaccination rates in patient populations. A、B、Vaccination rate (A) and infection rate (B) and 95% confidence intervals were surveyed in sequential combinations of sex

and sampling time.

In addition, the infection rate in some areas (20/106) was also calculated, where the sample size provided sufficient confidence to estimate infection rates. The estimated infection rate ranged from 11.90% (95% CI, 4.98-18.83) to 49.40% (95% CI, 38.64-60.15) (Table 1). Notably, G77, a region with a low infection rate, had the highest vaccination rate (84.52%, 95% CI, 76.79-92.26) (Table 1). Conversely, the G51 region has the lowest vaccination rate (40.96%, 95%CI, 30.38-51.54) and the highest infection rate. This suggests that vaccination may vary geographically, with different medical conditions in different regions, and areas with fewer vaccination sites may be more at risk of infection. Meanwhile, age composition in different regions may also be key to differences in infection and vaccination rates. However, the sample size was too small to do further analysis.

Postcode districts	Number of samples	Infection rate (95% CI)	Vaccination rate (95% CI)
G77	84	11.90（4.98-18.83）	84.52 (76.79-92.26)
G61	112	24.10（16.19-32.03）	71.43 (63.06-79.80)
G76	61	24.59（13.78-35.40）	63.93 (51.88-75.98)
G12	60	26.67（15.48-37.86）	63.33 (51.14-75.53)
G11	70	27.14（16.73-37.56）	58.57 (47.03-77.58)
G73	51	27.45（15.20-39.70）	66.67 (53.73-79.60)
G14	68	29.41（18.58-40.24）	55.88 (44.08-67.68)
G13	111	30.63（22.06-39.21）	60.36 (51.26-69.46)
G52	126	30.95（22.88-39.02）	60.32 (51.77-68.86)
G44	125	33.60（25.32-41.88）	62.40 (53.91-70.89)
G15	53	33.96（21.21-46.71）	58.49 (45.22-71.76)
G53	132	34.09（26.00-42.18）	58.33 (49.92-66.74)
G43	62	35.48（23.57-47.39）	58.06 (36.77-65.36)
G46	89	35.96（25.99-45.92）	57.40 (47.03-67.58)
G42	101	36.63（27.24-46.03）	54.46 (44.74-64.17)
G81	143	38.46（30.49-46.44）	52.45 (44.26-60.32)
G5	43	39.53（24.92-54.15）	48.84 (33.90-63.78)
G45	47	40.43（26.40-54.46）	51.06 (36.77-65.36)
G41	90	42.22（32.02-52.43）	46.67 (36.36-56.97)
G51	83	49.40（38.64-60.15）	40.96 (30.38-51.54)

Table 1. Infection rate, vaccination rate, and 95% CI in partial postcode districts of the Glasgow, Scotland, UK, study population with >40 samples.

4.2 sHCoVs

IgG antibodies against the spike (S) protein of sHCoV-229E, sHCoV-HKU1, sHCoV-NL63, and sHCoV-OC43 were tested in 2136 residual biochemical serum samples from NHSGGC patients using 4 ELISA assays [22]. According to the above ELISA assay for SARS-CoV-2, the samples were classified as infection (n=76), infection & vaccination (samples were vaccinated before but were infected in the ELISA assay) (n=612), vaccination (1150), and negative (n=70) (Figure 3A). Because vaccinated for the third dose had significantly higher mean corrected-absorbance (Figure 3B) and significantly increased levels of SARS-CoV-2 S1-specific IgG antibodies were seen after the third dose than the first and second doses[23]. Third-dose samples were screened from the infection & vaccination (n=520) and vaccination (n=1020) groups for further

study.

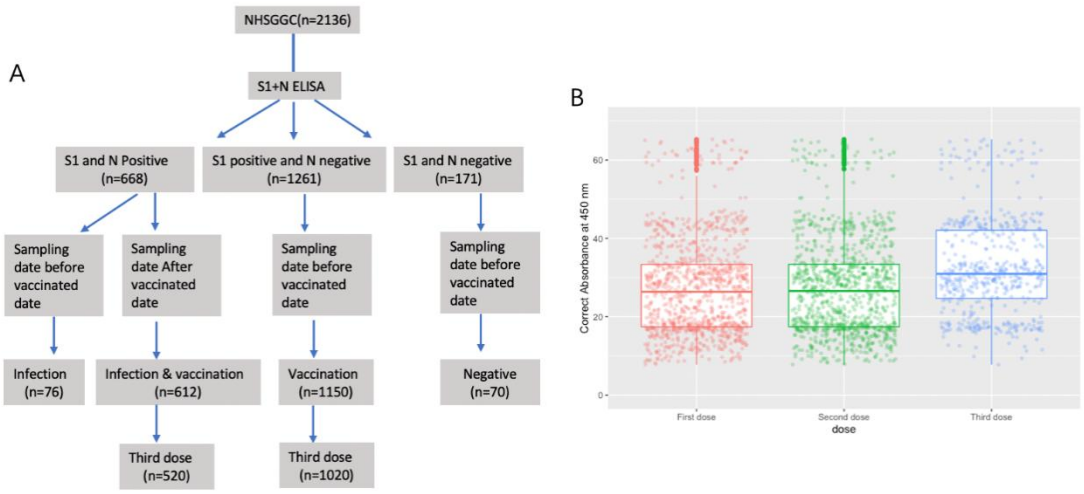

Figure 3. Sample selecting and correct absorbance of different doses. A、Diagram summarizing the sample flow used in the sHCoVs study. B、The correlation between ELISA assay corrected-absorbance and dose is shown as a scatterplot. Sample distribution between the first dose (red scatter), second dose (green scatter), and third dose (blue scatter). ELISA, enzyme-linked immunosorbent assay.

4.2.1 Infection (Aged 22-60) vs vaccination (aged 22-60)

In sHCoVs S-protein-ELISA-based assays, sHCoV-HKU1 exposure and vaccination differed significantly (R2=0.0091, P<0.01) (Figure 4A). However, it was the sera of the exposed group that showed more significant antibody reactivity (OD> 1.3-fold change) (Figure 4B); this was different from what we predicted. There were no differences detected in the sHCoVs of the other three groups. Still, it is worth noting that in the detection of sHCoV-NL63, the antibody reactivity of the exposed group was slightly higher than that of the vaccinated group. The antibody reactivity of the exposed group to sHCoV-NL63 was significantly higher than that of the other three sHCoVs (OD>1.4-fold change) (Figure 4B). Considering that the vaccine targets the S protein of SARS-CoV-2, the vaccine may have the same efficacy as the SARS-CoV-2 exposure for sHCoVs that do not differ among the three groups [8].

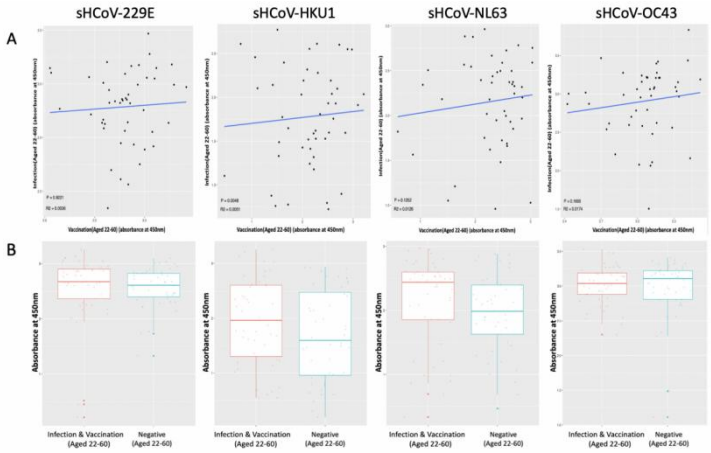

Figure 4. Difference between SARS-CoV-2 infection and vaccination samples against sHCoVs. A、The correlation between SARS-CoV-2 infection and vaccination in the 22-60 years old group was calculated by S-protein-ELISA assay absorbance at 450nm of sHCoVs. Differences were analyzed with the Wilcoxon matched-pairs signed-rank test. B、The correlation

between SARS-CoV-2 infection and vaccination aged 22-60 was calculated by S-protein-ELISA assay absorbance at 450nm of sHCoVs, shown by scatterplots. Sample distribution between infection aged 22-60 (red scatter) and vaccination aged 22-60 (blue scatter). ELISA, enzyme-linked immunosorbent assay.

4.2.2 Infection & vaccination (aged 22-60) vs negative (aged 22-60)

Different from the comparison in the previous group, in the comparison of Infection & vaccination and negative, sHCoV-NL63 infection & vaccination and negative showed a moderate significant difference (R2=0.0819, P<0.05) (Figure 5A). No differences were found among the other three sHCoVs, especially the sHCoV-229E mentioned above. In addition, the sera of Infection & vaccination of sHCoV-NL63 showed significantly higher antibody reactivity than negative (OD>1.7-fold change) (Figure 5B). There were no significant differences in sera antibody reactivity in the other three comparisons. Probably because this study focused on the S1 subdomain of SARS-CoV-2; however, some research suggested that S2-specific antibodies contribute more to cross-reactivity than S1-specific antibodies, which is consistent with the S2 subdomain's higher conservation than the S1 subdomain [24, 25]. Therefore, in addition to the SARS-CoV-2 S1 protein, other proteins may be targeted by sHCoVs.

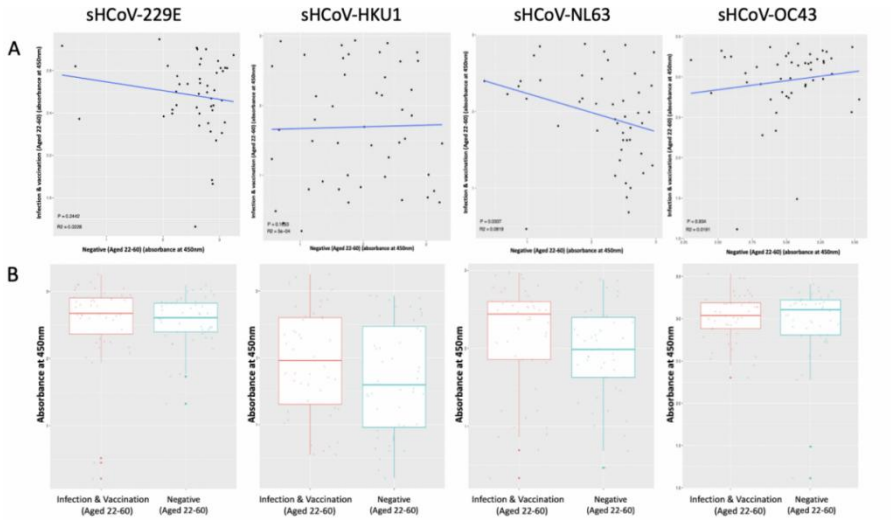

Figure 5. Difference between SARS-CoV-2 infection & vaccination and negative samples against sHCoVs. A、The correlation between SARS-CoV-2 infection & vaccination and negative in the 22-60 aged group was calculated by S-protein-ELISA assay absorbance at 450nm of sHCoVs. Differences were analyzed with the Wilcoxon matched-pairs signed-rank test. B、The correlation between SARS-CoV-2 infection & vaccination and the negative 22-60 years old group was calculated by S-protein-ELISA assay absorbance at 450nm of sHCoVs, shown by scatterplots. Sample distribution between infection & vaccination aged 22-60 (red scatter) and negative aged 22-60 (blue scatter). ELISA, enzyme-linked immunosorbent assay.

4.2.3 Vaccination (Aged>60) vs negative (Aged>60)

In the detection of sHCoV-229E and sHCoV-OC43, the sera of the SARS-CoV-2 vaccinated group and the negative group showed significant differences (R2=0.0055, R2= 0.0168, all P<0.01) (Figure 6A). Sera from the vaccinated group showed reactivity to sHCoV-OC43 in addition to significant antibody reactivity to 229E-S (>1.4 OD fold change) (Figure 6B). The difference between the sera of the vaccinated group and the negative group against NL63 showed a weak difference (P<0.05) (Figure 6A); however, the R-squared here is 0, so it has no value for statistical analysis. The OD fold rise of NL63 was slightly less than that of sHCoV-229E (>1.2 OD fold change) (Figure 6B). Like the previous group comparison, no

difference was found in the sera of the vaccinated group for sHCoV-HKU1 and the negative group. Therefore, the S1 antigen of the SARS-CoV-2 vaccine may produce cross-immune protection with sHCoV-229E and sHCoV-OC43.

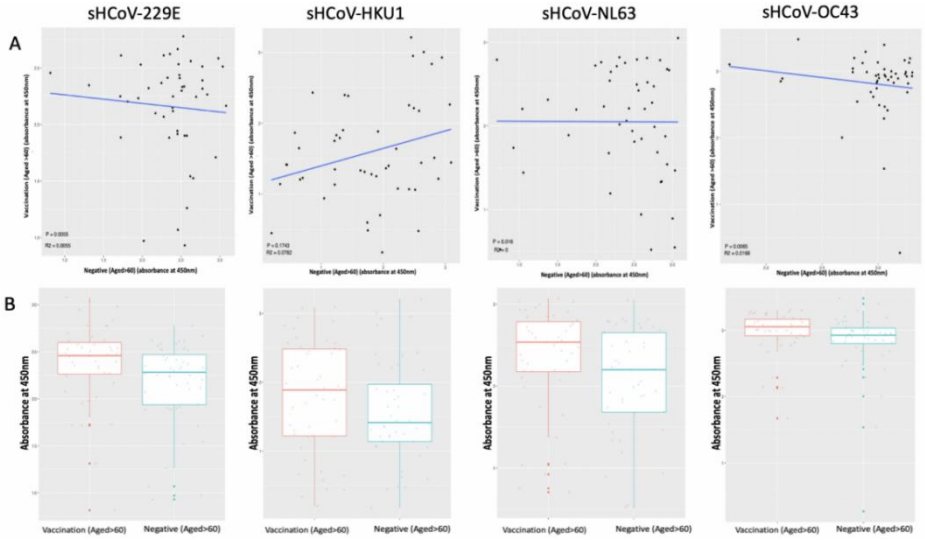

Figure 6. Difference between SARS-CoV-2 vaccination and negative samples against sHCoVs. A、 The correlation between SARS-CoV-2 vaccination and negative in more than 60 years old group was calculated by S-protein-ELISA assay absorbance at 450nm of sHCoVs. Differences were analyzed with the Wilcoxon matched-pairs signed-rank test. B、 The correlation between SARS-CoV-2 vaccination and negative aged more than 60 years old group was calculated by S-protein-ELISA assay absorbance at 450 nm of sHCoVs, shown by as scatterplot. Sample distribution between infection & vaccination aged 22-60 (red scatter) and negative aged more than 60 (blue scatter). ELISA, enzyme-linked immunosorbent assay.

5. Discussion

The start of the emergency authorization of several vaccines in late December 2020 has created a wave of vaccination campaigns around the world [26]. Determining current vaccination and infection rates is particularly important in mass vaccination. Serological surveys are a vital tool for counting vaccination and infection rates and controlling the spread of disease. Our study showed a clear gap in SARS-CoV-2 exposure over time during the Omicron pandemic and heterogeneous across different groups of patients in Glasgow. The sensitivity and specificity of our test remained above 95%, with a vaccination rate of 59.02% of the 2135 Glasgow samples tested. This was 10% lower than the 70% vaccination rate reported in Scotland [2]. This may be because the current minimum age for vaccination is 12 years old, while the minimum age of our sample was 15 years old [2]. In addition, our sample analysis relied on patients in the NHS seeking healthcare, including respiratory patients who were more likely to develop symptoms of SARS-CoV-2 infection and the general population with other diseases. Therefore, studies beyond this population analysis need to be cautious. For example, in the 65-74 age group, male patients were at significantly higher risk of infection than females, and females also have substantially higher vaccination rates than males, perhaps reflecting gender bias in COVID-19 vaccination [27] or sociocultural disparities that resulted in more exposure [28]. We still observed a vaccination rate of over 66% and an infection rate of less than 25% in the over-65 population. This means that the elderly group receives priority vaccine treatment.

It was crucial to note that in January 2022, the infection rate of SARS-CoV-2 had risen significantly to 43.02%. This was related to the sweeping of Omicron BA.1 in January, and the lack of a vaccine in time has led to high infection rates [2]. At the same time, the vaccination rate in Glasgow has also fallen to a low point (50.84%). However, it should also be considered that the sample size detected in January is too small (n=25). Hence the sample data in January may not reflect the

actual infection rate and vaccination rate.

Meanwhile, the sample in this study can be divided into primary care and secondary care patients, among which pregnant women in primary protection patients may receive exceptional care, and the exposure probability was lower than that of the general population. In addition, this study found that some people had secondary infection, so it cannot be ruled out that some patients were in the early stage of infection and had not been seroconverted at the time of sampling. Therefore, with the aforementioned qualifications, the infection rate in this study may be underestimated. But this study emphasizes the importance of vaccination, especially the third dose. Male in certain age groups with high vaccination rates was found to have lower infection rates. At the same time, compared with the first and second dose, the third injection had significant antibody reactivity (>1.3 OD-fold change).

With the relaxation of epidemic prevention measures in various countries, there is an optimism that SARS-CoV-2 will be suppressed with mass vaccination. However, the sweeping Omicron variants and the ever-present sHCoVs are still challenging. Some studies suggest that SARS-CoV-2 vaccines are insufficient to address increasingly human-adapted SARS-CoV-2 variants [29, 30]. Hence, it is vital to develop a broad SARS-CoV-2 vaccine against SARS-CoV-2 variants and sHCoVs.

In this study, infected & vaccinated samples had higher antibody reactivity to NL63 than negative donors, but we did not find this in vaccinated samples. This differs from previous reports that only NL63 binding antibodies cannot be depleted by the SARS-CoV-2 S protein [25]. This may be because mutations in SARS-CoV-2 were associated with vaccine updates. Since this study targeted the S1 subdomain of SARS-CoV-2, other subdomains may play a more influential role in the infection & vaccination population [25]. Meanwhile, studies have shown that spike protein between NL63 and SARS-CoV-2 can be recognised by T cells, and T cell responses induced or boosted by SARS-CoV-2 mRNA vaccines may be able to control SARS-CoV-2 variations and result in resistance to NL63 cross protection [31]. In addition, the sera of the vaccinated aged group (Aged > 60) had significant antibody reactivity to 229E and OC43, which was not found in the infection & vaccination (Aged 22-60) group. Therefore, we considered that the cross-protection of sHCoVs by the SARS-CoV-2 vaccine might be age-differentiated. Others demonstrated cross-reactive antibodies in SARS-CoV-2 patients due to enhanced pre-existing immunity following natural infection [32]. According to increasing age, the elderly population may have multiple innate immunities to sHCoVs, leading to enhanced vaccine cross-protection. With secondary infection, the sera of the infected and vaccinated groups may also enhance the cross-protection with NL63. Interestingly, the sera of the exposed group produced stronger antibody reactivity to HKU1 than the vaccinated group. It may be because the nucleocapsid (N) protein of SARS-CoV-2 can partially deplete the antibody bound to the sHCoVs N protein in the serum of the exposed group. The vaccine was directed against the S protein of SARS-CoV-2 to induce an immune response but not N protein, so there is no antibody against N protein in the vaccinated group. Therefore, targeting the N protein of SARS-CoV-2 may be the key to designing a broad coronavirus vaccine. Moreover, HKU1 is a β-coronavirus, which is more closely related to SARS-CoV-2 belonging to the β family than sHCoV-229E or NL63 [33], so the antibodies of the exposed group showed a stronger immune response to HKU1. Of note is that virus neutralisation tests were not applicable. It is unable to replicate sHCoV-HKU1 because there is no cell line of HKU1. The available strains of sHCoV-229E and sHCoV-OC43 cultured from 1960 and modified by the laboratory are not representative of the wild-type virus [34]. We suggested that the subsequent study can try to capture sHCoVs pseudotypes and do virus neutralisation assay. Taking SARS-CoV-2 as an example, the results of the pseudovirus neutralization assay correlate well with measurements using live SARS-CoV-2 [35].

This study provided data on the SARS-CoV-2 exposure and immunity population. The observed heterogeneity of exposure and immunity by region, sex, and age, suggests that in the absence of vaccination, SARS-CoV-2 still has the potential to become a pandemic in the future. At the same time, findings of differences in cross-reactive antibodies to other sHCoVs following SARS-CoV-2 exposure and vaccination underscore the feasibility of a broad coronavirus vaccine.

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Study on the Status and Influencing Factors of First Aid Knowledge and Skills of Community Residents

Xinping Xiao, Xuemei Duan, Rui Zhang, Wenhui Ren, Chen Yang
North Sichuan Medical college, Nanchong 637001, China.

Abstract: To analyze the current situation of first aid knowledge and skills of community residents in Yibin City and related influencing factors, and to explore effective ways to improve the knowledge and skills of community residents in Yibin City. A questionnaire survey was conducted with a convenience sample of 589 community residents in Yibin city. The first aid questionnaire designed by Li Li was used to investigate the knowledge of seven aspects, including first aid telephone, cardiac and respiratory arrest, trauma, accidental injury, common emergencies and other first aid. The score of first aid knowledge was (35.2±6.9), and the pass rate was 72.84%. It was found that there were statistical differences in the total pass rate of first aid knowledge and skills among community residents with different genders, ages, occupations, training experiences, and text studies, but there was no statistical difference in the total pass rate of first aid knowledge and skills among community residents with different health conditions and different first aid experiences. Community residents who were female, 18-25 years old, medical personnel/medical students, had training experience, and had obtained a first aid certificate had the highest pass rates and the best first aid knowledge and skills.

Keywords: First Aid Knowledge and Skills; Cardiopulmonary Resuscitation; Knowledge of First Aid

1. Background

In recent years, frequent disasters and accidents have posed great challenges to people's lives and health. Under such circumstances, the traditional in-hospital emergency mode has been unable to meet the emergency needs brought by unexpected events [1]. Correct, timely and effective pre-hospital emergency care is the key to improving the success rate of resuscitation and reducing the mortality and disability rates [2]. The construction and reform of China's emergency system has gradually changed from traditional in-hospital emergency care to pre-hospital emergency care, and rescuers have changed from professional first responders to "first witnesses". In this paper, the current situation of emergency knowledge and professional emergency skills of Yibin residents is studied, and relevant influencing factors are analyzed, so as to grasp and take relevant measures to improve the level of emergency knowledge and ability of residents.

2. Methods

In July, 2022, 605 community residents were selected from Yibin City to conduct on-the-spot questionnaire survey on first aid knowledge and skills. Inclusion criteria: (1) Community residents aged 18 and above; (2) Living in Yibin City for at least three months; (3) Ability to listen, speak, read and write. Exclusion criteria: (1) under 18 years old; (2) Living for less than three months; (3) Unwilling to be investigated; (4) Community residents with difficulties in listening, speaking, reading and writing, and mental disorders. A total of 605 questionnaires were distributed, and 589 were effectively recovered, with an effective recovery rate of 97.36%.

Using the questionnaire compiled by Li Li [3], Including emergency telephone (telephone number), first aid for cardiac

and respiratory arrest (cardiopulmonary resuscitation), first aid for trauma (poisoning, bandaging, fixation and handling), first aid for accidental injuries (poisoning, electric shock, drowning, burns, heatstroke, bite, sprain and trampling), first aid for common emergencies (airway foreign body, stroke, convulsion, asthma, angina pectoris, nosebleed), and so on. It is divided into three grades, with a score of 40 ~ 50 as good, 30 ~ 39 as medium and 0 ~ 29 as poor. Cronbach'sα coefficient of the questionnaire is 0.782.

SPSS23.0 statistical software was used to analyze the data. Descriptive analysis, single factor analysis and other statistical methods were used. In descriptive analysis, the mean and standard deviation are used for measurement data, and chi-square test is used in single factor analysis, with a=0.05 as the test level.

3. Results

According to the calculation, the score of community residents' first-aid knowledge is 35.2±6.9, and the passing rate is 72.84%. Generally speaking, this group of people has a high level of first-aid knowledge and skills, and their knowledge mastery is good. However, under different influencing factors, each group of people has different first-aid knowledge mastery. Community residents with different genders, ages, occupations, training experiences and textual research situations have statistically significant differences in the total pass rate of first aid knowledge and skills (all $P < 0.01$), but community residents with different health conditions and first aid experiences have no statistically significant differences in the total pass rate of first aid knowledge and skills.

4. Discussion

There is a significant difference in the passing rate of the total score of on-site first aid knowledge and skills test among the respondents of different age groups ($P<0.01$), which indicates that the age factor has an impact on the level of on-site first aid knowledge and skills of Yibin community residents[4], which is consistent with the research results of Hong Wang, etc. This result may be related to the experience, memory, life concerns and thinking tendency of people of each age group. Therefore, first aid trainers should provide different contents, ways and forms of training for different age groups in the training of on-site first aid knowledge and skills, so as to effectively improve their on-site first aid ability.

5.Conclusion

It is suggested that the government should put the popularization of first aid knowledge into the popular science plan, and focus on improving the popularization rate of self-help and mutual assistance. Give full play to the leading role of the government and drive the whole people to learn first aid knowledge.

Table 1 Comparison of test scores and passing rates of different age groups (n=589)

age bracket	Passed number	Number of failed students	Pass rate	Failure rate
	(n)		(%)	
18~25	330	95	seventy-eight	22
26~30	19	10	66	34
31~40	20	eight	71	29
41~50	forty-four	27	62	38
51~60	14	12	54	46
More than 60	2	eight	25	80
X^2		28.869		
P		＜0.01		

Establish a scientific training system, incorporate first aid knowledge into school teaching content and on-the-job training content, improve people's mastery of first aid knowledge and skills, change the learning of first aid knowledge from passive to active, improve people's health awareness and rescue ability, and solve the difficult problem of "unable to save, inconvenient to save and afraid to save.

The popularization of first aid knowledge and skills has become the standard to measure the comprehensive strength of a country's society, and first aid knowledge and skills are the basic qualities that citizens should possess [5]. The results of this study show that the community residents in Yibin City have a high level of knowledge and skills in on-site first aid, with a total pass rate of 72.84%, indicating that most people have a good sense of first aid, but there are great differences among different groups.

Cardiopulmonary resuscitation (CPR) refers to the on-the-spot first-aid technology that should be applied immediately to save lives when heart disease, electric shock, drowning, poisoning, trauma and other emergencies cause the heartbeat and breathing to stop. The number of deaths due to cardiac arrest in China is about 540,000 every year, and it is increasing year by year. When cardiopulmonary resuscitation is given within 4 minutes of cardiac arrest, the success rate of resuscitation can reach about 32%, and with the delay of time, the success rate of resuscitation drops significantly [6]. In foreign developed countries, emergency medicine has developed rapidly, and the popularization of on-site cardiopulmonary resuscitation (CPR) technology has become standardized, standardized and popularized. On average, more than 2/3 adults have mastered CPR technology [7]. Compared with foreign countries, in China, the popularization of cardiopulmonary resuscitation (CPR) is a very difficult task because of the limitations of people, property and other conditions, and the difficulty of CPR itself. Many studies have shown that after cardiopulmonary resuscitation training, if it is not consolidated for a long time, it will decline with the extension of time. It is gratifying to note that some regions and fields in China have realized the importance of first aid, and carried out cardiopulmonary resuscitation training. Some regions have already carried out a training mode that relies on hospitals, radiates to the surrounding areas, takes medical staff as the center, popularizes and spreads to non-medical staff in-hospital and out-of-hospital, and at the same time pays attention to technical retraining and consolidation, so that the masses can actually master cardiopulmonary resuscitation techniques.

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Influence of Section Orientation of Ultrasound Shear Wave Elastography on the Measurement of TI-RADS Category 4 Thyroid Nodules Stiffness

Xinru Zhang, Zhe Ma, Shuaiya Xv, Chenxi Ba

Department of Ultrasound, The First Affiliated Hospital of Shandong First Medical University, Jinan 250014, China.

Abstract: Thyroid shear wave elastography (SWE) is widely used as a noninvasive screening tool for thyroid nodules (TN) diagnosis. Herein, we assessed the effect of SWE section orientation on the stiffness measurement of TI-RADS category 4 TN. In this retrospective study, we followed up patients who had 2D ultrasound and elastography of the thyroid with pathological findings at our institution. The reliability and agreement between the aforementioned evaluations were further examined via calculation of the mean and maximum modulus values of the TN in both section orientations. As a result, there was good agreement in the measurement of the shear wave modulus of TN between the two different views, which provides relative flexibility for patients with anatomical or physiological defects.

Keywords: Ultrasound Shear Wave Elastography; Cross-Sectional Orientation; Thyroid Nodules; Modal Values

Introduction

With the widespread use of ultrasound technology, the diagnosis rate of thyroid cancer has increased year by year[1], and the 2022 China Cancer Ranking shows that thyroid cancer has risen to the third place among new malignancies in Chinese women. Recently, ultrasound elastography is widely employed as a noninvasive diagnostic tool to evaluate thyroid nodules (TN)[2]. At present, most clinics utilize two primary forms of ultrasound elastography: strain (SE) and shear wave elastographies[3]. SE, also called compressional elastography, was the initial elastographic procedure employed for TN assessment[4]. However, the main limitation of SE are the operator's dependence on the angle, intensity and duration of compression and the fact that quantitative elastography data cannot be obtained using this method[5-6]. More recently, shear wave elastography (SWE) received a lot of attention. This method measures tissue stiffness using shear wave velocity (SWV) and is used to reflect the nature of TN. SWE is a technique to quantitatively and objectively evaluate and image tissue elasticity in diagnostic imaging[1] , and various factors can affect the elastography assessment of TN, including carotid pulsation, patient body characteristics, tracheal motion, and peripheral muscle effects. Since the patient body characteristics, particularly a short neck and prominent carotid artery, may restrict the elastographic assessment of nodule stiffness, we focused on the transverse and longitudinal directional effects on the measurement of thyroid nodule stiffness.

1. Materials and Methods

1.1 Study subjects

Forty-two patients with TN, aged 22-68 years, with an average age of (47±10) years, with a maximum nodule diameter of 3-20 mm and a mean maximum diameter of (8.6±4.2) mm, attending the First Affiliated Hospital of Shandong First Medical University from February 2022 to June 2022 were selected. The inclusion criteria were: all patients received conventional preoperative ultrasonography, elastography, and nodules according to C -TIRADS classification criteria [7] for nodules conforming to C -TIRADS category 4, and all nodules were confirmed to be papillary thyroid carcinoma or micropapillary thyroid carcinoma by fine needle aspiration cytology and postoperative pathology. This investigation received ethical approval from our institution and obtained signed informed consents from all participants prior to the initiation of the study.

1.2 Instruments and methods

Instrument: Siemens ACUSON S2000 ultrasound diagnostic instrument was used for real-time elastography.

Conventional ultrasound: The patient is positioned supine with the head extended backward, fully exposing the thyroid gland in the neck. The instrument is adjusted appropriately to achieve optimal imaging quality and the target lesion is classified by C-TIRADS.

2D SWE elastography: The same suspicious nodule was found in the conventional ultrasound mode, and the SWE option in VT mode was selected. Patients were instructed to hold their breath and acquire both transverse and longitudinal elastograms of the nodule to reduce any breathing effects. After the acquisition is completed, the system automatically freezes and applies Velocity or Elasticity display mode. At least 3 measurements are taken, Emax is selected, and the average value is calculated after removing the highest and lowest values: Emean.

1.3 Statistical methods

SPASS version 25.0 was employed for all data analyses, and all data were provided as mean ± standard deviation, using fine needle aspiration cytology and postoperative pathological findings as diagnostic criteria. The intra-group correlation coefficient (ICC) was used to quantitatively summarize the reliability of the maximum and mean modulus values in transverse and longitudinal views. Bland-Altman plots were used to show the overall agreement between the stiffness measurements of transverse and longitudinal images.

Table 1

Maximum modulus value ICC intra-group correlation coefficient results

BI-directional mixing/random consistency	ICC intra-group correlation coefficient	95% CI
Single metric ICC(C,1)	0.720	0.535 ~ 0.839
Mean metric ICC(C,K)	0.837	0.697 ~ 0.912

Average modulus value ICC intra-group correlation coefficient results

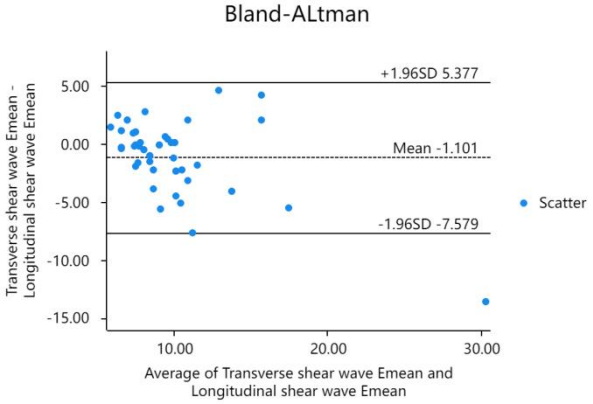
BI-directional mixing/random consistency	ICC intra-group correlation coefficient	95% CI
Single metric ICC(C,1)	0.726	0.543 ~ 0.842
Mean metric ICC(C,K)	0.841	0.704 ~ 0.914

Maximum modulus value ICC intra-group correlation coefficient results

BI-directional mixing/random consistency	ICC intra-group correlation coefficient	95% CI

C for consistency,1 for single measure, and K for mean measure

Figure 1 Bland-ALtman



2. Results

From February 2022 to June 2022, 42 nodes in 37 patients met the enrollment criteria.

As can be seen from Table1, the final ICC correlation coefficient values were 0.837 (95% CI: 0.697 - 0.912) and 0.841 (95% CI: 0.704 - 0.914), with correlation coefficient values higher than 0.75 within the ICC group, implying a high level of agreement in the effect, i.e., indicating a high level of agreement in the measurement of SWE modulus of TN for the two different views. In particular, the mean modulus values were measured. Thus, for the mean modulus values, the Bland-Altman plots(Fig 1) show that there is almost no deviation in the stiffness values between the transverse and longitudinal measurements over a wide range, indicating a good level of agreement. However, as can be seen from Table 2: The data has 42 samples, and the mean values of the measurements in both longitudinal and transverse directions are 10.488 and 9.387, respectively, and the use of paired t-test shows that a 0.05 level of significance (t=2.158, p=0.037) is presented between the longitudinal shear wave Emean and the transverse shear wave Emean, as well as the particular comparison differences were such that the average longitudinal shear wave Emean value (10.49) would be markedly elevated, compared to the average transverse shear wave Emean value (9.39).

Table 2：Bland-altman description statistics

project	quantitative value
Sample size	42
Mean value (longitudinal section)	10.488
Mean value (Transverse section)	9.387
Mean value (difference)	1.101
Standard deviation (difference)	3.305
95% CI(Mean value of difference)	0.071 ~ 2.131
95% CI(difference)	-5.377 ~ 7.579
T value (H0: average difference =0)	2.158
P value (H0: average difference =0)	0.037
CR value(Coefficient of Repeatability)	6.754

3. Discussion

Ultrasound elastography is highly sensitive to tissue stiffness. More recently, it has been developed and refined even further to provide the quantitative assessment of tissue stiffness. SWE uses a sequence of acoustic radiation force pulses to produce transverse waves, which move perpendicular to the ultrasound beam, resulting in transient displacements[9]. The generation process is as follows: shear waves are first produced via focused acoustic radiation force using a linear US array, which itself produces local stress and local displacement within the tissue; then, the newly formed shear waves move along the adjoining tissue in the transverse plane at a slower speed, perpendicular to the main wave thus producing the acoustic radiation force, resulting in shear tissue displacement; then, fast plane wave excitation is employed to detect the shear waves as they propagate through the tissue, then, the fast plane wave excitation is employed to detect tissue displacement and SWV as the shear wave propagates, and the tissue displacement is computed via the scatter tracking algorithm; finally, the tissue displacement map is utilized for SWV (cs) calculation, expressed in m/s, and its velocity increases with the increase of structural stiffness. The SWV distribution at each pixel is directly proportional to the Young's modulus E, which is computed using a simple formula and expressed in units of pressure (usually kPa) for tissue stiffness and elasticity. Young's modulus $E = 3\rho c^2$, where E is the Young's modulus, ρ is the tissue density, and c is the shear wave propagation velocity[3,8]. Herein, we compared the results of the two acquisition directions of the images to assess whether there are differences between them. In our study, there was an agreement between the maximum and average modulus values in the transverse and longitudinal sections, as presented in Figures 1.

The main benefits of SWE over other techniques are as follows: it is operator independent, reproducible, and quantitative. Nevertheless, multiple factors hinder SWE use in the evaluation of TN.Kim et al. revealed that elastography results were less reliable in 32% of the nodules. Thus, they concluded that elastography must be employed to TN that show reliable results only[11]. Similarly, most other elastography studies have examined diagnostic efficiency, diagnostic precision, inter and intraobserver agreements, and other factors. However, there is no specific statement on the usage of specific image orientations to compute the maximum and average modulus values of TN, so this study discusses the effect of transverse and longitudinal views on the elastography assessment of TN. There is good agreement between the maximum and mean modulus values of TN in transverse and longitudinal views, although a particular comparison of the differences reveals that the average longitudinal shear wave Emean value (10.49) would be markedly elevated, compared to the average transverse shear wave Emean value (9.39). This may be because of reduced frequency of influence by carotid pulsation on the longitudinal section and the absence of thyroid tracheal compression; the mechanical characteristics of the surrounding tissue may affect the tissue density and propagating shear wave speed, and the muscle tissue is highly anisotropic[9], which may disrupt the propagation of shear waves perpendicular to the muscle fiber orientation. In terms of thyroid, the shear wave propagates perpendicular to the direction of the anterior thyroid neck muscle fibers during the longitudinal sweep, and it will have a lower propagation velocity and modulus, so the mean value of the longitudinal thyroid will be higher than the transverse one, and therefore the SWE in the longitudinal view will be a little more accurate for malignant nodules. Our study shows that both directions of SWE can be used more flexibly for the analysis and evaluation of TN.

Limitations of our study: (1) Both transverse and longitudinal images do not show the exact same area within individual nodules. Thus, some of the measurement variation between orientations may be owing to the heterogeneity of the nodules themselves. This problem can be mitigated by obtaining several images in each direction of individual nodules. (2) The total sample size of 42 nodules is small and may be subject to bias. (3) The TN selected for this study were all papillary thyroid carcinoma or micropapillary thyroid carcinoma by cytopathological analysis, which is too homogeneous in pathological type and malignant only. Herein, the focus was on measurement consistency, and not diagnosis, thus restricting the influence of benign and malignant nodules on the relevant outcome.

Conclusion

In summary, this investigation reveals that SWE in both section directions (transverse and longitudinal) can provide good diagnostic performance. Transverse and longitudinal views showed good agreement and reliability for maximum and mean modal values of TN, with only small deviations. This good agreement provides flexibility in cases such as patients with limited neck mobility, patients with difficulty in fully extending the neck, and nodules that cannot be fully and clearly visualized in a single view in the transverse or longitudinal plane.

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Conflict of interest disclosure—All authors declare that they have no conflict of interest.

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Treatment of Complications of Orthopedic Surgery and Consideration of Basic Medical Research Based on Intelligent Science-Guangzhou Medical University and Chifeng College as Examples

Yi Qin[1], Liangyu Li[1], Yixian Lin[1], Guangyuan Li[2]

1. The Second Affiliated Hospital of Chifeng University, Chifeng 024000, Inner Mongolia Autonomous Region, China.

2. Jishou University, School of Medicine, Jishou 416000, China.

Abstract: With the rapid development of modern medical technology, the maturity of orthopaedic technologies, and the improvement of people's quality of life, more and more people choose surgical treatment. The improvement of the overall medical concept requires us to pay equal attention to the psychological education and care of patients while improving the level of diagnosis and treatment. Compared with other surgical operations, orthopedic surgery is characterized by large trauma, more bleeding, long operation time and slow postoperative functional recovery. The psychological burden of patients before and after surgery is heavy, which directly affects the success rate of surgery . Whether the operation can achieve the desired effect depends not only on the success of the operation itself, but also on whether the preparation and nursing before and after the operation are correct and perfect. The research team made specific analysis and report in combination with Guangzhou Medical University and Chifeng University and make a visual medical information management system for research.

Keywords: orthopaedic surgery; basic medical science; research prospect analysis

Introduction to complications

Bone surgery often includes the following types of diseases: first, spinal diseases, such as cervical spondylosis, cervical disc herniation, cervical spinal stenosis, lumbar disc herniation, lumbar spinal stenosis, spondylolisthesis, and other diseases. Second, limb and joint diseases, such as femoral head necrosis, knee osteoarthritis, limb fracture and dislocation, rotator cuff tear, shoulder periarthritis, etc. Third, hand and foot diseases, such as hand trauma, flatfoot, heel pain and other diseases. Fourth, peripheral nerve diseases, such as piriformis syndrome, cubital tunnel syndrome, carpal tunnel syndrome, etc.Medical engineering refers to a comprehensive and high-tech discipline that uses the principles and methods of modern natural science and engineering technology to study the structure, function and interrelationship of the human body at multiple levels from the perspective of engineering, reveals its life phenomena, and provides new technical means for disease prevention, diagnosis, treatment and rehabilitation services. Therefore, the research team innovated and elaborated this model.

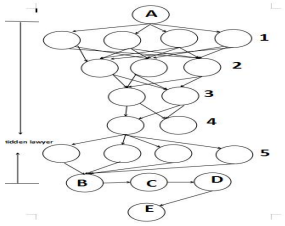

Figure 1

A: The patient's immediate post-operative care starts. Cloud data transmits digital signals to the input terminals and signals to the neural network after opening the authority of the hospital information department through API. The hidden working layer is activated through the activation function.

1: Calculation layer 2 of patient's postoperative nursing days: transfer calculation layer of patient's current laboratory examination results

3: Current grouped clinical drug use record calculation layer 4: Chinese traditional medicine drug selection layer

5: Calculation layer B of big data management principle for each drug: output end, responsible doctor obtains corresponding drug recommendation form

C: Disease communication, entering the hospital management system, and incorporating suitable drugs D: 5-10 days of clinical treatment records

E: The medical department reviews relevant data and submits treatment records to the cloud database

Design concept: Chinese traditional medicine has been widely used in the rehabilitation and treatment of postoperative patients in China. In our experience in the management of postoperative patients in spinal surgery in Beijing Shijitan Hospital affiliated to Capital Medical University, we clearly found the role of Chinese traditional medicine in the rehabilitation process. Based on the guiding treatment philosophy of Chinese traditional medicine, we believe that this technology is not suitable for global promotion, Therefore, we believe that the data association principle layer calculation of design health statistics and its connection with global big data will play an important role in our experience in using traditional Chinese medicine for spine surgery. It is undeniable that the patient's data association with the corresponding antibiotics such as ceftriaxone sodium, levofloxacin, gentamicin and other commonly used antibiotics and the necessary proton pump inhibitors and hydrogen ion receptor antagonists after surgery in the process of postoperative infection prevention is also quite persuasive in the doctor-patient communication, transforming abstract philosophy of Chinese medicine into objective and visual medical data, serving patients, It is also conducive to the promotion of experience.

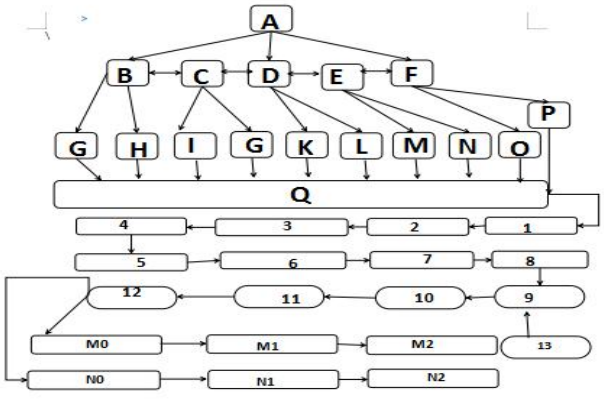

Figure 2

A: All vital signs and postoperative medical related information of patients are broadcast via network data.

B: Nursing workstation C: Nursing department D: Doctor workstation E: Medical department F: Computer management center.

G: Nursing operation recording equipment H: nursing consumables use recording equipment.

1: Nursing management recording equipment G: nursing record review equipment.

K: Doctor work record layer L: doctor work medical consumables use statistics layer.

M: Working medical record inspection equipment N: overall department inspection result recording equipment O: working equipment inspection recording equipment.

P: Working equipment running time record.

Q: In hospital storage and recording equipment 1: Chinese medicine use information extraction layer 2: nursing information extraction layer.

3: Clinical operation information extraction layer 4: hospital data analysis department conducts quality assessment and data screening.

5: Agree or disagree to connect to the cloud database to upload relevant information 6: 5G based network access.

7: Cloud database inclusion procedure 8: Cloud database extraction procedure.

9: Network channel under 5G network based on terminal of extracted network 13:5G network network slicing function.

10: Hospital data processing center 11: doctors get the big data they need to extract.

12: Data acquisition at medical device input.

MO, N0 and subsequent procedure steps are the relationship diagram between the medical workstation of the internal department of the hospital and the nursing workstation of the internal department of the hospital.

M0: doctor workstation M1 doctor operation treatment management system M2: treatment equipment for information collection.

N0: nursing workstation N1: nursing console management system N2: nursing equipment for information collection.

Design concept: We have designed a big data system with real-time updates on the cloud data side, which is conducive to improving the overall optimization of postoperative nursing effect and drug selection.

Basic medical thinking

In terms of clinical research in orthopaedic surgery, it is also necessary to further study basic medicine, which is the basis of medicine. Basic medical education not only undertakes the training task of students of basic medicine related majors, but also undertakes the training of clinical medical students at the basic stage, participates in the teaching of preventive medicine, health management, pharmacy, nursing and other medical specialties, and helps medical students understand and master the basic theoretical knowledge and experimental skills of medical science, It will lay a solid foundation for their future medical professional study and practice. Basic medicine is an important force to promote medical science and technology innovation and improve human health. In the long river of human history, the innovation of basic medical theories and technical methods has influenced and driven the development and progress of the whole medicine.

Conclusion

Psychological intervention before orthopedic surgery can make patients have healthy psychology and correct understanding, and achieve the best physical and mental state; Cooperate with doctors and nurses to jointly improve the treatment effect and the success of the operation, so as to achieve twice the result with half the effort. We need to develop basic medicine to overcome necessary clinical problems in the future. Taking Guangzhou Medical University and Chifeng University as examples, it is very important to carry out cooperation between universities. More cooperation is needed to promote the development of medical research in the future.

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Corresponding author: Luo Qinglu (1973 -), male, doctor, professor, engaged in modern rehabilitation research of bone and joint diseases.

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Meteorological factors and asthma in Hangzhou, China, a time-series study

Yifan Bo[1], William Goggins[2]

1. The Inner Mongolia Autonomous region Comprehensive Center for Disease Control and Prevention, Hohhot 010000, China.

2. School of public health, Chinese University of HongKong, HongKong 999077, China.

Abstract: Many studies have linked meteorological factors to asthma attacks. However, few studies have been conducted in the subtropical monsoon climate zone. The relationship between age, temperature, humidity (other meteorological factors) and asthma attacks has not been analyzed.Disease data were collected from medical records of Xinhua hospital in Gongsu district. Meteorological data were collected from Chinese terrestrial climate data daily value data sets.Poisson generalized additive models was used and combined with distributed lag nonlinear models and piecewise linear models to model associations between daily asthma hospitalizations from 2010 to 2013 and meteorological factors. Subgroup analyses by age and season were performed.Risk of asthma hospitalizations peaked at a mean daily temperature of 10℃ and declined approximately linearly until 35℃.High humidity and low humidity were both associated with more asthma admissions. Wind speed had no significant association with asthma hospitalization. No seasonal difference in associations were observed.Asthmatic patients should limit outdoor activities in low temperature, unsuitable humidity to avoid exposure to adverse conditions.

Keywords: Asthma; Meteorological Factors

1. Introduction

Asthma is one of the noncommunicable diseases whose characters are recurrent attacks of breathlessness and wheezing[1]. Asthma is a kind of airway obstructive disease, which is a kind of airway hyperreactive, reversible and remodeling disease involving a variety of inflammatory cells, immune cells and it is triggered by persistent airway inflammation. Inflammation also increases when asthma attacks occur.According to WHO estimates, over 235 million people worldwide are suffering from asthma. One prediction is that an additional 100 million people will unfortunately have this disease by 2025. The prevalence of asthma in Chinese adults was 1.09%(95%CI:0.95~1.22) .The prevalence of male asthma was 1.17%, higher than that of female asthma 1.00%. From 1990 to 2010, the incidence of asthma in children under the age of 14 increased threefold, which was more than 3% in 2010. And the control rate of childhood asthma in China is less than 1/3. This disease has become a serious public health problem, which not only brings harm to people's health, but also brings a great economic burden to the society.Previous studies have assessed risk factors for asthma, including meteorological and environmental risk factors. Some studies have reported that changes in weather and air quality have a measurable effect on the morbidity and the mortality of patients who were suffered from asthma. The earth is becoming warmer due to the concentration of many greenhouse gases increasing, especially carbon dioxide (CO2). This can lead to severe and sustained high temperatures. The continued high temperatures will increase air pollution, forest fires, droughts and floods. These adverse climate changes will increase public respiratory health risks. Preliminary evidence which was

based on a large number of epidemiological studies, suggests that environmental meteorological conditions, especially extreme temperatures, contribute to the exacerbation of adult asthma[2].

Hangzhou is located in Zhejiang province, China, and belongs to the Yangtze river delta region. It is subtropical monsoon climate and has a high population density.

While few previous studies have looked at the association between meteorological factors like temperature, humidity, wind speed and asthma and were done in areas with sub-tropical climates. Since prior studies of the inducing factors of asthma have indicated that the air pollution is an important issue, the lack of studies of temperature areas represents a significant knowledge gap.

2. Methods

2.1 Data

A time-series study has been conducted on 17497 males and 13913 females aged between 2 to 97 years from the same hospital in Hangzhou, China. Disease data were collected from medical records of Xinhua hospital in Gongsu district. Meteorological data were collected from Chinese terrestrial climate data daily value data sets. Meteorological data including daily mean temperature (°C), daily mean relative humidity percentage (RH%) and mean wind speed (m/s). The data came from a hospital in a heavily populated area.

2.2 Statistical models

Our study uses a combination of Poisson generalized additive models (GAMs) and distributed lag nonlinear models (DLNMs) to assess the potentially nonlinear association between meteorological variables and the hospitalizations of asthma allowing for lagged effects. The model was as below:

M = gam(P ~ cb.temperature + cb.relative humidity + cb.wind speed + s(t,k=28) + factor(dow)+factor(holiday), optimizer = "perf", family = negbin(c(1,100),link = log) , data=data1)

cb: cross basis of independent variables built up using the dlnm() package in R s(): smoothing function of independent variables

k: limitation of degree of freedom in smoothing function factor(): indicator of categorical independent variables

DOW: day of week (1, 2, 3, ..., 7). DOW was modeled as a categorical variable using indicator variables.

Variables relating to meteorological factors were modelled simultaneously using DLNM. The generalized cross validation (GCV) score can be minimized in the mgcv() package in R which can choose the number of degrees of freedom (df) for variable terms.

2.3 Model checking and sensitivity analyses

Sensitivity analysis was done to observe the robustness of the results by adopting different df lag terms of the model. All statistical analyses were performed with R Studio 1.1.463.

3. Results

During this 4-year study period, there were a total of 31410 asthma admissions. Among these people, 72.75%, 19.76% and 7.49% were in children, adults and the elderly, respectively. The daily average numbers of hospitalizations were 21.50, 10.80 and 11.59 for the whole year, hot season and cold season, respectively. Daily mean temperatures ranged from -2°C to 35.7°C. The median daily mean temperatures (3rd, 97th per- centile) were 19.1°C (1.50°C, 32.6°C), 25.7°C (16.5°C, 33.3°C)

and 10.1°C (0.6°C, 21.4°C) for the whole year, hot and cold seasons, respectively. Table 1 shows the descriptive statistics of the total number of asthma hospitalizations and meteorological variables during the study period.

The maximum lag time for df of 3 is 15 days, respectively, for the lag parameters of temperature/relative humidity and other environmental factors in DLNM.

3.1 The whole year regression analyses

The minimum morbidity temperature (MMT) was about 30°C for the overall population. The RR for asthma admissions increased when the mean temperature rose from 5°C to about 10°C . The 95% CI of RR for temperature is less than 0 when the temperature is more than 30°C which means high temperature is a protective factor for asthma attack. And low temperature has significant association with asthma hospitalization. 95%CI of RR for temperature 10°C VS 30°C is 2.58 (1.92, 3.48).

3.2 Subgroup analyses by age group

In all age groups, lower temperature and higher or lower relative humidity were associated with more hospital admissions for asthma. Sensitivity to these three meteorological factors was similar among these three age groups. But adult has wider 95%CI between 40%~60% RH which means adult were more sensitive to relative humidity . Wind speed did not seem to correlate significantly with asthma incidence in any age group.

Subgroup analyses by season were done but the associations between the meteorological variables and asthma were similar for the hot and cold seasons so there was no need to report them in detail.

4. Discussion

Our study found that risk of asthma hospitalizations peaked at a mean daily temperature of 10℃ and declined approximately linearly until 35℃.High humidity and low humidity were both associated with more asthma admissions. Wind speed had no significant association with asthma hospitalization. No seasonal difference in associations was observed.

The nature of associations reported from past studies of asthma morbidity and temperatures have not been consistent, because of the differences in climate, study design and statistical methodology. Some studies have found positive associations between temperatures and asthma admissions, some have reported negative associations, while a few have reported significant associations with high and low temperatures . In this study, the correlation between RH and hospitalization for asthma was observed. While previous studies have only shown an association between high humidity and asthma, our study found a significant association between asthma and low humidity.

Previous studies have found that hypothermia can lead to decreased lung function, increased risk of airway inflammation, and decreased lung capacity .Low temperature and humidity can cause bronchial constriction and dry airway mucosa, which is why low temperature and low humidity can also increase the risk of acute exacerbation of asthma .Cold and dry air can reduce mucosal moisture, which increases susceptibility to respiratory bacterial and viral infections, as well as irritation from allergens and other irritants.Low temperatures and low humidity also favor the survival of viruses such as influenza and respiratory syncytial viruses, which increases the risk of infection triggers.The influence of seasonal changes on the correlation between RH and asthma may reflect the interaction between temperature and RH. High RH can aggravate the heat stress in high temperature period, while low RH may be related to asthma in low temperature period.

Airborne allergens may be another possible link between high humidity and asthma. Many airborne allergens, such as tree pollen and fungal spores, are better suited to high humidity. Mold grows more easily in moist areas. Aphids, which also produce ozone through photosynthesis, have higher concentrations at high humidity and temperatures. With the increase of the concentration of allergens and air pollutants in the air, the asthma patients will have greater stimulation of reactive

respiratory tracts and more severe airway inflammation.Air pollutants and allergens spread more widely through high wind speeds. Therefore, it is necessary to reduce the number of asthma hospital admissions by reducing exposure to irritants in severe weather conditions[3].

Compared with children's lung function, adult's airway has longer duration of inflammation which is associated with lower airway inflammation. In addition, adults are the main working population and may have a more active social life than children or the elderly. This may increase their exposure to environmental triggers because they cannot avoid going out under adverse environmental conditions.

Childhood is a high incidence and sensitive period for asthma because the immune function and respiratory system are not fully developed during that period. If the children cannot get timely and appropriate diagnosis and treatment, it may cause repeated asthma attacks. In severe cases,airway remodeling may lead to lung function damage or irreversible airway narrowing, which may have an impact on the growth and development of children and may even develop into adult asthma. Even some children suffer from asthma for a lifetime. Children are also susceptible to temperature and humidity and to respiratory disease. This is why children are more sensitive and need to be protected.

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CIC Rearrangement Sarcoma: A Case Report and Literature Review

Haobin Chen, Shi Cheng, Wenhan Huang, Yuan Yan, Yu Zhang *
Department of Orthopaedics, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510000, China.

Abstract: Background: CIC-rearranged sarcoma (capicua transcriptional repressor- rearranged sarcoma, CRS) is a rare type of undifferentiated small round-cell sarcoma. There are few reported cases of CRS; in 2017, 115 cases were reported abroad and 10 cases were reported in China. Case summary: The patient is a 41-year-old male who presented with a mass in the left lumbar region for more than 1 month. Tumor excision was performed at another hospital. Pathology results indicated CRS. PET-CT indicated changes in the left lumbar region, and postoperative tissue repair changes were considered. However, combined with the medical history and imaging features, the clinical diagnosis was considered recurrence of tumor in the left lumbar region. Postoperatively, the patient was transferred to the burn department for pedicled skin-flap repair. Conclusion: CRS is rare, and the prognosis of these patients is poor. Surgical resection of the lesion is the first choice for patients without metastasis.

Keywords: Undifferentiated Sarcoma; CIC; Diagnosis; Differential Diagnosis; Treatment; Unplanned Surgery

Introduction

Undifferentiated small round-cell sarcomas, including Ewing sarcoma, round-cell sarcoma with EWSR1-non-ETS fusion, CIC-rearranged sarcoma (capicua transcriptional repressor-rearranged sarcoma, CRS), and sarcoma with BCOR genetic alteration, occur mainly in children and adolescents.[1-3] CIC-rearranged sarcomas have similar clinical manifestations, histological morphology, and immunophenotype, but there are differences in molecular genetics.[4] CIC-rearranged sarcoma is a rare type of undifferentiated small round-cell sarcoma.

Case presentation

Chief complaints

A 41-year-old man was admitted to hospital in April 2022 for 1-week recurrence of a tumor in the lower back.

History of present illness

One month prior to presentation, the patient noticed a mass with mild tenderness in the left lumbar region while taking a bath. The mass was excised at another hospital. The size of the lesion was approximately 2.8×2.5×1cm.

History of past illness

The patient underwent tumor resection in other hospital 1 month ago, and the tumor size was approximately 2.8×2.5×1cm. Pathological examination and immunohistochemistry indicated CIC-rearranged sarcoma.

Personal and family history

There was no significant personal or family history.

Physical examination

Orthopedic examination revealed a 5-cm scar on the left back, slightly hard, not easily depressed, no skin redness, no ulceration or fistula formation, and mild tenderness.

Laboratory examinations

The laboratory examinations were all within the normal range.

Imaging examinations

On April 14, 2022, spiral-enhanced CT of the lumbar spine was performed, which indicated that several slightly high-density lesions remained after left lumbar surgery. Considering the postoperative changes, local scar evaluation was performed, and the maximum layer was 31×16 mm. On April 14, 2022, MRI of the lumbosacral vertebrae was performed, and there was an abnormal subcutaneous signal in the left posterior lumbar region. We considered postoperative changes and noted fascia changes. PET-CT was performed on April 14, 2022; changes were noted in the left lumbar region, and postoperative tissue repair changes were considered.

Final diagnosis

The final diagnosis is CIC-rearranged sarcoma recurrence.

Treatment

On April 14, 2022, extended resection of the lumbar tumor was performed. After the pathological results confirmed that the incision margins were negative, the patient was transferred to the burn department, and pedicled skin-flap transplantation was performed on April 29, 2022. After the operation, the blood supply of the skin flap was good, and the recovery was good. On August 27, 2022, infusion port implantation was performed in our department, and the postoperative chemotherapy was administered.

Outcome and follow-up

The wound healed well There was no complaint of discomfort during the 4-month follow-up. The patient's wound healed well, the flap survived, and there was no complaint of discomfort. MR re-examination revealed abnormal signal shadows in the subcutaneous tissue of the posterior lumbar region. Considering the changes in the repair period of the surgical incision.

Discussion

Antonescu *et al* reported that CIC-DUX4 gene fusions resulting from t(4;19) or t(10;19) translocations are the most common genetic abnormalities detected in EWSR1-negative small round cell tumors.[5] The CIC-DUX4 fusion is caused by a t(4;19) (q35; q13) or t(10;19) (q26; q13) translocation, and the gene involved in the fusion is the transcriptional repressor CIC located on chromosome 19q13.1.[6, 7] Specht *et al* used fluorescent *in-situ* hybridization (FISH) to detect EWSR1-negative small round-cell sarcoma, and the results showed that about 64% (21/33) of the cases had CIC gene translocations.[8]

CRS is more common in young and middle-aged people; the average age of onset is 32 years old. Males are slightly more affected than females, and about 90% of tumors are located in the deep soft tissues of the limbs or trunk (trunk > lower limbs > upper limbs > head and neck > retroperitoneum). About 10% of CRS are found in internal organs (e.g., gastrointestinal tract, kidney, prostate), and it is extremely rare in bone. CRS can also occur in superficial soft tissues. [4, 5, 9-15]

Histologically, CRS generally shows diffuse, patchy distribution with fibrous septa, and necrosis is common. Although most tumors contain small, blue round cells, 10% may have spindle cell components;[5] the cytoplasm is generally rich, the nuclei have different degrees of pleomorphism and are irregular, the nucleoli are visible, the mitotic figures are visible, and myxoid degeneration may be present. When myxoid degeneration is obvious, it can resemble a myoepithelial tumor or extraosseous myxoid chondrosarcoma.[15] Regarding immunophenotype, CRS is characterized by the expression of CD99 to varying degrees, usually mottled positive, and a small number are diffuse strong positive.[13] Tumor cells are positive for WT-1 and are generally diffusely positive in the nucleus and cytoplasm.[15] Some cases are positive for ERGFli1, and most are negative for S-100, Syn, and CgA. For CIC-DUX4 round-cell sarcoma, Siegele *et al* reported that the immunohistochemical marker DUX4 has high sensitivity and specificity in CRS.[16]

CRS is highly invasive, with about 16% of cases presenting with distant organ or lymph node metastasis at the time of diagnosis. Initially, chemotherapy and radiotherapy have a local control effect. *In vitro* studies by Oyama *et al* found that molecular targeted drugs (such as crizotinib) could control tumor growth to a certain extent in CRS.[17] After healing, CAV/IE chemotherapy was administered. Extended resection requires adequate resection margins; in practice, many surgeons often determine resection margins based on their personal experience rather than objective studies.

Conclusion

In conclusion, CRS is a new classification of undifferentiated small round-cell sarcoma. The main recommendation is extended resection and wound coverage, and CAV/IE chemotherapy is preferred after wound healing.

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Combination of Chinese and Western medicine in the Treatment of Orthopaedic Diseases

Lizecheng Chen
Shaanxi University of Traditional Chinese Medicine, Xianyang 712099, China.

Abstract: **Objective:** To observe the effect of the combination of Chinese and Western medicine therapy in the clinical treatment of traumatic orthopaedic diseases. **Methods:** The clinical data of patients with traumatic orthopaedic diseases treated in hospitals between June 2020 and October 2022 were retrospectively collected. 60 cases were taken as the study subjects and divided into a control group (consisting of 30 patients who took conventional Western medicine treatment) and an observation group (consisting of 30 patients who took combined Chinese and Western medicine treatment) with the aid of an Excel sheet to compare the treatment effects. **Results:** The rates of wound swelling and pain relief in the control group and the observation group were 66.67% and 90.00% respectively, with the observation group having a higher rate ($p<0.05$); the rates of soft tissue repair in the control group and the observation group were 50.00% and 80.00% respectively, with the observation group having a higher rate ($p<0.05$); the fracture healing time in the observation group was shorter than that in the control group ($p<0.05$). **Conclusion:** The effect of combining Chinese and Western medicine in the treatment of traumatic orthopaedic diseases is ideal, which is mainly reflected in the three aspects of promoting wound swelling, promoting soft tissue recovery and promoting fracture healing, and is worth promoting.

Keywords: Combination of Chinese and Western Medicine; Orthopaedic Diseases; Effect Analysis

Introduction

[1]Traumatic orthopaedic diseases include fractures of the lower limbs, pelvis and other parts of the body, as well as joint injuries of the shoulder and knee joints, which will not only cause serious pain but also have adverse effects on normal life and work. At present, the clinical treatment for traumatic orthopaedic diseases mostly adopts plaster fixation, surgical repositioning and medication for pain relief to restore the normal state of bones and soft tissues and relieve patients' pain symptoms. However, clinical studies in recent years have pointed out that the above treatments have certain limitations in improving patients' blood flow , which hinders the recovery and healing of traumatic fractures, while many Chinese herbal medicines have the effects of tonifying qi and nourishing blood, invigorating blood circulation, eliminating decay and creating new blood, which is conducive to the growth of granulation tissue and skin, achieving the goal of promoting bone scab formation and fracture healing[2] . The aim of this study is to observe the effect of combined Chinese and Western medicine treatment in traumatic orthopaedic diseases, which is reported below.

1. Materials and methods

1.1 General information

The clinical data of patients with traumatic orthopaedic diseases admitted from June 2020 to October 2022 were retrospectively collected, and 60 of them were taken as the study subjects. The 60 patients were randomly divided into a

control group and an observation group of 30 cases each, of which 16 were male and 14 were female; ages 18~66 (48.16±1.57) years. In the observation group, there were 17 males and 13 females; ages ranged from 19 to 67 (48.29±1.61) years. After statistical analysis, there was no significant difference between the two groups in terms of age, gender, fracture type, clinical symptoms and other general information ($p>0.05$), which was comparable.

1.2 Research Methodology

The control group was treated with conventional Western medicine, mainly by plaster fixation, internal and external fixation of plates, surgical repositioning, traction and medication.

The observation group was treated with a combination of Chinese and Western medicine, and the Western medicine treatment was the same as that of the control group, i.e. depending on the actual situation of the patients, a targeted treatment was chosen. The specific plan of the Chinese medicine treatment is as follows: the main treatment is internal and external application of Chinese medicine. For patients with subcutaneous tissue defects of 2-2.5cm and skin defects of 3-4.5cm in diameter, external application of muscle-generating cream gauze or burn moistening cream gauze is used. For patients with soft tissue infections and bone infections, on the basis of surgical dilation, the wound is first drained of pus using Exorcise and Raw Muscle Paste or Qi San Dan medicated thread, and after confirming that the pus has drained away, the wound is wrapped with Raw Muscle Paste gauze. It is worth mentioning that the patient's wound needs to be cleaned before each dressing change. The cleaning solution can be a mixture of metronidazole and gentamicin. For patients with severe soft tissue damage and large wounds that cannot be treated with a transfer flap or a phase I free flap, a gauze dressing is applied and a phase II flap is applied after the wound has been reduced and the granulation has grown. For patients with skin erythema and swelling, treatment with Si Miao Yong An Tang with addition and subtraction; for patients with grey muscle skin and poor soft tissue blood flow, treatment with oral tori disinfection and Ten Quan Da Teng Tang with addition and subtraction. If this condition does not occur in the patient, the use of herbs with blood-vitalising properties is sufficient.

1.3 Observed indicators

(1) Efficacy of wound swelling and pain relief. There are 4 ratings of excellent, good, acceptable and poor: if the swelling of the wound disappears and the pain disappears within 6 d of treatment, it is considered excellent; if the swelling and pain disappear within 7-11 d of treatment, it is considered good; if the swelling and pain disappear within 12-15 d of treatment, it is considered acceptable; if the time taken for the swelling and pain to disappear exceeds 17 d, it is considered poor. (2) Soft tissue repair. There were four ratings: excellent, good, acceptable and poor: repair time within 6 d was considered excellent; repair time between 7 and 11 d was considered good; repair time between 12 and 15 d was considered acceptable; repair time over 20 d was considered poor. (3) The healing time of fractures in both groups was counted.

1.4 Statistical methods

The data from this experiment were entered into SPSS 28.0 software for processing and analysis. The count data n (%) was tested by x^2 and $P< 0.05$ indicated a significant difference in material comparison.

2. Results

2.1 Comparison of the efficacy of the two groups in reducing swelling and pain in wounds

The excellent rate of wound swelling and pain relief was 90.00% and 66.67% in the observation group and control

group respectively, which was higher in the observation group ($p<0.05$), detailed data are shown in Table 1.

Table 2 Comparison of pain relief efficacy of wounds between the two groups [n (%)

Group	n	Excellent	Good	Available	difference	Excellent rate
Control group	30	6	14	6	4	20 (66.67)
Observation group	30	14	13	2	1	27 (90.00)
x^2						4.8118
p						0.0283

2.2 Comparison of soft tissue repair between the two groups

The excellent rate of soft tissue repair in the observation group (80.00%) was significantly higher than that in the control group (50.00%), and the difference was statistically significant ($p<0.05$), the detailed data are shown in Table 2.

Table 2 Comparison of soft tissue repair between the two groups [n (%)

Group	n	Excellent	Good	Available	difference	Excellent rate
Control group	30	7	8	5	10	15 (50.00)
Observation group	30	15	9	6	0	24 (80.00)
x^2						5.9341
p						0.0149

2.3 Comparison of fracture healing time between the two groups

In the observation group, the fracture healing time was 8.2 weeks for patients with trunk femur fractures, which was significantly shorter than that of the control group (9.4 weeks) ($p<0.05$); the fracture healing time was 7.3 weeks and 10.5 weeks for patients with tibial fractures in the observation and control groups respectively, which was shorter in the observation group ($p<0.05$).

3. Discussion

[3]The common symptoms of traumatic orthopaedics include foot fractures, pelvic fractures, femur fractures and joint injuries, etc. Plaster or plate fixation, surgical traction and repositioning, medication and rehabilitation exercises are commonly used in the treatment of traumatic orthopaedic diseases, which can effectively relieve patients' symptoms and promote fracture healing. In addition, studies have shown that Western medicine has limitations in improving blood flow in traumatic orthopaedic diseases. Therefore, in order to ensure that patients recover as soon as possible, it is necessary to use a combination of Western and Chinese medicine based on a comprehensive consideration of the patient's condition .[4]

According to Chinese medicine, traumatic orthopaedic diseases are related to the internal organs, meridians, tendons, bones, qi and blood, etc. Therefore, "holistic treatment" should be the basic principle in treatment, and the effects of tonifying qi and nourishing blood, eliminating decay and regenerating new blood, activating blood circulation and removing blood stasis should be taken into consideration. The aim is to improve local blood flow, promote the growth of granulation tissue and early formation of bone scabs.[5] The results of this study showed that compared with the control group treated with conventional Western medicine, the observation group treated with a combination of Chinese and Western medicine had a higher rate of swelling and pain relief and soft tissue repair, as well as a shorter healing time for the fracture, indicating that

the combination of Chinese and Western medicine could effectively relieve swelling and pain symptoms, improve soft tissue repair and facilitate early recovery. It should be noted that in order to ensure the effectiveness of combined Chinese and Western medicine treatment, a comprehensive assessment of the patient's degree of illness, symptoms and recovery at each stage is required, and the results should be used as the basis for selecting the appropriate treatment modality and Chinese and Western medicines.

In conclusion, the application of combined Chinese and Western medicine treatment in traumatic orthopaedic diseases can achieve ideal results, not only promoting wound swelling and relieving painful symptoms, but also promoting soft tissue recovery and fracture healing, which has high promotion value.

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Research on the Oxidative Stress Status of Patients with Phlegm-Damp Polycystic Ovary Syndrome and the Intervention of Traditional Chinese Medicine

Yanjun Dong
Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China.

Abstract: **Objective:** To study the oxidative stress status of patients with phlegmatic polycystic ovary syndrome and the effect of important interventions. **Methods:** Sixty patients with phlegm-damp polycystic ovary syndrome admitted to our hospital between January 2021 and January 2022 were selected. According to the random number table method, the patients were divided into control group (n=30) and observation group (n=30), the control group was treated with metformin hydrochloride tablets, and the observation group was treated with the formula of Jia Wei Qi Gong Wan, and the levels of basal sex hormones (LH, E2), FPG and FINS were compared before and after treatment between the two groups.Serum SOD, MDA, GSH-Px levels before and after treatment, Chinese medicine evidence score before and after treatment. **Results:** Before treatment, the levels of basal sex hormones, FPG and FINS were compared between the two groups ($P > 0.05$), and after treatment, the levels of basal sex hormones, FPG and FINS were better in the observation group than in the control group ($P < 0.05$). Before treatment, the serum SOD, MDA and GSH-Px levels of patients in both groups were compared ($P > 0.05$), and after treatment, the serum SOD, MDA and GSH-Px levels of patients in the observation group were better than those in the control group ($P < 0.05$). Before treatment, the TCM evidence points of patients in the two groups were compared ($P > 0.05$), and after treatment, the TCM evidence points of patients in the observation group were lower than those in the control group ($P < 0.05$). **Conclusion:** Patients with phlegm-damp polycystic ovary syndrome have shown remarkable results with herbal interventions, which is worth promoting.

Keywords: Phlegm-Damp Polycystic Ovary Syndrome; Oxidative Stress State; Herbal Intervention; Intervention Effect

1. Introduction

Patients with polycystic ovary syndrome (PCOS) are characterized by hirsutism, obesity, and infertility, they are often associated with more long-term complications, including metabolic syndrome and atherosclerotic disease, which pose a serious threat to their physical and mental health. The incidence of polycystic ovary syndrome is increasing, with a current incidence of up to 18% in women of childbearing age, and has become a major cause of menstrual irregularities in adolescent women and infertility in women of childbearing age [1]. Oxidative stress is a state of imbalance between oxidation and antioxidation triggered by the excessive production of free radicals by the body, or the reduced ability of the body to scavenge free radicals, which causes tissue damage in patients and is a common factor in secondary diseases. Modern research has revealed that oxidative stress is present in the physiopathological processes of various diseases. As clinical research continues, it has been found that patients with polycystic ovary syndrome also experience oxidative stress, and it is hypothesized that this condition is related to the influence of inflammatory signaling pathways, so the clinical treatment of patients can be carried out for this reason [2]. It has been found that although the treatment system of Western medicine is

perfect, the treatment is single, has a high recurrence rate, and can bring greater side effects to patients, while the interventional treatment of Chinese medicine can enhance the clinical results of patients with high safety. In this study, the authors selected 60 patients with phlegm-damp polycystic ovary syndrome admitted to our hospital between January 2021 and January 2022, aiming to analyze the effect of phlegm-damp polycystic ovary syndrome patients under the application of Chinese herbal medicine intervention, which is described below [3,4].

2. Materials and Methods

2.1 General Information

Sixty patients with phlegm-damp polycystic ovary syndrome admitted to our hospital between January 2021 and January 2022 were selected. According to the random number table method, they were divided into control group (n=30) and observation group (n=30), the control group was treated with metformin hydrochloride tablets, while the observation group was treated with the formula of Jia Wei Qi Gong Wan [5]. The general information of the patients in both groups is shown in Table 1.

Table 1 Comparison of general information of patients in the two groups

Group	Number of cases	Age group Age	Average age	Disease duration Years	Average duration of illness
Observation group	30	21-43	28.15±7.64	1-7	3.89±1.03
Control group	30	20-43	28.10±7.61	1-6	3.86±1.01
X2/t	-	0.025		0.114	
P	-	0.980		0.910	

2.2 Methods

The control group was treated with metformin hydrochloride tablets, and the observation group was treated with the formula of Jia Wei Qi Gong Wan [6].

The usage of Metformin (State Drug Quantifier H33020526 Zhejiang Guoguang Biopharmaceutical Co., Ltd.): 1 tablet/time, 3 times/d.

Plus Flavor Qigong Pill Formula: The formula is composed of 18g Xian Ling Spleen, 18g Semen Cuscutae, 15g Atractylodes Macrocephala, 15g Poria, 15g Radix Astragali, 12g Salviae Miltiorrhizae, 12g Rhizoma Ligustici Chuanxiong, 12g Tangerine Red, 12g Radix Panax Notoginseng, 12g Atractylodes Macrocephala, 9g Fructus Crataegus, 9g Shen Qu, 9g Radix Rehmanniae, 9g Huangzen, 6g Glycyrrhiza Uralensis, 6g Huang Lian.Dosage: On the fifth day after the complete elimination of the patient's menstruation, take Plus Flavor Qigong Pill, one sachet in the morning and one sachet in the evening, while the menstruation needs to be stopped, every 21 is a course of treatment, a total of three menstrual cycles need to be treated [7].

2.3 Observed Indicators

Compare the basal sex hormone (LH, E2), FPG, FINS levels before and after treatment between the two groups. Serum SOD, MDA, GSH-Px levels before and after treatment, Chinese medicine evidence score before and after treatment.

2.4 Statistical Processing

SPSS 21.0 was used to process the data using X2/t checks, and P < 0.05 indicates statistical significance.

3. Results

3.1 Comparison of Basal Sex Hormone, FPG and FINS Levels before and after Treatment between Two Groups of Patients

Before treatment, the basal sex hormone, FPG, and FINS levels were compared between the two groups (P > 0.05). After treatment, the basal sex hormone, FPG, and FINS levels in the observation group were better than those in the control group (P < 0.05), see Table 2.

Table 2 Comparison of basal sex hormone, FPG, and FINS levels before and after treatment between the two groups (±s)

Group	Number of cases	LH（mIU/ml）		E2（pg/ml）		FPG（mmol/L）		FINS（μU/ml）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	3.05±0.86	10.92±1.68	40.56±10.15	53.65±11.38	4.03±0.35	5.05±0.49	7.02±1.03	9.35±1.46
Control group	30	3.11±0.89	4.23±1.05	40.13±8.98	45.65±10.62	4.11±0.36	5.82±0.51	7.08±1.06	15.65±2.19
t	-	0.266	18.496	0.174	2.815	0.873	5.963	0.222	13.110
P	-	0.792	0.000	0.863	0.007	0.386	0.000	0.825	0.000

3.2 Comparison of Serum SOD, MDA and GSH-Px Levels before and after Treatment between Two Groups of Patients

Before treatment, the serum SOD, MDA, and GSH-Px levels of patients in both groups were compared (P > 0.05). After treatment, the serum SOD, MDA and GSH-Px levels of patients in the observation group were better than those in the control group (P < 0.05), see Table 3.

Table 3 Comparison of serum SOD, MDA and GSH-Px levels before and after treatment between the two groups (±s)

Group	Number of cases	SOD（U/L）		MDA（nmol/ml）		GSH-Px（uU/l）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	93.65±9.68	58.43±7.16	5.06±1.15	14.68±3.26	261.65±30.49	163.21±21.49
Control group	30	93.81±9.76	81.37±13.68	5.01±1.19	10.65±2.16	260.45±30.19	217.56±26.49
t	-	0.064	8.138	0.112	5.644	0.115	8.727

P	-	0.949	0.000	0.911	0.000	0.909	0.000

3.3 Comparison of the TCM Evidence Points of the Two Groups of Patients

Before treatment, the TCM symptom scores of patients in both groups were compared (P > 0.05). After treatment, the TCM evidence points of patients in the observation group were lower than those in the control group (P < 0.05), as shown in Table 4.

Table 4 Comparison of TCM evidence points between the two groups (±s) (points)

Group	Number of cases	Before treatment	After treatment
Observation group	30	19.62±2.31	10.16±2.35
Control group	30	19.71±2.26	12.76±2.41
t	-	0.153	4.231
P	-	0.879	0.000

4. Conclusion

Oxidative stress refers to the fact that after the body is stimulated, active substances are synthesized and dysfunctional signaling pathways are involved, resulting in abnormal metabolic regulatory diseases in patients. Due to excessive formation of oxidized free radicals or the presence of scavenging barriers, which play an important role in mediating IR and apoptosis, SOD belongs to common antioxidant enzymes in the body, which can scavenge free radicals, alleviate the degree of cell damage and can repair cells. MDA belongs to lipid oxidation end products, which can assess the peroxidation capacity of reactive oxygen species into, and GSH-Px belongs to a peroxidolytic enzyme, which can scavenge oxygen radicals and protect the function of the body. The results of this study found that before treatment, the patient's SOD, MDA, and GSH-Px levels were abnormal, indicating that the patient had an oxidative stress state. The reason for the effective improvement of SOD, MDA, and GSH-Px levels after treatment with Gaji Qigong Pill is that the main effect of ginseng is to promote normal lipid metabolism, which can reduce blood cholesterol and lipid levels. In addition, ginseng can also play a role in enhancing heart contraction, which is beneficial to play an anti-arrhythmic effect and protect the capillary function of the heart. Ginsenoside in ginseng can enhance the anti-stress effect and strengthen the stress capacity in the organism. The β-eucalyptol in Atractylodes macrocephala can play an antioxidant stress response. β-eucalyptol can regulate gastrointestinal motility in both directions, and its ability to promote gastrointestinal motility significantly resists the stress response of gastrointestinal function. Radix Panax, Atractylodes macrocephala and Rhizoma tangerine can play the effect of drying dampness and dispelling phlegm, among which Atractylodes can increase the peritoneum's ability to absorb water. The fluid in the abdominal cavity can be accelerated by lymphatic or blood circulation of the special cabinet, elevating the blood volume, achieving diuresis and regulating the peritoneal capillaries, and the aromatic herbs and Shen Qu can eliminate stagnation. Chuanxiong can have the effect of invigorating blood and moving Qi, which can completely eliminate stagnation and relieve the patient's symptoms. Chuanxiong can also enter the liver meridian, which can enhance the draining and draining effect of the liver meridian. At the same time, it is also able to move Qi. When Qi moves, blood runs more easily, and when blood moves, stagnation disappears, and when stagnation disappears, pain is reduced. Poria as well as licorice can neutralize drugs, where the neutralizing effects of licorice include moderating drug properties, two-way regulation, monitoring drug toxicity, and correcting taste and flavor effects. Modern pharmacology also found that licorice can play a harmonizing property, which can enhance the effect of drugs and reduce their toxicity.

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Application Study of Nebulized Low-Dose Azithromycin in the Treatment of Community-Acquired Pneumonia

Rong Fan[1], Wei Xiao[2], Weihua Hu[3], Zhu Wu[*]
Jingzhou First People's Hospital, Jingzhou 434000, China.

Abstract: Objective: To analyze the effect of nebulized low-dose azithromycin in the treatment of community-acquired pneumonia. Methods: The selected research subjects were 68 patients with community-acquired pneumonia admitted to our hospital from January 2020 to January 2021. The patients were divided into control group and experimental group by random number table method. The control group was treated with normal saline inhalation (34 cases), and the experimental group was treated with aerosol low-dose azithromycin (34 cases). The treatment effects of the two groups were compared. Results: There were significant differences in the effective rates of treatment between the two groups, and the experimental group was higher (P<0.05). There were significant differences in inflammatory cytokine indexes between the two groups, and the experimental group was lower (P<0.05). Conclusion: The treatment effect of low-dose azithromycin in the treatment of patients with community-acquired pneumonia is definite, and it can be applied and promoted in clinical practice.

Keywords: Nebulized Low-Dose Azithromycin; Community-Acquired Pneumonia; Treatment Response Rate; Inflammatory Cytokines

Introduction

Community-acquired pneumonia is an inflammation of the lungs caused by infections such as bacteria, mycoplasma, and chlamydia outside the hospital. Symptoms of the disease include nasal congestion, sneezing, and sore throat, as well as cough, hemoptysis, and chest pain. If the patient does not receive timely and effective treatment, a variety of serious complications can occur, such as meningitis and pericarditis, which can threaten the patient's life in severe cases. The current clinical treatment of this disease is mostly antibacterial drugs, which can obtain a certain therapeutic effect, but it is very prone to adverse reactions [1]. For this reason, the selected research subjects were 68 patients with community-acquired pneumonia who were admitted to our hospital from January 2020 to January 2021. To analyze the effect of nebulized low-dose azithromycin in the treatment of community-acquired pneumonia. The results of the study are detailed below.

1. Materials and methods

1.1 Basic information

The selected research subjects were 68 patients with community-acquired pneumonia admitted to our hospital from January 2020 to January 2021. The patients were divided into control group and experimental group by random number table method. The control group was treated with normal saline inhalation (34 cases), and the experimental group was treated with aerosol low-dose azithromycin (34 cases). Among them, there were 16 males and 18 females in the experimental group, aged 34-68 years, with an average of (45.65±3.25) years. The control group consisted of 17 males and 17 females, aged 35-66 years, with an average of (45.54±3.65) years. After statistical analysis, there was no significant difference in the basic data

between the two groups (P>0.05).

1.2 Methods

1.2.1 Control group

The group received normal saline inhalation therapy, and the patients were given anti-infection, antitussive and antiasthmatic treatment. Treat every 2-3 days.

1.2.2 Experimental group

The group received normal saline inhalation therapy, and the patients were given anti-infection, antitussive and antiasthmatic treatment. Treat every 2-3 days.

1.3 Performance criteria

(1) Evaluate the therapeutic effect according to the improvement of the patient's symptoms, markedly effective means that the symptoms disappear, effective means that the symptoms are improved ideally, and ineffective means that the symptoms have not improved. Calculation method: (markedly effective + effective)/total number of cases × 100%.

(2) Observe the inflammatory cytokine indexes of patients after treatment, including TNF-α, IL-6 and IL-8.

1.4 Statistical methods

The data obtained in the study were processed by SPSS 23.0 software. ($\bar{x}$±s) is used to represent measurement data, using t test; (%) is used to represent count data, using (x^2) test. When the calculated P<0.05, it was suggested that there was a significant difference between the compared subjects.

2. Results

1.5 Comparison and analysis of the effective rate of treatment between the two groups

There were significant differences in the effective rates of treatment between the two groups, and the experimental group was higher (P<0.05). See Table 1 for details.

Table 1 Comparative analysis of the effective rate of treatment between the two groups [n, (%)]

Groups	Number of cases	Markedly effective	Effective	Invalid	Treatment effective rate (%)
Experimental group	34	24（70.59%）	8（23.53%）	2（5.88%）	94.12%（32/34）
Control group	34	17（50.00%）	7（20.59%）	10（29.41%）	70.59%（24/34）
χ^2	-	3.009	0.085	6.476	6.476
P	-	0.083	0.770	0.011	0.011

1.6 Comparative analysis of inflammatory cytokine indexes between two groups

There were significant differences in inflammatory cytokine indexes between the two groups, and the experimental

group was lower (P<0.05). See 2 for details.

Table 2 Comparative analysis of inflammatory cytokine indexes between the two groups($\bar{x} \pm s$)

Groups	Number of cases	TNF-α（pg/ml）	IL-6（pg/ml）	IL-8（pg/ml）
Experimental group	34	23.45±4.32	18.76±5.42	7.65±2.36
Control group	34	13.43±4.46	13.42±5.68	3.26±1.87
t	-	9.409	3.966	8.501
P	-	0.001	0.001	0.001

3. Discussion

Pneumonia is a common clinical disease that endangers human health. Due to the abuse of antibiotics and the continuous increase of drug-resistant bacteria, the incidence of the disease is increasing. Community-acquired pneumonia is caused by infection with pathogenic microorganisms outside the hospital, and its symptoms include nasal congestion, sneezing, and sore throat, which can seriously affect the quality of life of patients. Azithromycin is a macrolide antibacterial drug. This drug has a high antibacterial effect on Gram-positive bacteria and Gram-negative bacteria. At the same time, it has a long half-life. Taking a small amount of drug every day can achieve the minimum inhibitory concentration [2].

Relevant studies have pointed out that the physical and chemical properties of azithromycin aerosol particles can be administered by inhalation, and sufficient lung deposition can be achieved [3]. Another study showed that aerosolized azithromycin administration has a good feasibility. Compared with the same dose of oral administration, the drug concentration of nebulized administration in alveolar macrophages and pulmonary epithelial mucous layer is higher, and the plasma drug concentration is lower [4]. The results of this study showed that there were significant differences in the effective rates of treatment between the two groups, and the experimental group was higher (P<0.05). It is suggested that nebulized low-dose azithromycin treatment can improve the treatment efficiency of patients. There were significant differences in inflammatory cytokine indexes between the two groups, and the experimental group was lower (P<0.05). It is suggested that aerosol low-dose azithromycin treatment can reduce inflammatory cytokine indexes, which are closely related to bacterial infection. Taking low-dose azithromycin aerosol treatment can reduce the production of cytokines by M1 airway epithelial cells, and inhibit the apoptosis of human leukocytes and lymphocytes. , Inhibit the formation of natural killer cells, thereby reducing the production of inflammatory cytokines such as IL-8 and TNF-α by monocytes, thereby improving the related symptoms of patients and promoting their recovery.

In conclusion, the treatment effect of aerosol low-dose azithromycin in the treatment of patients with community-acquired pneumonia is definite, and it can be applied in clinical practice.

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An Association Between Periodontal Disease and Ischemic Stroke with Specific Dental Therapy: An Integrated Review

Ching-I Huang
Department of Stomatology, Suzhou Medical College of Soochow University, Suzhou 215123, China.

Abstract: Numerous researches have mentioned the interaction between periodontal disease (PD) and ischemic stroke. However, whether treatment of PD reduces ischemic stroke remains controversial. In this study, we review how periodontitis is a risk factor for stroke among the identified inflammatory mechanisms and how different types of specific periodontal treatments reduce the hazard of ischemic stroke. Based on the concept of inflammatory mechanisms between two diseases, whether all types of dental treatment can be effective to interrupt ischemic stroke development or instead lead to an irritating effect. The possibility of preventing recurrent stroke by treating PD is present in the discussion.

Keywords: Periodontal Disease; Ischemic Stroke; Inflammation; Dental Therapy

1. Introduction

This article aims to review the relationship between periodontal disease (PD) and ischemic stroke and examine the impact of specific dental therapy, both prophylactic and periodontal, on the occurrence of stroke. Stroke has become one of the top-ranked diseases leading cause of death worldwide. Around 20% of strokes are haemorrhagic, whereas the other 80% cause localized cerebral ischemia[1]. PD is a common, complex, and chronic inflammatory illness affecting a large population. Signs and symptoms of PD encompass gum infection, bleeding problems, and resorption to the unstable attachment between the tooth and its surrounding alveolar bone. These two diseases link through inflammatory mechanisms, with dental plaque and oxidative stress playing an important role. However, there is still insufficient evidence that dental treatment provides adequate protection against subsequent ischemic stroke. Clarifying and exploring different dental or combination treatments to reduce the incidence and recurrence of ischemic stroke is essential.

2. Periodontal disease is a factor in raising stroke incidence

Last decade, it has been widely adopted the correlation between ischemic stroke and PD in the field of medicine[2]. A combination of two prospective studies indicated PD was associated with a nearly 3-fold increased risk of stroke[3]. In recent meta-analysis, it investigated the interaction between PD and the incidence of various strokes separately. PD showed an association with a 1.6-fold increased risk of stroke with focal cerebral ischaemia[2]. Ischemic stroke refers to situations in which an obstruction prevents perfusion in the blood vessel in the regional brain, with four categories. The occurrence rate of cardioembolic, atherothrombotic and lacunar stroke especially had a strong connection with PD[4].

Dental plaques as a type of bacterial biofilm having attachments to the teeth induce inflammatory mechanism. Periodontal tissue inflammation not only leads to the destruction of periodontium and alveolar bone but also causes dysfunction of the endothelium of the arterial wall by body circulation. The dominating pathogens in the periodontal pockets are *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, which exist in atherosclerotic plaques as well[5]. In addition, elevated serum antibody titers to *Prevotella intermedia* and *Fusobacterium nucleatum* are related to people with

atherothrombotic stroke[6] and lead to adverse consequences after stroke. It is crucial to minimize the number of pathogens and control the accumulation of dental plaque in the oral environment.

3. Role of inflammation between two diseases

Several studies concluded that diabetes mellitus, cardiovascular, cerebrovascular diseases and some systemic diseases linked to PD by chronic inflammation. Pathogenic bacteria and metabolites in periodontal pockets enter the bloodstream temporarily or repeatedly, causing or exacerbating systemic inflammation, and increasing atherosclerotic plaque. *Porphyromonas gingivalis* induce platelet aggregation and adheres to endothelial cells[5]. Oxidative stress has great dominance in the development of dysfunctional endothelium and atherosclerosis (Fig 1.). It also reduces total serum antioxidant concentrations and salivary antioxidant capacity[7].

In periodontal injuries, stimulated by periodontal pathogens, neutrophils and other phagocytes along with other periodontal cells enhance the production of reactive oxygen species (ROS). Altered redox signalling due to increased bioavailability of ROS stimulate the form of atherosclerosis, hypertension and even the progression of related diseases. Oxidative stress due to its induction of inflammation further enhance the production of ROS[8].

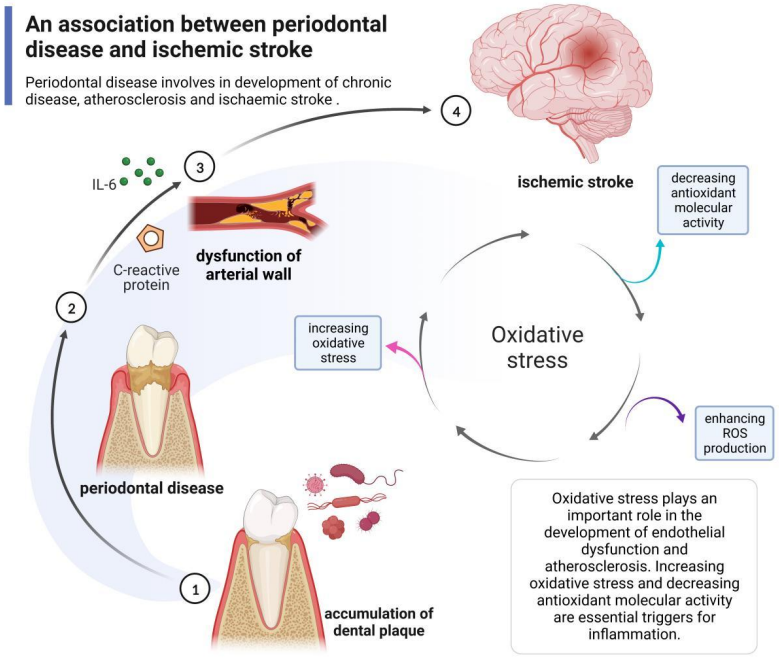

Figure 1. Inflammation between periodontal disease and ischemic stroke[7] [Created with BioRender.com]

4. Specific dental therapy comparison

Based on the pathogenesis, periodontal therapy is available for reducing ischemic stroke events and controlling the spread of inflammation. The previous studies showed that there was an opposite impact on the risk of ischemic stroke from treatment options for different levels. The association between stroke and periodontitis is clear, but the relationship with gingivitis is controversial[3].

For preventive treatment such as dental scaling, a retrospective cohort study conducted by Lin et al. concluded that gingivitis (Hazard ratio (HR) = 0.76; 95%CI = 0.66–0.86) and periodontitis groups (HR = 0.79; 95%CI = 0.66–0.92) show a significant reduction of the risk of stroke[9]. In the other cohort study conducted by Lee et al., people with PD receiving dental prophylaxis had the lowest stroke incidence rate (0.14%/year)[10]. These studies revealed the effectiveness of the

prophylactic treatment is expectable. Assuming the possible reasons, one is preventive treatment lowers the amount of dental plaque and avoids the over-accumulation of biofilm; another is patients who receive dental prophylaxis are often in gingivitis or mild periodontitis.

Intensive treatment is the main surgery to cure the periodontal disease, alleviate the periodontal inflammation and minimize the stimulus of infection. Both gingivitis (HR = 0.73; 95% CI = 0.56–0.95) and periodontitis groups (HR= 0.77; 95% CI = 0.66–0.89) with intensive treatment had a considerably lower risk of stroke[9]. The incidence of stroke (0.39%/year) in patients receiving intensive treatment or tooth extraction was higher than in receiving dental prophylaxis[10]. It seemed that these two studies showed the contrary. The previous one emphasized the significance associated with a lower risk of stroke for both periodontitis and gingivitis groups; the latter one used different measurement metrics focusing on a higher possibility of stroke incidents for patients with intensive treatment or tooth extraction when compared to preventive treatment. Thus, this contrast is explicable since people who have intensive treatment is meaning in the more severe stage of PD. Poor oral conditions raise the risk of ischemic stroke and tooth extraction refers to the final resort in treating the most serious conditions.

Moreover, the study found that the dental prophylaxis and intensive treatment groups had a significantly lower HR for stroke than the group without PD after adjusting for age, sex, and comorbidities in a Cox regression analysis. Combination therapy resulted in a better reduction in stroke events than a single treatment. Dental prophylaxis has as much impact on oral health and reduces the incidence of stroke as an intensive treatment when it does not go as far as irreversible periodontitis[9].

5. Discussion and future direction

Although the effectiveness of dental therapy being a preventive strategy for stroke has not reached an agreement in the field, the association that could lead to serious consequences is worth exploring. The result of the chronic inflammation may induce vascular dysfunctional endothelium, and promote inflammation in existing atherosclerotic lesions, even stimulating subsequent disease development. To decline the serum of systemic pro-inflammatory mediators, the frequency of tooth brushing is the daily method to improve.

One limitation of this review is that PD and ischemic stroke can separate into more detailed subtypes or levels of disease progression. To evaluate precisely, a classic cohort study applied 7 distinct periodontal contour classes to reflect population disease patterns at the subject and tooth level[1]. It clarified the association between ischemic stroke subtypes and PD more thoroughly with precise classification. Another limitation consists of potential risks of misdiagnosis of periodontitis and stroke, bias from different oral assessment measures, the influence of other risk factors, patients' lifestyles and so on. The influence of age, sex, comorbidity or smoking habits also needs to consider.

For now, it is time to research the efficacy of dental treatment as an intervention way in the direction of disease progression in clinical trials. An ongoing clinical trial (ClinicalTrials.gov Identifier: NCT04956211), investigates the link between periodontitis and recurrent vascular events in ischemic stroke survivors. They utilize non-pharmacological anti-inflammatory treatment to see if reducing local and systemic inflammation and enhancing vascular endothelium function reduces the risk of ischemic stroke recurrence in patients.

6. Conclusion

Specific dental care is an intervention for PD and ischemic stroke inflammation. People can prevent it in the early stages, maintain good oral hygiene, and appoint prophylaxis regularly. For people with periodontitis, specific treatments to control the inflammation and reduce the hazard of spreading the infection are necessary.

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Surgical Treatment of Hypertensive Cerebral Hemorrhage

Wengan Ji[1], Ruixue Xie[1], Shaoze Qin[1], Long Wang[2]*, Wenlong Tang[2]*

1. Department of Changzhi Medical College, Changzhi 046000, China.

2. Department of Neurosurgery, Heping Hospital Affiliated to Changzhi Medical College, Changzhi 046000, China.

Abstract: Intracerbral hemorrhage (ICH) refers to primary non-traumatic hemorrhage in the parenchyma, also known as spontaneous cerebral hemorrhage, accounting for 20%-30% of acute cerebrovascular diseases. Every year 2 million to 3 million people in the world suffer from intracerebral hemorrhage, accounting for 10%-15% of all new strokes, and the total incidence of intracerebral hemorrhage in the world is 24.6/ (100,000 · year). In China, the incidence of cerebral hemorrhage is 60-80/ (100,000 · year), which is much higher than that of other Asian countries. Primary intracerebral hemorrhage accounts for 80%-85%, and primary hypertensive intracerebral hemorrhage combined with hypertension accounts for 50%-70% [1]. Hypertensive intracerebral hemorrhage accounts for about 50% of the causes of non-traumatic intracerebral hemorrhage, and its mortality rate takes the first place in non-traumatic intracerebral hemorrhage [2]. Hypertensive intracerebral hemorrhage has rapid onset, high mortality rate and slow recovery, and often leaves various degrees of neurological dysfunction. This paper analyzes the pathological features of hypertensive intracerebral hemorrhage, the clinical features of the bleeding site, the indications, timing, surgical methods and the advantages and disadvantages of surgical treatment, hoping to provide reference for the selection of surgery for clinicians.

Keywords*:* Hypertension Cerebral Hemorrhage; Surgery; Treatment

1. Regional Pathological features of cerebral hemorrhage

Hypertensive intracerebral hemorrhage is caused by the rupture of intracerebral arterioles on the basis of chronic lesions caused by long-term hypertension stimulation. The perforating vessels with a diameter of about 100-200μm directly emanate from the intracranial aorta, including the bean-stripe artery, the thalamic perforating artery and the brainstem perforating branch of the basilar artery. [3]

2. Clinical features of bleeding sites

2.1 Basal ganglia hemorrhage

Basal ganglia is the most common site of hypertensive cerebral hemorrhage, accounting for more than half of all cerebral hemorrhage. Putamen hemorrhage was the best site of hemorrhage, because the hematoma was mainly located outside the inner sac, so it was called lateral type, and the source of bleeding was mostly the lateral group of the bean stripe artery. Bleeding usually begins in the posterior part of the putamen, and may spread in different directions, involving the radiocarpa, occupying the insula, and even extending to the subtemporal cortex. The opposite hematoma located on the medial side of the inner sac (thalamus) is called medial type [4].

2.2 Thalamic hemorrhage

Thalamic hemorrhage accounts for about 10% to 15% of cerebral hemorrhage. The source arteries of thalamic hemorrhage are the perforating arteries supplying the thalamus, mainly the geniculate thalamic artery supplying the lateral thalamic nucleus and the posterior thalamic perforating artery supplying the medial thalamic nucleus. [5].

2.3 Brain stem hemorrhage

The pons are a common site for bleeding from the brain stem. It accounts for more than 10% of cerebral hemorrhage. The source artery is the perforating branch of the basilar artery supplying the brain stem. The clinical manifestations include sudden onset, sudden severe headache and vomiting, immediate disturbance of consciousness, and even rapid fall into a deep coma. Pin-like pupils are usually characteristic changes of pontine hemorrhage, quadriplegia and nuclear facial paralysis, and bilateral pyramidal bundle sign is positive [6].

2.4 Cerebellar hemorrhage

Cerebellar hemorrhage accounts for about 10% of cerebral hemorrhage, mostly located in and near the dentate nucleus of one cerebellar hemisphere. The main bleeding source arteries were superior cerebellar artery, anterior inferior cerebellar artery and posterior inferior cerebellar artery branch. The main symptoms are sudden violent vomiting, occipital headache, dizziness, and falling due to ataxia. Physical examination may include stiffness of the neck, nystagmus and dysarthria. If the amount of blood loss is roughly pressure on the fourth ventricle and the latter hematoma breaks into the ventricle to cause obstructive hydrocephalus, the intracranial pressure can increase rapidly, and even acute forumoccipital hernia, disorder of vital signs, and rapid death can occur in severe cases [7-8].

2.5 Cerebral lobe hemorrhage

Cerebral protein and subcortical hemorrhage account for about 10% of all cerebral hemorrhage. It can occur in the frontal, temporal, parietal and occipital lobes. Most of the bleeding source arteries were amyloidosis arterioles in cerebral cortex and pia meninges. Different cerebral hemorrhage manifestations: frontal lobe, higher neural activity disorder, mental abnormality, convulsive attack, contralateral hemiplegia, dominant hemispheric hemorrhage with aphasia; Temporal lobe, partial hemiblindness, seizures and sensory aphasia; Parietal lobe, partial body sensory disorder, aphasia, apraxia; Occipital lobe, hemiblindness in the opposite visual field [9].

3. Surgical Treatment

3.1 Surgical indications

The patient's general condition, age, state of consciousness, hematoma volume, bleeding site, and whether there was hydrocephalus were comprehensively evaluated. Conscious patients with small amounts of bleeding do not need surgery. But deep coma, dilated pupil and even unstable vital signs, the operation effect is not good. Cerebral lobe and basal ganglia hemorrhage, feasible craniotomy to remove hematoma; The surgical treatment of thalamic hemorrhage should be more cautious, and ventricular trepanation and drainage are feasible for patients with ventricular rupture. The main treatment of brain stem hemorrhage is medical treatment. The treatment of cerebellar hemorrhage should be more active, such as hematoma more than 10ml or compression of the fourth ventricle to form hydrocephalus, supratentorial bleeding more than 30ml, midline displacement more than 10mm, the medical conservative is not effective, the disease continues to worsen, the patients without absolute contraindication of surgery can be operated.

3.2 Timing of Surgery

The indications for surgery are clear and should be performed as soon as possible. Surgery within 6 hours after bleeding, or even earlier, to remove the hematoma before irreversible damage to the surrounding brain tissue, promises to better save nerve function.

3.3 Surgical Methods

(1) The surgical approach was designed according to the site of the hematoma, the hematoma was removed under the direct view of craniotomy, and the decompression was full (if necessary, the bone flap was removed); (2) Neuroendoscopy-assisted removal of intracerebral hematoma is to introduce the endoscope into the hematoma cavity under the guidance of stereotactic, and aspirate the hematoma through repeated flushing. It can effectively stop bleeding and biopsy suspicious tissues [10]. (3) In case of emergency or can not tolerate general anaesthesia, the fluid components of the hematoma can be drilled and drained. Local use of thrombolytic agents such as urokinase or streptokinase to promote hematoma dissolution for drainage, secondary decompression is not complete; (4) Ventricular puncture and drainage are feasible for patients with obstructive hydrocephalus caused by intraventricular hemorrhage or posterior fossa hemorrhage [11].

4. Summary

Open surgery for hypertensive intracerebral hemorrhage includes conventional craniotomy and small window craniotomy [12]. Compared with small bone window craniotomy, craniotomy has greater damage to the scalp and skull, but can completely remove hematoma under direct vision, reliable hemostasis, rapid decompression, and can also be feasible when necessary, craniotomy decompression is the most commonly used and classic craniotomy approach for hypertensive cerebral hemorrhage. Small bone window craniotomy has little damage to scalp and skull, relatively simple operation, rapid removal of hematoma, and hemostatic leaves are satisfactory under direct vision. With the continuous maturity of neuroendoscopy technology, small bone window craniotomy is used in neuroendoscopy-assisted hematoma removal. Due to the rapid postoperative recovery, patients generally extubation with sobriety the next day. It is considered to be the most valuable surgical procedure due to its low trauma, short operation time, satisfactory removal of hematoma, minimal secondary brain injury, and satisfactory postoperative recovery of patients [13]. However, surgical treatment of hypertensive intracerebral hemorrhage is controversial and should be based on the patient's systemic condition and hematoma site. The size and the evolution of the disease were analyzed in detail.

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About the author: Wenqian Ji(1994--), male, Han nationality, Zizhou County, Shanxi Province, postgraduate student, Changzhi Medical College, research direction: Surgery (Neurosurgery).

Clinical Characteristics and Survival Analysis of Two Groups of Patients with Colon Cancer with Different Social Support

Sichao Jiang[1], Linxuan Zou[2*], Chengzhong Xing[3*]

1. Fuxin Central Hospital, Fuxin 123000, China.

2. The First Hospital of Dalian Medical University, Dalian 116000, Liaoning Province, China.

3. The First Hospital of China Medical University, Shenyang 110000, China.

Abstract: Colon cancer is the third largest cancer in the world at present[1], which is very common in developed countries, and the incidence rate in developing countries is also increasing year by year. The latest epidemiological report shows that 376000 new colon cancer patients and 191000 deaths have occurred in China. In the past ten years, our understanding of cancer has made new progress [2]. However, in the current research, there has been no progress in the research on the occurrence, development and prevention of colon cancer related to physical and mental diseases. In the latest research, there are studies on the influence of psychological factors in the molecular field from the perspective of psychology, which is of great help to the research on the occurrence, development and prognosis of colon cancer. In order to explore the influence of social psychological factors on the occurrence, development and prognosis of colon cancer, the experiment collected clinical data, social support scores, and followed up disease-free survival period and total survival period of colon cancer patients.

Keywords: Colon Cancer; Psychological Factor

1. Introduction

In order to explore the impact of psychosocial factors on the occurrence, development and prognosis of colon cancer, this experiment collected the clinical data and social support scores of colon cancer patients, followed up the disease-free survival period and total survival period of colon cancer, and grouped them according to the quantitative indicators of patients' social support, compared the clinical characteristics and prognosis of colon cancer patients with different social support, and discussed the role of psychosocial factors in the occurrence and prognosis of colon cancer, To provide new ideas for clinical prevention and treatment of colon cancer.

2. Research objects and methods

2.1 Acquisition of clinical data

This study collected the case data of patients who received laparoscopic colorectal cancer radical surgery in the First Affiliated Hospital of China Medical University from October 2018 to March 2019 in a total of six months. With the consent of the patient, the patient was instructed to complete the social support assessment scale according to their own real situation, record the social support assessment score of the patient, collect and record the patient's age, first symptom and other case information, and record the patient's tumor diameter, differentiation degree, stage and other clinical data indicators through preoperative CT examination and postoperative pathological data. Finally, according to the interpretation method of the social support scale [3], groups are divided by 30 points. The social support rating of low groups is ≤ 30, and that of high

groups is ＞ 30.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

1. Laparoscopic radical resection of colon cancer was performed without palliative resection. Patients with liver metastasis were those who could undergo radiofrequency ablation or surgical resection; 2. Colon cancer was confirmed by pathology after operation, and the number of lymph nodes was effective; 3. The pathological type was adenocarcinoma; 4. The patients agreed to fill in the social support rating scale.

2.2.2 Exclusion criteria

1. Patients with familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer were excluded; 2. Exclude patients with complications who underwent emergency surgery, such as colon cancer with perforation and bleeding; 3. Patients with stage IV colon cancer who had peritoneal metastasis and could not be treated by radical surgery were excluded; 4. Exclude patients who do not agree to fill in the social support rating scale; Patients with malignant tumors from other sources were excluded; 6 Exclude patients with problems or untruthfulness in filling in the social support scale; 7 Exclude patients whose clinical data cannot be collected or are incomplete.

2.3 Follow-up

Follow up will be started from the discharge of the last patient in the group until the end of the follow-up in December 2020. The follow-up method is mainly telephone follow-up, including outpatient or readmission, etc. Follow up the survival of the patients, and record the disease-free survival and total survival of the patients in the group. The disease-free survival time is from the discharge of the patient to the discovery of recurrence of colon cancer, and the total survival time is from the discharge of the patient to the death of the patient.

2.4 Data analysis and statistics

This study uses SPSS25.0 statistical software to analyze relevant data [4]. The number of cases and composition ratio were used for the description of classified data, chi square test was used for the comparison of components, K-M test was used for the comparison of ordinal classified data, wilcoxon rank sum test was used for the comparison of pairs, and Kaplan Meier method was used to draw the survival curves of progression free survival period and total survival period. $P < 0.05$ means the difference is statistically significant.

3. Result

After retrospective analysis and inclusion exclusion criteria, 177 colon cancer patients were finally included in the group out of the initial 200 colon cancer patients. The following is the correlation results between social support and clinical characteristics of colon cancer patients who were divided into two groups according to social support. The disease-free survival time and total survival time of the two groups of colon cancer patients were obtained through follow-up, and the survival curve was drawn with Kaplan Meier method to compare the prognosis of patients with different social support, so as to analyze the impact of social support on the prognosis of colon cancer patients.

3.1 Gender comparison between the two groups

Of the 177 patients enrolled, 78 were colon cancer patients with low social support, and 99 were colon cancer patients with high social support. In the 78 cases of colon cancer with low social support, there were 43 males and 35 females, with a male to female ratio of 1.22: l. There were 99 cases of colon cancer with high social support, including 69 males and 30 females. The male to female ratio was 2.3:1. Among the patients enrolled in this experiment, the majority of male patients had high social support, with a proportion of 1.60:1, while the proportion of female patients with colon cancer with low social support was relatively high, with a statistically significant difference ($p<0.05$). See Table 1

Table 1 Gender comparison of high and low social support

Gender	total	Low social support	High social support	χ2	P
Male	112	43（38.39%）	69（61.61%）	5.815	0.016
female	65	35（53.85%）	30（46.15%）		
total	177	78	99		

3.2 Age comparison between the two groups

The following data are obtained by grouping the two groups of patients according to their age, as shown in Table 2. According to the data in Table 2, the median age of patients in the group was 60 years old, slightly higher than the national level. Among them, the patients aged 50-59 years were the most, up to 70, accounting for 39.55%. Most of them are 60 to 69 years old, accounting for 37.29%. From the perspective of high and low social support groups, the median age of the high social support group is 55 years old, and the 50 to 59 year old group is the majority, accounting for 47.47%. The median age of patients in the low social support group was 65 years old, and the majority of patients in the 60-69 year old group reached 52.56. There was significant difference in age distribution between the two groups, which was statistically significant by chi square test ($p<0.05$).

Table 2 Age distribution of high and low social support

Age group	Low social support	High social support	χ2	P
≤40	1（1.28%）	3（3.03%）		
40-49	7（8.97%）	15（15.15%）		
50-59	23（29.49%）	47（47.47%）	9.628	0.047
60-69	41（52.56%）	25（25.25%）		
≥70	6（7.69%）	9（9.09%）		

3.3 Comparison of main clinical initial symptoms between two groups

According to the clinical data recorded by the patients at the hospital, the patients with colon cancer with different social support were grouped according to the first symptom, and Table 3 was obtained. It can be seen from Table 3 that the first symptoms of patients with different levels of social support are obviously different. In patients with colon cancer with low social support, the first symptoms were mainly abdominal pain, abdominal mass and intestinal obstruction, while in patients with colon cancer with high social support, the first symptoms were mainly bloody stool and change of bowel habits. Statistical analysis showed that the distribution of the first symptoms of colon cancer patients with different social support had significant differences ($p<0.05$).

Table 3 Comparison of clinical initial symptoms with high and low social support

First symptoms	Anorexia	Weig ht loss	Abdominal pain, distension and diarrhea	Altered bowel habit	Hematochezi a	Abdominal mass	intestinal obstruction
Low social support （78）	20	31	65	15	35	60	26
High social support(99)	26	45	28	73	70	13	13

3.4 Comparison of histopathological characteristics between two groups

According to the pathological characteristics of patients collected by preoperative CT examination and postoperative pathology, the differences between patients with different social support are compared. The results are shown in Table 4. Table 4 shows that there is a significant difference in tumor volume between the two groups. The tumor volume of patients with low social support is generally large, while that of patients with colon cancer with high social support is generally small. The majority of patients with colon cancer with low social support have large tumors. The difference between them was statistically significant (P<0.05). At the same time, it can be found that the distribution of patients with different social support in the general classification is also significantly different. The patients with low social support of colon cancer are mostly ulcerative and protuberant, and the number of ulcerative and protuberant types is similar. The patients with high social support were mostly bulging. In terms of the degree of tumor differentiation, there is also a significant difference between the two groups of patients. Most patients with low social support for colon cancer are poorly differentiated, while most patients with high social support are highly differentiated. The difference was statistically significant (p<0.05).

Table 4 Comparison of clinicopathological characteristics of colon cancer patients with high and low social support

Pathological characteristics		Low social support（78）	High social support（99）	χ2	P
volume	＜5cm	27（34.62%）	57（57.57%）	5.724	0.017
	≥5cm	51（65.38%）	42（42.42%）		
gross type	Ulcerative type	41（52.56%）	27（27.27%）	8.972	0.011
	Protuberant type	30（38.46%）	60（60.60%）		
	Infiltrating type	7（8.97%）	12（12.12%）		
Differentiation degree	Low differentiation	63（80.77%）	28（28.28%）	6.522	0.038
	Highly differentiated	15（19.23%）	71（71.71%）		

3.5 Comparison of tumor metastasis between two groups

By comparing and analyzing the data of lymph metastasis and distant metastasis of colon cancer patients with different social support in two groups, the results are shown in Table 5. It can be seen from the comparison in Table 5 that the proportion of lymph metastasis in colon cancer patients with low social support is more (58.97%), with a statistically

significant difference (P<0.05). However, there was no significant difference in the distribution of patients with distant metastasis between the two groups.

Table 5 Comparison of tumor metastasis of colon cancer patients with high and low social support

Transfers		Low social support（78）	High social support（99）	X^2	P
Lymph node metastasis	No lymph node metastasis	32（41.02%）	69（69.69%）	11.424	0.001
	Lymph node metastasis	46（58.97%）	30（30.30%）		
Transfer	No transfer	63（80.77%）	89（89.89%）	3.671	0.299
	Liver metastasis	15（19.23%）	10（10.10%）		

3.6 TNM staging of two groups of patients

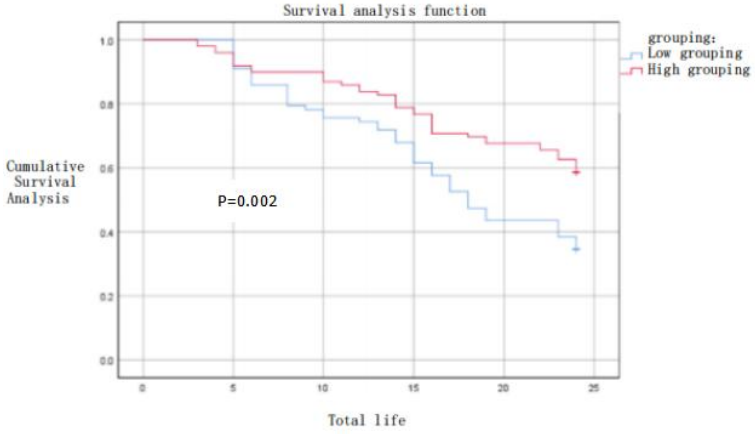
According to the collected patient data, and according to the 2011 AJCC TNM staging standard for malignant tumors (the 8th edition), patients with colon cancer with different social support were divided into TNM staging. The TNM pathological staging of patients with colon cancer with high social support and low social support was compared, as shown in Table 6. It can be seen from Table 6 that there was a difference in pathological stages between the two groups at the time of diagnosis, P<0.05, which was statistically significant.

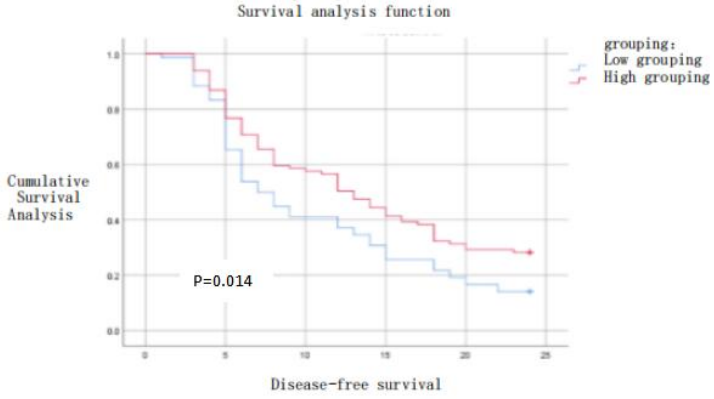
Table 6 Comparison of TNM Stages of Colon Cancer Patients with High and Low Social Support

TNM		LOW SOCIAL SUPPORT（78）	HIGH SOCIAL SUPPORT（99）	X^2	P
TNM staging	I	7（8.97%）	26（26.26%）	11.893	0.008
	II	32（41.03%）	44（44.44%）		
	III	20（25.64%）	19（19.19%）		
	IV	19（24.36%）	10（10.10%）		

3.7 Comparison of survival rates between the two groups

The study began in October 2018, and the last patient was discharged from the hospital on April 2, 2019 to the end of the study on December 31, 2020. A total of 92 patients survived and 85 died. The survival rate of patients with low social support rate was 38.46%, and the survival rate of patients with high social support rate was 62.62%. The survival rate of patients with high social support was significantly higher than that of patients with low social support, P<0.05, with statistical significance. The total survival analysis curve is Figure 1, and the disease-free survival analysis curve of patients in high and low groups is Figure 2.





4. Discussion

The occurrence, development and prognosis of colon cancer involve a complex evolutionary process involving multiple factors. This study is to explore the role of social psychological factors in the occurrence, development and prognosis of colon cancer. It is a cross study of clinical surgery and social psychology to explore the possible findings of colon cancer in the field of physical and mental diseases [5].

In the current researc,, the mechanism of social psychological factors in the occurrence and development of cancer is described as follows: 1. Personality factors affect the occurrence, development and prognosis of cancer. Depressive and negative personality traits have a negative impact on human health and disease recovery, and keeping healthy and positive personality traits has a positive effect on physical health. 2. Influence the occurrence and development of cancer through adverse psychological factors directly caused by life events. Life events refer to changes in social life that people encounter in their lives. Bad life events will produce bad psychological state, affect people's immunity, and thus affect people's health. 3. Social support. Social support refers to the sum of material and spiritual help that people can get from society in social life. It is the main way for people to get love and sense of value from society in social life. Relevant research shows that low social support or low utilization of social support is also related to low survival rate of cancer patients. A one-year prospective study showed that immature defense mechanisms could lead to sleep disorders in colorectal cancer patients, and irregular sleep might lead to poor prognosis in cancer patients.

In many survival analysis studies of colon cancer, the 2-year survival rate of colon cancer patients is generally about 60%. In this study, from the discharge of the last patient to the end of the study on December 31, 2020, a total of 92 patients

survived and 85 died. The total two-year survival rate was 51.98%, the survival rate of patients with low social support rate was 38.46%, and the survival rate of patients with high social support rate was 62.62%. The survival rate was lower than that of most studies. This may be due to the selection bias caused by the single center, small sample and retrospective study. However, this study found that patients with colon cancer with high social support had higher disease-free survival and total survival than patients with colon cancer with low social support, and the difference was statistically significant. In this study, we found that social support was correlated with multiple clinical indicators. Patients with high social support generally had smaller tumors, earlier staging, and fewer metastases, which may be the main reason why patients with high social support had better conditions in disease-free survival and overall survival. Secondly, in the field of psychology, social support also plays a positive role in the postoperative recovery of cancer [6]. In a word, to improve social support, strengthen psychological counseling and education for colon cancer patients can effectively prevent metastasis and recurrence after radical surgery, prolong the survival period of patients, and improve the quality of life of patients after surgery.

To sum up, social support is related to many clinical features[7] and plays a positive role in the prognosis of colon cancer patients.

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Changes of Acylating Stimulating Protein (ASP) and Blood Lipid in Patients with Acute Myocardial Infarction

Honglei Jiang[#], Bei Tan[#], Yang Ge, Ying Liu, Xiaoyan Lu, Chunlin Cao*, Shujing Yang*
Department of Cardiology, Shandong Second Provincial General Hospital, Jinan 250022, China.

Abstract: **Objective:** To study the changes of acylating stimulating protein (ASP) and blood lipid in patients with acute myocardial infarction. **Method:** There were three groups,25 cases of acute myocardial infarction patients (acute myocardial infarction group), 32 cases of coronary heart disease patients without myocardial infarction (CHD group) and 30 cases of healthy people (control group). They respectively detected the ASP, low density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C), and analyzed the correlation between them. **Results:** (1) ASP, TG, TC and LDL-C of acute myocardial infarction group and coronary heart disease group were significantly higher than those of control group, while HDL-C was lower than control group, the difference was statistically significant ($P < 0.05$). (2) TG in coronary heart disease group was higher than that in acute myocardial infarction group, while ASP, TC, LDL-C and HDL-C had no significant difference. **Conclusion:** ASP and blood lipid are risk factors of CHD, ASP can be used as risk index of CHD. There was no significant difference in plasma ASP between patients with acute myocardial infarction and patients with coronary heart disease without myocardial infarction. ASP cannot be used as a surrogate marker of acute myocardial infarction.

Keywords*:* Acute Myocardial Infarction; Acylating Stimulating Protein; Blood Lipid

Introduction

Acylation Stimulating Protein (ASP) is a fatty hormone produced by fat cells, which increases glucose transport, fatty acid esterification, and triglyceride (TG) synthesis. Acylating stimulating protein is produced in the alternative pathway of complement system activation. In the process of tissue injury, complement C3 interacts with lipase to produce C3a, which is rapidly cleaved by plasma carboxypeptidase to produce acylating stimulating protein [1]. Acylating protein is positively correlated with dyslipidemia, insulin resistance, obesity and coronary heart disease [2]. A number of studies have shown that multiple complement bodies, including C3, C4, C5B-9, etc. after acute myocardial infarction are much higher than those of normal people. It suggests that myocardial infarction may be closely related to the activation of complement system [3]. Some studies have shown that the changes of ASP are positively correlated with troponin I in patients with acute myocardial infarction and ASP can be used as a substitute marker for patients with acute myocardial infarction [4]. Although at present the pathogenesis of coronary heart disease have different studies and theories, but lipid metabolic abnormalities is still the most main risk factor for coronary heart disease. Whether it is low density lipoprotein cholesterol (LDL - C) which is the most focused in clinic at present, or triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL - C), they all play an important role in the occurrence and development of coronary heart disease. Studies have shown that patients with different types of coronary heart disease have certain differences in abnormal lipid metabolism [5]. In this study, the correlation between ASP and blood lipid among patients with acute myocardial infarction, patients with non-myocardial infarction coronary heart disease and healthy people were analyzed to explore the relationship between ASP, blood lipid and

acute myocardial infarction and the influence of ASP on the occurrence and development of coronary heart disease.

1. Objects and Methods

1.1 Objects

A total of 57 patients were selected from cardiology of Shandong second provincial general hospital in January 2020 - July 2021. They were divided into two groups,25 cases of acute myocardial infarction group, 32 cases of coronary heart disease group. All the 25 patients in the acute myocardial infarction group met the diagnostic criteria of the Guidelines for the Diagnosis and Treatment of acute myocardial infarction, including 16 males and 9 females, with an average age of (61.67±10.30) years. The patients of coronary heart disease group were all done coronary arteriography.There was at least a 50% or greater narrowed coronary arteries, including 27 cases of unstable angina, 4 cases of chronic stable angina, 1 case of latent coronary artery disease,but ruled out in patients with acute myocardial infarction.This group was including 20 males and 12 females, with an average age of (66.45-13.27) years. Other exclusion criteria for both groups were valvular heart disease, malignancy, infectious disease, autoimmune disease, and severe hepatic and renal insufficiency. In addition, 30 healthy volunteers were selected as the control group, including 18 males and 12 females, with an average age of (62.55±9.40) years. All subjects had no history of taking lipid-regulating drugs within 6 months. There was no significant difference in age, gender and other general information among the three groups, which was comparable.

1.2 Methods

All subjects were fasted at night and venous blood was taken the next morning. In the acute myocardial infarction group, the onset time was different at admission, but venous blood was taken within 72 hours after the onset. Serum ASP was determined by enzyme-linked immunosorbent assay (ELISA), and TG, TC, HDL-C and LDL-C were determined by enzyme-conjugate method.

1.3 Statistical analysis

Data were analyzed by SPSS 22.0 statistical software, and measurement data were expressed as $\bar{x} \pm s$. Differences between groups were compared by independent sample T test, and $P < 0.05$ was considered statistically significant.

2. Result

It was found that ASP, TG, TC and LDL-C in acute myocardial infarction and coronary heart disease groups were significantly higher than those in control group, while HDL-C was lower than those in control group. There was no significant difference in ASP between acute myocardial infarction group and coronary heart disease group. TG in CHD group was higher than that in AMI group, TC, LDL-C and HDL-C had no significant difference. See table 1.

Table 1 Comparison of ASP and blood lipid among three groups

	AMI (n=25)	CHD (n=32)	Control (n=30)
ASP（ng/ml）	57.50±22.63*	61.67±19.72*	43.81±14.05
TG（mmol/L）	2.15±0.99*#	2.93±1.23*	1.43±0.64
TC（mmol/L）	4.29±1.00*	4.37±1.20*	3.85±0.42
LDL-C（mmol/L）	3.14±0.78*	3.30±1.04*	2.49±0.51
HDL-C（mmol/L）	1.16±0.31*	1.22±0.33*	1.37±0.27

*vs control group，$P<0.05$；#vs CHD group，$P<0.05$

3. Discussion

The relationship between dyslipidemia and coronary heart disease has been well proved, and the increase of triglyceride is one of the independent risk factors of coronary heart disease. Acylating stimulating protein can activate phosphodiesterase of adipocytes, stimulate adipocytes to store triglycerides and inhibit lipolysis, so serum acylating stimulating protein is strongly correlated with triglyceride level and weakly correlated with low density lipoprotein cholesterol [6]. In this study, ASP, TG, TC and LDL-C were significantly increased and HDL-C was decreased in both acute myocardial infarction and coronary heart disease groups,suggesting that dyslipidemia is correlated with abnormal ASP, which are all risk indicators of coronary heart disease. The study of Sivakumar K et al. [7] showed that ASP receptor dysfunction led to delayed clearance of triglycerides in the body and resulted in hypertriglyceridemia and low HDL-C, which led to the increase of TG/HDL-C and further affected the change of LDL-C, ultimately led to the occurrence of coronary heart disease.

A number of studies have confirmed that in the early stage of acute myocardial infarction, blood lipids will decline and gradually recover with the evolution of the disease [8-10]. This study did not follow up and observe the changes of blood lipid in patients with acute myocardial infarction, but in the comparison of blood lipid between the coronary heart disease group and the acute myocardial infarction group, it was found that the TG of the coronary heart disease group was significantly higher than that of the acute myocardial infarction group, which supported the viewpoint of decreased blood lipid in patients with acute myocardial infarction.

Some studies have shown that ASP can be used as a substitute marker for acute myocardial infarction [3], but this study did not reach the same point of view. ASP is closely related to lipid metabolism. From the perspective of the mechanism of action, the increase of ASP can accelerate the storage of triglyceride, reduce serum triglyceride concentration, and has the greatest influence on the change of triglyceride. In this study, triglyceride in the acute myocardial infarction group was significantly lower than that in the coronary heart disease group, but ASP concentration did not increase to the same extent, indicating that the change of triglyceride in patients with acute myocardial infarction was not directly related to ASP.

The close relationship between ASP and lipid metabolism determines the role of ASP in the pathogenesis and development of CHD. Further research will help to reveal the mechanism of abnormal lipid metabolism and provide new ideas for the prevention and treatment of CHD.

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#, *, The authors contributed equally.

*Corresponding author: Chunlin Cao.

Co-corresponding author: Shujing Yang.

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Research progress of MicroRNA in podocytes autophagy in diabetic nephropathy

Ruixue Xie[1], Wengan Ji[1], Pengfei Fang[1],Feifei Wu[2*], Haoyu Dong[2*]

1. Department of Changzhi Medical College, Changzhi 046000, China.

2. Department of Endocrinology, Heping Hospital Affiliated to Changzhi Medical College, Changzhi 046000, China.

Abstract: Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes, and is a kind of abnormal microangiopathy of kidney structure, function or clinical indicators caused by diabetes. Podocyte injury has been considered as a major contributor to the progression of diabetic nephropathy(DN). microRNA can participate in podocytes injury through autophagy.In this paper, the mechanism of microRNA involved in DN podocytes autophagy was reviewed to provide reference for the treatment of DN in the future.

Keywords: Diabetic Nephropathy; Podocytes; Microrna; Autophagy

Introduction

Diabetic nephropathy (DN), a microvascular complication of diabetes, has a high incidence in many countries[1].At present, the pathogenesis of DN is still being explored. Studies have shown that podocyte loss or injury is one of the earliest observed features in the pathogenesis of diabetic nephropathy[2].Podocytes, which are visceral epithelial cells of the renal capsule, are attached to the outside of the glomerular basement membrane. This membrane, together with podocytes and the capillary endothelium, forms the glomerular filtration barrier。 Podocyte viability and apoptosis as well as autophagy can affect glomerular function.MicroRNAs (miRNAs or miRs) are a class of short noncoding, highly conserved RNAs with 19–25 nucleotides in length, which can bind to the 30-untranslated region (30UTR) of target mRNAs, and thereby promote mRNA degradation or mRNA translation inhibition.Autophagy[3]refers to the process involving the decomposition of intracellular components via lysosomes. Autophagy plays an important role in maintaining and regulating cell homeostasis by degrading intracellular components and providing degradation products to cells.In pathological environment, cells usually repair damage by forming autophagosomes to remove damaged proteins and organelles. Thus, disruption of autophagy disturbs cellular homeostasis and contributes to the development of various diseases. This paper reviews the signaling pathways related to miRNA in DN podocytes autophagy.

1. SOX2OT induces podocyte autophagy through miR9/SIRT1 axis

Long non-coding RNAs (lncRNAs) play an important role in the pathogenesis of various human diseases, A study showed[4] that the lncRNA SOX2-overlapping transcript (SOX2OT) is significantly down-regulated in DN mice and high glucose (HG)-treated human podocytes cells (HPCs).SOX2OT overexpression significantly promoted cell proliferation and inhibited cell apoptosis und.r HG stimulation. Furthermore, SOX2OT overexpression notably decreased protein levels of pro-apoptotic Caspase-3 and Bax, whereas increased levels of anti-apoptotic Bcl-2 under HG stimulation. In contrast, SOX2OT knockdown exerted the opposite effect. These data indicate that SOX2OT overexpression alleviates the

HG-induced HPCs injury. SIRT1 is a deacetylase and can induce autophagy via deacetylation of autophagy-related marker Beclin-1 and other autophagy mediators, Other studies have shown[5] that SIRT1 has been shown to promote cell survival by suppressing p53-dependent apoptosis in response to DNA damage and oxidative stress, and recent data suggests that the interplay of SIRT1-p53 pathway controls cellular senescence.Furthermore, SIRT1 was also shown to modulate PGC-1a activity and to attenuate aldosterone-induced mitochondri damage and podocyte injury.bioinformatics analysis revealed that SOX2OT harbors predicted binding sites of miR-9 and sirtuin 1 (SIRT1) might act as a putative target of miR-9. Data revealed that SOX2OT overexpression significantly decreased miR-9 expression, but notably increased SIRT1 mRNA and protein levels.By contrast, SOX2OT knockdown exerted the opposite effect. The protective effects of SOX2OT on podocytes injury were mediated through autophagy induction by the miR-9/SIRT1 axis.

2. CASC2 induces podocyte autophagy through miR-9-5P/ PPARγ axis

LncRNA cancer susceptibility candidate 2 (CASC2),located on chromosome 10q26, plays a regulatory role as an anti-cancer factor in various cancers. Recently[6], Wang et al. revealed that CASC2 was specifically reduced in serum and renal tissues of type 2 diabetes patients with chronic renal failure, and follow-up identified that the serum of patients with low CASC2 expression had higher incidence of chronic renal failure. there were complementary sites between miR-9-5p and CASC2 by bioinformatics website starBase v2.0.The Peroxisome proliferator-activated receptor gamma (PPARγ) protein, located in the cellular nucleus, contains 505 amino acids and has a molecular weight of 57.6kDa. PPAR-γ is best known for its abilities to regulate pathways linked to adipocyte differentiation and metabolism .PPARγ is implicated in several metabolic syndromes, including DN. Down-regulated PPARγ could activate β-catenin signaling to destroy podocyte architectural integrity and increase cell apoptosis in DN. Data revealed[7] that CASC2 mainly up-regulated the expression of PPARγ by acting as the ceRNA of miR-9-5p, thus alleviating HG-induced podocytes injury through increasing cell viability, autophagy and reducing cell apoptosis.

3. MiR-21 inhibits podocyte autophagy through the PTEN-PI3K/ Akt/m TOR pathway

MiR-21 can regulate cell differentiation, proliferation and apoptosis, and the serum concentration of DN patients is significantly higher than that of normal people, [7] Tensin homolog gene (PTEN) is a tumor suppressor gene on chromosome 10q23.3, which has lipid and protein diphosphate activity and plays an important role in cell growth, proliferation, survival, apoptosis, angiogenesis, cell migration and invasion. Phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt)/Mammalian target of rapamycin (mTOR) signaling pathway is involved in the regulation of glucose metabolism, cell proliferation, cell transcription and apoptosis, and is closely related to the occurrence and development of DN.microRNA-21 (miR-21) [8] as the molecular link between high glucose and PTEN suppression. Renal cortices from OVE26 type 1 diabetic mice showed significantly elevated levels of miR-21 associated with reduced PTEN and increased fibronectin content. In renal mesangial cells, high glucose increased the expression of miR-21, which targeted the 3'-UTR of PTEN mRNA to inhibit PTEN protein expression. Overexpression of miR-21 mimicked the action of high glucose, which included a reduction in PTEN expression and a concomitant increase in Akt phosphorylation. In contrast, expression of miR-21 Sponge, to inhibit endogenous miR-21, prevented down-regulation of PTEN and phosphorylation of Akt induced by high glucose. Other studies[9] have shown that ursolic acid (UA)can lead to the recovery of autophagic function in podocytes through the inhibition of miR-21 expression, which leads to up-regulated PTEN expression and decreased abnormal activation of the PI3K/Akt/mTOR pathway.

4. MiR-21 inhibits podocellular autophagy through the FOXO1 axis

Cell autop-hagic activity was obviously reduced in podocytes after HG treatment,as evidenced by reduced LC3II/LC3I ratio and increased p62 protein expression in HG. Also, the depletion of miR-21 weakened HG-mediated autophagy inhibition in podocytes. these data showed that miR-21 loss alleviated HG-induced podocyte injury.The Forkhead Box O1 (FOXO1) is mainly expressed in adipocytes, muscle cells, hepatocytes and islet cells, and is involved in the physiological processes of glucose and lipid metabolism, proliferation, differentiation and apoptosis of islet B cells. FOXO1 can alleviate inflammation and induce autophagy at the cellular level. showed that hepatic expression levels of microRNA-21 (miR-21) were decreased in high-fat diet (HFD)-induced diabetic mice. Adenovirus-mediated overexpression of miR-21 decreased the expression ofphosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) and inhibited glucose production in primary mouse hepatocytes. Furthermore, overexpression of miR-21 in mouse hepatocytes and mouse livers decreased the protein levels of FOXO1 and increased hepatic insulin sensitivity. By contrast, silencing of miR-21 increased the protein levels of FOXO1, subsequently leading to a decrease in insulin sensitivity and impaired glucose intolerance in mice fed with high-fat diet for 4 weeks. These results suggest that FOXO1 was a potential target of miR-21[10] MiR-21 exerted its pro-apoptosis and anti-autophagy effects by targeting FOXO1 in HG-cultured podocytes. Atr enhanced FOXO1 expression by downregulating miR-21 in HG-cultured podocytes. We concluded that Atr mitigated kidney injury in DN mice and alleviated HG-mediated apoptosis increase and autophagy inhibition in podocytes by regulating miR-21/FOXO1 axis.

5. The p53/miR-34a/SIRT1 axis inhibits podocyte autophagy

MiR-34a, a p53-regulated miRNA, directly targets SIRT1 and contributed to DN progression. MiR-34a represses SIRT1 to activate p53 and establish a positive feedback loop[11]. we observed that serum miR-34a level was positively correlated with podocyte injury in DN patients. The expression of acetylated p53 and miR-34a was upregulated, SIRT1was downregulated in glomeruli from patients with DN and STZ induced diabetic mice, as well as in human podocytes treated with advanced glycation end (AGE). MiR-34a antagonism in vitro and vivo in STZ induced diabetic mice developed alleviated glomerulus injury as reflected by attenuated albuminuria, reduced podocyte loss and restored autophagic flux. In human podocyte, inhibition of AGE formation by pyridoxamine prevented miR-34a dependent repression of SIRT1, p53 acetylation and activate podocyte autophagy in a dose-dependent manner. MiR-34a overexpression increases acetylation of p53 by translational repression of SIRT1. SIRT1 overexpression also impacts AGE induced apoptosis through deacetylating p53,whereas silencing of SIRT1 by EX527 attenuated the cytoprotective functions of miR-34a knockdown.Moreover, blockade of p53 acetylation significantly rescued miR-34a-induced apoptosis through SIRT1 restoration. Collectively, Targeting modulation of p53/miR-34a/SIRT1 feedback by miR-34a knockdown or overexpression of SIRT1 could rescue podocyte injury during DN.

6. Expectation

DN appears to be strictly related to some mirnas in its pathophysiological processes. miRNA can be involved in cell differentiation, pyrodeath, oxidative stress and so on[12].As a result, DN appears to be strictly associated with certain miRNAs during its pathophysiological process. DN patients may benefit from therapy targeting DN-associated miRNAs.In addition, miRNA is specifically expressed in both urine and blood, and is easy to obtain and detect, which also has great potential in the early diagnosis of DN, observation of disease progression and prognosis.

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About the author: Ruixue Xie (1997 --), female, Han nationality, Wanrong County, Shanxi Province, master candidate, Changzhi Medical College, research direction: Internal Medicine (Endocrinology and metabolism)

A Study on the Correlation Between Sleep Quality and Accidental Injuries Among University Students in Hainan

Jiaxuan Li, Kang Lu, Jinyu Lin, Qiao Li*

International School of Public Health and One Health, Hainan Medical University, Haikou 571199, China.

Abstract: **Objective:** To analyze the correlation between sleep quality and accidental injuries among university students in Hainan, and to provide reference for improving injury prevention among university students. **Methods:** A total of 1100 college students from freshman to Senior Students in three universities in Hainan were selected by multilevel random sampling method, and investigated by Pittsburgh Sleep Quality Index (PSQI) and injury questionnaire. **Results:** The average PSQI score of Hainan university students was 7.645. In the five dimensions of sleep latency, sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction, as well as the PSQI total score, the differences between the accidental injury group and the non-accidental injury group were statistically significant ($P<0.01$), except for sleep quality and sleep time, all other dimensions and PSIQ total score were higher in the accidental injury group than in the non-accidental injury group. **Conclusion:** The problem of poor sleep quality among university students in Hainan were widespread, and the occurrence of accidental injuries among university students were related to the sleep quality.

Keywords: University Students; Sleep Quality; Accidental Injury

Introduction

Sleep was an important part of the body's physiological rhythm and was closely related to daily life. Having a good quality of sleep was the guarantee of a good life. Nowadays, univerity students faced pressure from various aspects such as study, employment, family and social changes, and long-term emotional tension and psychological overload caused a decrease in sleep quality, and poor or even very poor sleep quality could easily triggered a series of adverse reactions affecting physical and mental state. Relevant studies had confirmed that sleep problems in childhood and adolescence increased the risk of injury occurrence [1-3]. In this study, the correlation between accidental injuries and sleep quality among univerity students in Hainan was investigated by questionnaire, and to provide references for improving sleep quality and injuries prevention and control among univerity students in the future.

1. Subjects and methods

1.1 Research subjects and sampling method

Simple random sampling method was used to draw three universities in eight undergraduate institutions in Hainan Province, and then the stratified cluster sampling was used to draw a total of 1000 college students from three universities. 1200 questionnaires were distributed and 1017 valid questionnaires were actually returned, with an efficiency rate of 84.8%.

1.2 Research tools

1.2.1 Pittsburgh sleep index scale

The Pittsburgh sleep quality index was developed by Dr. Buysse, a psychiatrist at the University of Pittsburgh, USA, and others in 1989. This scale was used to assess the quality of sleep of the subject in the last 1 month, and consists of 19 self-rated and 5 other-rated items. The cumulative score of each component was the total PSQI score, which ranges from 0 to 2l. The higher the score, the worse the sleep quality. A PSQI score greater than 7 was usually used as the reference threshold for sleep quality problems in adults.

1.2.2 Injury assessment

The external causes of injuries are classified into 14 types, including road traffic injuries, poisoning, fall injuries, burns, crush injuries, sprains, cuts, animal bites, drowning, accidental asphyxiation,electric shock, consumer goods injuries, medical accidents and others, with reference to the International Classification of Diseases (ICD)-10 [5-6]. Injury assessment was based on the occurrence of the above-mentioned injuries in the past 1 year, and those who had one of the following conditions were judged to be the statistical subjects of injury [7]: (1) make a diagnosis and give treatment at medical units and diagnosis of a certain type of injury; (2) emergency treatment or care of the injured person by family members, teachers, colleagues or peers; (3) leave of absence (school closure, rest) for half a day or more due to injury.

1.3 Statistical methods

SPSS22.0 statistical software was applied for analysis. The t-test was used to compare between groups for measurement data. The test level was $\alpha=0.05$.

2. Results

2.1 General situation

Among the 1017 people surveyed, 500 (49.2%) were male and 517 (50.8%) were female; 160 (15.7%) were freshmen, 341 (33.5%) were sophomores, 286 (28.1%) were juniors, and 230 (22.6%) were seniors.

2.2 The relationship between the university students' sleep quality and the accidental injury

The mean score of PSQI for university students in Hainan was 7.645 ,with a standard deviation of 3.047.In the study population, the incidence rate of accidental injuries was 25.6%(260/1017).According to the injury assessment criteria, the surveyed students were grouped into the group with injuries and the group without injuries, and compared the difference of sleep quality between the two groups, the results showed that the dimensions of sleep latency,sleep efficiency, sleep disturbances, sleep medication, daytime dysfunction and the total PSQI score, the difference of accidental injury rate between the two groups was statistically significant ($P<0.01$). In addition to the dimensions of sleep quality and sleep duration, all other dimensions and PSIQ scores were higher than those of the no-injury group.

Table 1 The scores of each dimension in two groups of university students with and without accidental injuries (x±s)

	Had an accidental injuries（N=230）	No accidental injuries had occurred（N=787）	*t*	*P*

Sleep quality	2.813±1.009	3.181±0.949	4.862	＜0.01
Sleep latency	2.548±0.677	2.391±0.810	2.943	0.003
Sleep duration	2.261±0.857	2.487±0.937	3.438	0.001
Sleep efficiency	0.770±0.811	0.494±0.700	4.663	＜0.01
Sleep disturbances	2.970±0.767	2.358±0.749	10.686	＜0.01
Sleep medication	2.487±1.023	1.607±0.916	11.740	＜0.01
Daytime dysfunction	2.987±0.828	2.437±0.945	8.572	＜0.01
PSQI total score	16.834±2.708	14.939±2.654	9.486	＜0.01

3. Discussion

In this study, the results showed that the average PSQI score of Hainan university students was 7.645, which indicates that the problems of poor sleep quality among Hainan university students were widespread.It was found that the scores of sleep latency, sleep efficiency, sleep disturbances, sleep medication, daytime dysfunction dimensions and the PSQI score were higher for those who had experienced injury than for those who had not, indicating that sleep problems in the above aspects were potential risk factors for injury occurrence. It may be due to the long sleep latency, short sleep duration at night and sleep disturbances seriously affect the quality of sleep, which in turn leads to poor mental state during the day; as well as, the use of sleep medication, which to some extent affects physical health, and leads to the occurrence of accidental injuries.

For university students, the sleep problems exacerbated mental regulation and cognitive dysfunction under the influence of various factors, had making them prone to impulsive behavior[8]. In addition, for college students, frequent outings increase the probability of exposure to external hazards, poor sleep quality and poor personal state, poor resilience and slow reaction when dangerous situations arise, them more likely to get injured[9-11].

In summary, it can be seen that some of the Hainan college students have poor sleep quality problems, leading to accidental injuries. To improve the poor sleep quality of Hainan college students and reduce the occurrence of accidental injuries, it is recommended to start from the following aspects: first, the school should hold a lecture about sleep quality, explaining the importance of sleep quality, causing most male college students to pay attention to improving sleep quality. Second, schools should appropriately reduce the academic tasks of majors with heavy academic assignments, which will help improve students' sleep quality and thus improve their study efficiency. At the same time, schools should strengthen the management of dormitory lights-out bedtime situation, try to unify the sleeping time of college students and improve their sleeping habits. Finally, class counselors should care more about the psychological state of students in their classes, hold appropriate psychological counseling class sessions, and contact students to create a more harmonious relationship between them.

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About authors:

First Author: Jiaxuan Li , Undergraduate

Co-First Author: Kang Lu, Graduate Student

*Corresponding author: Qiao Li,Associate Professor,Research direction:Injury epidemiology

Triphenylphosphonium (TPP) Cation as a Promising Strategy in Mitochondria-Targeting and the Current Studies of the TPP-Based Mitochondria-Targeting Medicines in Ischemia-Reperfusion Injury and Cancer

Sheng Liew
Huazhong University of Science and Technology, Tongji Medical College, Wuhan 430030, China.

Abstract: Mitochondria are known as the "powerhouse" of a cell, in charge of the generation of respiratory ATP. On the other hand, mitochondria are also involved in cell metabolism, the formation and regulation of reactive oxygen species (ROS), mitophagy, and cell signalling. As a result, diseases like ischemia-reperfusion (IR) injury, neurological disorders, diabetes, and cancer may be caused by mitochondrial malfunction. Hence, mitochondrial dysfunction treatment has become a great interest in the research direction for the therapeutic strategy. To treat the dysfunctional mitochondria and facilitate the transportation of drugs, we need to accomplish accurate mitochondria-targeting. In this review, I will discuss triphenylphosphonium (TPP) as one of the most prevalent strategies in targeting and facilitating the drugs into mitochondria. Furthermore, the current studies of TPP in IR injury and cancer resulting from mitochondria dysfunction will be reviewed.
Keywords: Triphenylphosphonium; Mitochondria-Targeting; Cancer; Ischemia-Reperfusion Injury

Introduction

Mitochondria are important organelles responsible for multiple functions. The dysfunction of mitochondria could result in IR injury, cancer, diabetes and some neurological disorders. [1] Mitochondrial dysfunction is related to many high-prevalence diseases, thus it will provide a huge potential contribution to saving countless lives and medical resources. The concept of mitochondria-targeting is important because conventional drug delivery systems to mitochondria have shown unfavourable outcomes such as low bioavailability, poor biodistribution, lack of water solubility, side effects, drug resistance, low therapeutic response despite high dosages, and unable to penetrate through the barriers in the body[2].

It is very challenging in developing a mitochondria-targeting drug, as mitochondria possess different barriers to molecule transmission which are different from other organelles. The mitochondrion is enclosed by a double-layer membrane, and the inner membrane is folded into cristae according to the baffle model. The current strategies for mitochondria drug delivery could be divided into active and passive targeting. Limited by its morphological properties, passive targeting is difficult to achieve, hence active delivery is the mainstream of the current study. Active targeting is referred to the specific interactions that happen at mitochondrial sites, including antigen-antibody binding and ligand-receptor associations. The rationale behind active targeting is to take advantage of the compatibility between the mitochondrial compartment and the carrier molecule's physicochemical features (electric charge, hydrophilicity, size, and mass). To date, the common methods and pharmacological approaches toward mitochondria-targeting are lipophilic cations, nanotechnology, cationic plastoquinone derivatives, mitochondrial uncoupling, and peptide-based targeting[2]. Among these methods, the TPP which belongs to the lipophilic cations category has proven to be a strong candidate. Herein this review

will provide an overview of the advancement of TPP and TPP-based mitochondria-targeted medicines in IR injury and cancer.

1. Overview of Triphenylphosphonium (TPP)

TPP is the most researched lipophilic cation among mitochondrial targeting strategies at the moment. It is a member of the group of tertiary phosphines, which are phosphanes with three hydrogens substituted by phenyl groups (Fig.1) [3]. The localization and uptake of TPP by the mitochondria are based on 1) TPP's hydrophobic surface; 2) TPP possesses low activation energy for the transportation across the hydrophobic membrane core; 3) The huge potential difference between mitochondria inner membrane and TPP molecules.

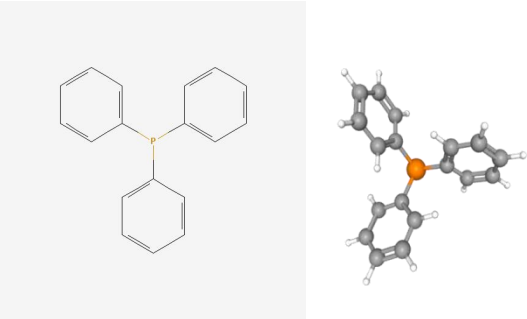

Figure 1. 2D and 3D structure of TPP. [3]

First, TPP could easily pass through the mitochondria's phospholipid because of its high hydrophobicity. This property is proportional to the ability to cross through the cell membrane. TPP's hydrophobic surface causes the high affinity between the mitochondria's phospholipid bilayer and the TPP compound itself, thus creating a pathway through the membrane.

Second, TPP has a unique property which is the low activation energy for transportation across the hydrophobic membrane core. This property is the main feature that differentiates TPP from other common lipophilic cations. Due to the three hydrophobic phenyl groups, the TPP cation possesses a big ionic radius. The activation energy required to drive the cation into the membrane is inversely related to the ionic radius. Hence, this makes TPP has lower activation energy in penetrating biological membranes.

Last, the potential difference drives the transportation of TPP-based compounds into mitochondria. The TPP-compounds are bringing positive charges, while the mitochondrial membrane potential is negatively-charged (150-180mV). The strong negative membrane potential of mitochondria is found nowhere else in the cell, resulting in exceptional molecular selectivity. The huge potential difference between them is the primary force that drives TPP into mitochondria. Furthermore, the Nernst equation states that for every 60mV of membrane potential, the absorption of these TPP-compounds is around 10-fold higher, resulting in a substantial uptake into mitochondria. [4][5]

2. TPP-based Mitochondria-targeted Compounds with the Common Diseases

As mentioned before, mitochondria have several important functions in the human body and dysfunctional mitochondria will lead to many diseases. This paper will elaborate on the current studies of TPP-based mitochondria-targeted compounds on IR injury and cancer.

2.1 Ischemia-Reperfusion (IR) Injury

Ischemia-reperfusion (IR) injury happens when a tissue's blood flow is interrupted (ischemia) and then restored

(reperfusion). IR injury is a very commonly happening situation in clinical settings such as myocardial infarction, stroke, hypovolemic shock, or organ transplantation. Furthermore, It's also related to many significant clinical symptoms, including multiple organ dysfunction syndromes, brain dysfunction, and sudden heart failure. The currently mainstream belief suggests for the cause of IR injury is mainly because of the sudden increase of reactive oxygen species (ROS) production at the reperfusion stage. Mitochondria produce most of the ATP by OXPHOS and are also the primary source of ROS. ROS produced by mitochondria is an important signalling molecule and actor in many cellular adaptive mechanisms. The ROS become toxic when the redox equilibrium is disrupted and will result in IR injury [6].

Current research on TPP-based mitochondria-targeted drugs for IR injury is the mitochondria-selective S-nitrosating agent (MitoSNO). MitoSNO is a mitochondria-targeted drug that prevents complex I from producing reactive oxygen species (ROS) during early reperfusion following IR injury. MitoSNO is made up of the NO donor S-nitroso-N-acetylpenicillamine and the TPP cation. MitoSNO will be driven into the mitochondrial matrix within a few minutes after intravenous injection. MitoSNO immediately binds with intramitochondrial thiols and S-nitrosated cysteine 39 on complex I subunit ND3, leaving the enzyme inactive and preventing an uncontrolled burst of ROS upon reperfusion. MitoSNO not only protected against IR injury in vivo but also showed a drastically improved long-term cardiac performance after IR injury[7].

2.2 Cancer

There are many mechanisms explaining the relationship between cancer and mitochondria dysfunction. The 5 mainstreams beliefs are 1) The DNA mutations that affect mitochondria, causing the alterations of the electron transport chain's subunits; 2) The abnormal oxidative stress from the ROS as the stimulus for cancer generation; 3) The dysregulation of mitochondria's apoptosis function; 4) The metabolic reprogramming concerning several mutations in genes encoding TCA cycle enzymes; 5) Multiple molecular changes result in long-term cellular proliferation.[1][8]

TPP-based Mitocans primarily target cancer cells with high mitochondrial membrane potential and deliver medications or bioactive substances to the cancer cell mitochondria to achieve therapeutic or cytotoxic goals. The majority of these compounds target a specific element of cancer cell mitochondrial operations, such as high levels of reactive oxygen species (ROS), aberrant oxidative phosphorylation, or other physiological functions (11). To date, there are many ongoing pieces of research on the development of Mitocans. All the designs are categorized according to their rationale in dealing with cancer. The types of anticancer agents are, 1) TPP-linked antioxidants: MitoQ, Mito-CP and Mito-ChM; 2) TPP-linked with natural products: Mito-resveratrol, Mito-HNK and Mito-dihydro; 3) TPP-linked with commercialized drugs: Mito-chlorambucil, Mito-metformin, and Mito-doxorubicin; 4) TPP-linked with enzyme inhibitors: DPC, DAP and DCA; 5) TPP-linked with photosensitizers: MitoPhotoDNP and Mito-CCy; 6) TPP-linked with thermo-sensitive agents: TPPV; 7) TPP-linked with small cytotoxic molecules: APPI, APPCL and MitoDNP-SUM.[2][4][5]

Numerous investigations were conducted for decades on the possibility of non-targeted treatment to restore the normal physiology of mitochondria. In general, the outcomes are less than ideal, therefore researchers are currently focused on developing a mitochondrial-targeting strategy. Mitochondria stand up as a prominent therapeutic target when considering their involvement in human pathophysiology. Multiple drugs with distinct targets and modes of action have been produced to treat mitochondrial dysfunction in various clinical circumstances. This paper has covered the properties and applications of TPP as the mitochondria-targeted strategy.

Furthermore, several innovative delivery mechanisms such as cationic plastoquinone derivatives, peptide-based targeting, nanotechnology and mild mitochondrial uncoupling are also showing great potential and are now being evaluated.Many of these treatments appear promising based on in vitro or cell-free outcomes; however, more research, especially in vivo, is needed to guarantee that findings are translated to clinically relevant settings. To evaluate a compound's

ability to prevent and/or treat mitochondrial dysfunction, specific animal illness models are required. Finally, human clinical studies in physiologically appropriate situations are required to determine the therapeutic utility of these compounds.

Conclusion

In summary, this paper has provided a general introduction to TPP and its current progress in the treatment of IR injury and cancer. Mitochondria therapeutic approach is actually in its infancy, many further investigations still need to be done such as the dosage pattern, the long-term effect, side effects, best administration method and time. However, according to the current research direction focusing on mitochondria as the therapeutic target seems to be a glimpse of light on many diseases that have been haunting humankind.

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A Review on Biocompatibility of Graphene-Based Material

Yiheng Liu

Huazhong University of Science and Technology, Wuhan,430074, China.

Abstract: This review mainly focuses on the research of biocompatibility of graphene-based material in the past few years. As graphene-based material has been considered a great candidate for biomedical use, it attracts great interests of many researchers.It is not clear yet that whether the graphene and its derivatives are safe enough to be the biosensor in human's body. Common graphene is always to have reaction with human's substance inside and produce harmful substance. However, some of its derivatives may do not have the same problem. So, this research proposal wants to find out the cytotoxicity of the graphene and its derivatives. In addition, the review wants to conclude a standard about to what extent of cytotoxicity is the graphene-based material allowed to be used in human's body and do not produce harm to our health.Therefore, biocompatibility of graphene-based material has gradually become the topic of various scientists. This review summarizes the latest researches in the past few years and different results. In conclusion, future path of the research is given and what has to be emphasized is that before graphene-based material is in vivo applications, its biocompatibility must be clearly examined.

Keywords: Graphene-Based Material; Biocompatibility; Cell

Introduction

In 2010, Andre Geim and Novoselov was prized the Noble Prize for their excellent research in the material of graphene. Since then this kind of material is used in various area for its brilliant characteristic, such as batteries, chips, transistors, and so on. Not long after that, many scientists begin to notice its great behavior in sensor industry. After that, scientists begin to research its affection in biosensor area. In a recent study, the researchers put the concept of nano-graphene and nano-graphene-oxide, which has been used in many biomedical area. From the research, when the cancer cell in human's body is in a high level, they will combine with a substance on it which is called target ligand. When this happens, the computer will raise the data and put the relevant function on the screen. By this way, the doctors will be able to judge whether the patients are suffering the cancer. As a new-fashioned material, graphene also has been reported to have antibacterial, antiplatelet, and anticancer properties. It also has the potential to deliver drugs to a specific part of human's body. Even if the technology is not mature yet, it will probably to have some breakthrough in the near future. In this way, biocompatibility of graphene has become crucial for its applications related to human. Therefore, this review collects data from various paper about their view of biocompatibility of graphene-based materials. Next, the review raised some data and figures to clearly show the experiment result about biocompatibility of graphene based material to the cells. At the end of the view, the review makes a conclusion and write about some conclusion about future works on researches of biocompatibility of graphene-based materials.

1. Main body:(GBMs=graphene-based materials) (conclusions from different authors' angles)

Graphene is a kind of newly fashioned material which has been used in different industries. Owing to its characteristic of one-thick compound, it has been used to diagnose many kind of diseases. [1] Graphene can penetrate a single cell in a small volume, so it can be used as a drug carrier to provide more paths for medicine to be a candidate for ; it is believed that the future technological development brought by other fields will also provide greater support for the precision medicine industry. [2] For example, it is the best material known for conducting electricity and heat. According to a recent research, it is found that graphene and its derivatives are also an excellent material used for detecting cancer in human's body. [3] After attaching the graphene with the biosensor, it can greatly improve the biosensor's function. In addition, the biosensor is able to have specific detection with its help.Graphene is a layer of carbon which is connected with overlapping sp2 bonds. The most significant properties of graphene comes from the 2p structure, which makes the p-band to the carbon which produces graphene. From past studies of graphene, researchers have noticed that graphene is very rigid, which makes it reveals much high heat conductivity, and it is particularly impressive to gases. Owing to these properties, graphene is found to be very fit for similar materials, which has been used in different applications. As a result, a good graphene is needed for commercial applications.[12] Graphene has the biggest tense with stiffness which is almost linked with graphite. As a result, it has attracted the attention of many researchers. A technique which can administrate statistic stress and make frequency under great tensile. A strain of graphene layer was seen which is using a method through administrating change in a peak. Conclusively, the most significant properties is decided on the distribution in the host matrix, destruction concentration, face bonding, some ratio, and so on. An deliberation in tensile strength of the components with destruction concentration represents improved mechanical function of the component and is able to effectively transmit loading in both graphene and polymer.

2. What decides the effect of GBMs to human's cell:

1: Sometimes GBMs gained from different sources or ways are dcalled the same names. However in fact their chemical and physical properties are totally different. For this reason, it is difficult to give exact conclusions.[1]

2: Graphene oxide can lower cell adhesion and therefore produce cell apoptosis. GO can also enter lung cells and make people get inflammation. Therefore, maybe graphene oxide do not have a good application prospect used in human's body.[2]

3: Studies should focus more on synthesis of graphene using biological molecules. Owing to the functions of graphene based materials depend on the size, surface, the number of layer, lateral dimensions and so on. There might be fitness.[3]

3. Problem existed

It is not clear yet that whether the graphene and its derivatives are safe enough to be the biosensor in human's body. Normal graphene is possibly to have chemical reaction with human's body and produce harmful substance. However, some of its derivatives may do not have the same problem. So, in this research proposal wants to find out the cytotoxicity of the graphene and its derivatives. In addition, the review wants to conclude a standard about to what extent of cytotoxicity is the graphene-based material allowed to be used in human's body and do not produce harm to our health.If we are able to select the safe graphene or its derivatives from others, we are able to use these material to attach the biosensor, and then our fighting against the cancer will step a little further. Because if we are able to diagnose the cancer cell in the early time, the chance to cure it will greatly improve. In addition Graphene is regarded as the best material known to be used in a sensor.

The most tricky problems now is that whether the graphene and its derivatives are harmful to human's body is not sure

yet. Unless its safety is well examined, the technology will not be put into use. So it is an urgent thing to try to solve the problem which has disturbed the scientists for a long period of time about the issue.According to a theory, most graphene and its derivatives are able to process chemical reaction and produce harmful substance inside human's body. To get a relatively safe material, it is possible to need to process a kind of human-made derivatives to avoid reaction. So it is still a long way to go to find a kind of absolutely safe derivatives to human's body.

1.Some data and pictures

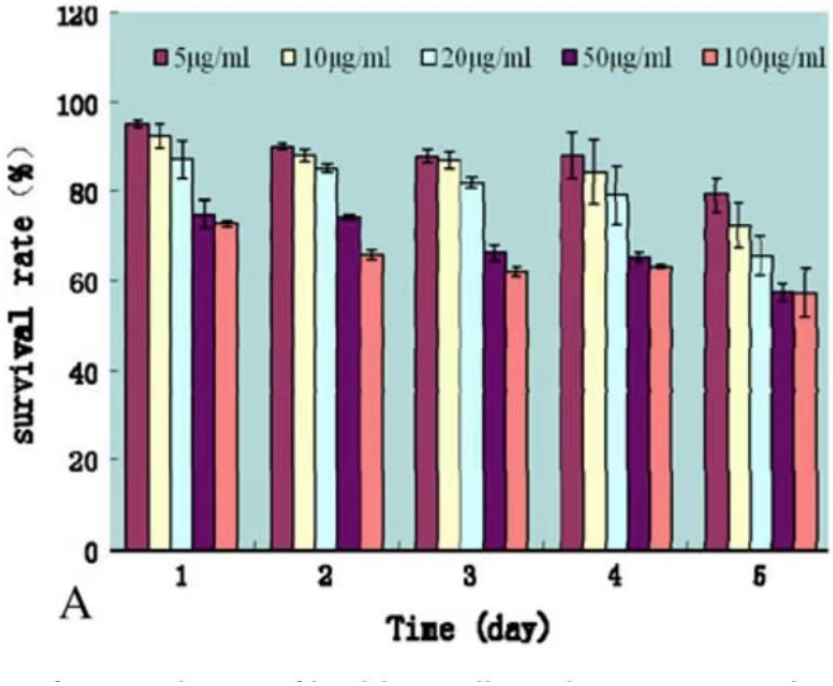

Figure 1 The effects of GO on human fibroblast cells

Figure 1 shows the effects of GO on human fibroblast cells: the existing rate at different levels of GO and different time,the right picture shows location of GO inside HDF cells.[4] This figure clearly shows that this kind of graphene oxide decrease the survival rate of human's fibroblast cells. And as the concentration gets higher and days go by, the survival rate will become lower.

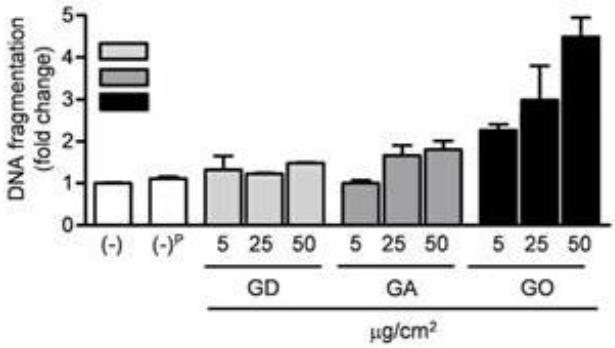

Figure 2

In another research, as the figures show, researchers find out that minimizing oxidation will lower the DNA blast. And graphene oxide, which decreases the mitochondrial generation and cell destruction in a specific kind of cell. Cells is able to stably express a localized oxidant sensitive GFP probe were exposed to increasing concentrations of dispersed graphene in 2 per cent, aggregates of graphene in water, graphene oxide, water or water with 2 percent and oxidation of the probe was

measured using flow a few hours later. MLE-12 cells were exposed as in and cell death was measured 24 hours later using a DNA destruction ELISA.[5] As their conclusion shows, minimizing oxidation and stable nanoscale dispersion improves the biocompatibility of graphene in the lung.

A recent research shows the damage function of graphene. [6] Graphene is able to go into the cells through all kinds of ways. It is also very likely toproduce physical damage to the cell membrane through penetration. As long as it enters, it can decrease oxidative stress through improving production causing changes in cell membrane potential. Graphene is also likely to be an electron acceptor stopping the electron transmission chain and lowering ATP level. Therefore ROS formed can decrease DNA damage; release of cytokines which causes inflammation. Cells experience apoptosis and programmed cell death as a result of more DNA damage, oxidative stress or inflammation.There are two main methods: penetrating cell membranes and inhibiting the electron transport.

4. Conclusion（Approaches to reduce toxicity）

As far as what have been found, nearly all kinds of GBMs will decrease human cell viability. However, in my opinion, it does not mean that all GBMs do not fit for human's body. If we can use chemical methodology to make synthesis of graphene, and with some guidelines of to be set standards, probably safe kinds of GMBs will be produced.

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Comparison and Analysis of Various Representative Schools of Head Needling

Yuanyuan Liu[1], Junming An[2]

1. Shaanxi University of Traditional Chinese Medicine Xianyang, Xi'an 712046, China.

2. Hospital of Traditional Chinese Medicine, Xi'an 710021, China.

Abstract: In this paper, by studying and reading the literature related to head acupuncture, its aim is to summarize and compare the similarities and differences in the principle of action, positioning and operation methods of different schools of head acupuncture. At present, the more widely used schools of head acupuncture include Jiao Shunfa head acupuncture, Fang Yunpeng head acupuncture, and Tang Songyan head acupuncture. The principles of stimulation site selection vary among schools, and their principles of action range from basic meridian doctrine principles to biological holographic principles. In terms of acupuncture method, Fang Yunpeng emphasizes that the depth of acupuncture needs to reach the periosteum, and the acupuncture site is inconsistent among different schools, which should be clinically and experimentally confirmed to confirm the scientific nature of the theory of scalp acupuncture, to protect the clinical experience of each school of acupuncture, to gather the strengths of all schools, to determine the best scheme of head acupuncture, to reduce blind clinical operations, to improve the efficacy, and finally to promote the promotion of head acupuncture.

Keywords: Head Acupuncture; Genre; Needling; Comparison

1. Introduction

Head acupuncture is a therapy in which specific zones and lines on the scalp are needled to treat diseases, which is especially applicable to brain-derived diseases such as stroke, cerebral palsy, and insomnia [1]. There are more head acupuncture schools used in clinical practice, and the common ones include Fang's head acupuncture by Yunpeng Fang, Jiao's head acupuncture by Shunfa Jiao, Tang's head acupuncture by Songyan Tang, Lin's head acupuncture by Xuejian Lin, and Zhu's head acupuncture by Mingqing Zhu. These head needles in the principle of acupuncture points, head point positioning, acupuncture operation and other aspects of different, the following is a brief comparison and analysis.

2. Principle of Action

There are various principles of head acupuncture, including the principles of traditional Chinese medicine's meridian theory, modern medicine's biological holographic theory or cortical function localization theory, based on which the corresponding stimulation zones are divided on the scalp for acupuncture [2]. Among them, Zhu's head acupuncture is mainly based on the principle of meridian theory, with Baihui as the division of yin and yang, which is divided into nine zones with "inverted correspondence" between the main treatment of the zone and the body position [3]. Jiao's head acupuncture and Lin's head acupuncture are both based on the theory of cortical functional localization, which means that the functional localization of the nerve centers coincides with the projection areas of the scalp, thus treating the corresponding functional disorders [4-5]. Tang's head acupuncture, on the other hand, is based on the biological holographic theory, which divides the human body into two parts as a coronal section, then reduces them in equal proportion, and finally hangs them on the front

and back of the scalp according to yin and yang, respectively [6]. Fang's head acupuncture combines the theory of cortical function localization and biological holographic theory, proposing a theoretical system of head acupuncture based on voodoo, voodoo, inverted voodoo, and inverted image [7].

3. Head Point Positioning

3.1 Jiao's Head Pin

Jiao's head pin is closest to the international standard head pin positioning. Two standard lines were set according to the cranial appearance as the anterior-posterior median line (the line connecting between the eyebrows to the middle of the head at the lower edge of the external occipital ridge), and the brow-occipital line (the horizontal line connecting the midpoint of the upper edge of the eyebrows to the lateral aspect of the head at the tip of the external occipital ridge) [8]. A total of fourteen lines are distributed here, including motor zone, sensory zone, choreo-tremor zone, vasodilation zone, dizzy hearing zone, speech zone II, speech zone III, use zone, foot transport sensory zone, visual zone, balance zone, stomach zone, thoracic zone, and genital zone.

3.2 Tang's Head Pin

Tang's actual is based on Jiao's head acupuncture therapy, which follows Jiao's naming sites on the motor zone, sensory zone, foot transportation sensory zone, blood zone (i.e. vasodilatation zone), visual zone, balance zone, stomach zone, and application zone, etc. In addition, it also determines the positioning of five stimulation points: the perineum point, umbilical point, jiantu point, fate point and dazhong point. On this basis, it determines the positioning and efficacy of the upper jiao zone, middle jiao zone, lower jiao zone, lumbar recommendation zone, back zone, and head and neck zone, which are within one inch and five minutes on both sides of the head median line [9]. The sensory zone, motor zone, sensory zone II, motor zone II, and blood zone were creatively combined as the "transport-sensory zone". Tang also identified the wind zone and static zone in the occipital region.

3.3 Lin's Head Pin

Needle selection is based on the study of the relationship between brain function and blood flow, in addition to locating the selected area according to the cerebral cortex function [10]. The temporal 3 needles correspond to the posterior part of the frontal lobe below the lateral fissure of the brain, visual, auditory and speech, which activates the blood flow in this area to add up. Frontal 5 needles are located in the anterior frontal area in the frontal lobe, and thinking activity activates the most increased blood flow in this area, which is scalloped in the corresponding part of the scalp is 2 cm from the hairline. The premotor area, which is located in a diamond-shaped area 3-4 cm in front of the motor area, its anterior edge meets the prefrontal area.

3.4 Zhu's Head Pin

Zhu's head acupuncture differs from the positioning of other head acupuncture points, specifically in that the back is yang, i.e., after the hundredth meeting is yang. The abdomen is yin, and the front of Baihui is yin [11]. The nine zones are divided into frontoparietal zone, frontoparietal 1 zone, frontoparietal 2 zone, parieto-temporal zone, parieto-occipital zone, parieto-knot posterior zone, anterior temporal zone, and posterior temporal zone. Each belt area corresponds to the head, upper jiao (hand), middle jiao (foot) and lower jiao.

3.5 Fang's Head Pin

The acupuncture zones of Fang's head acupuncture therapy are mainly composed of 4 central stimulation zones (voxel, voxel, inverted voxel, and inverted voxel) and 11 cortical functional stimulation points, of which voxel and thinking are taken unilaterally, while the rest are taken bilaterally [12]. The fuxiang is a miniature of the human body with open limbs and is located between the coronal, sagittal, and herringbone sutures. The fuchsia is a symmetrical miniature of the human body that lies across the frontal hairline, which is the embodiment of a holographic scalp point in the frontal region. The inverted elephant and inverted dirty are miniatures of an upside-down inverted human figure, so they are called "inverted elephant" and "inverted dirty". The remaining eleven points are for thinking, memory, speaking, writing, leveling, signaling, hearing, smelling, balance, and circulation.

All of the above schools have motor and sensory zones except Zhu's head acupuncture. In Fang's head acupuncture, Fu Xiang and Fu Dao correspond to motor and sensory areas respectively, but their specific positioning is different. Lin's head acupuncture is unique in that it has a static zone and a new cerebellar zone. The zoning of the Fang's head acupuncture voxel is similar to the entire acupuncture zoning of the Tang's head acupuncture, both of which are projections of the human body with the limbs open. However, the characteristic feature of Tang's head acupuncture is that the head projection is delineated by the yin-yang point, which is divided into two parts: supine and prone. The center line is the Ren line, which is Yin. From the center of the lower edge of the external occipital ridge to the point of yin and yang, the posterior median line between these is the Directing Vessel, which is Yang. Zhu's head acupuncture, on the other hand, distinguishes between yin and yang by the Baihui point. The yin and yang point of Tang's head acupuncture is not the Baihui point, but before the Baihui point, which is the midpoint of the front and back median line, which is also called the Huiyin point.

4. Needling Operation

4.1 Needling depth

Fang Yunpeng emphasized the need to reach the periosteum directly, Lin Xuejian asked for acupuncture close to the periosteum, and the rest of the doctors advocated acupuncture to the subcapitellar tendon membrane, Zhu Mingqing asked for acupuncture to reach the subcapitellar tendon membrane and then enter 1 inch, Jiao Shunfa asked for acupuncture to reach the subcapitellar tendon membrane and then enter 0.5-1.5 inch.

4.2 Needle Insertion Technique

Fang's head acupuncture uses the "flying needle straight stab" technique to enter the needle, which is characterized by stability, accuracy and speed. This technique emphasizes rapid needle entry, and the moment the patient feels the needle, the needle reaches the periosteum with a "pop" sound [13]. Jiao Shunfa also emphasizes rapid needle entry [14]. The left hand presses the selected mapping area and point, and the right hand holds the needle handle with the thumb, index and middle fingers, aligning it with the entry point, and stabbing into the scalp at an angle of 15-30 degrees, making a small twist, and leaving the needle when there is a good feeling of Qi under the fingers, which emphasizes softness.

4.3 Needle Manipulation

Tang Songyan advocates small amplitude lifting and twisting to get gas. Jiao Shunfa requires rapid twisting of the needle up to about 200 r/min for 1-3 minutes, which is repeated 3 times. Lin Xuejian and Zhu Mingqing advocate only lifting and inserting without twisting to obtain qi, Lin Xuejian in the acupuncture point area when a large area of stimulation to pump the method of needle 10 times. Zhu Mingqing emphasizes the "pumping method" and the "entering method" to

supplement diarrhea. Fang Yunpeng uses 1-3 needle movements during the needle retention period, using the unique triplex method of "light twisting, heavy pressure and trembling".

4.4 Needle Retention Time

Jiao Shunfa advocates regular needle retention within 30min. Fang Yunpeng, Tang Songyan, needle retention time is generally about 30min or according to the condition of the extended retention time. Such as Fang Yunpeng retaining needles more than 8h, Lin Xuejian retaining needles more than 1h, Zhu Mingqing requires retaining needles 2-48h. All of them use intermittent dynamic needle retention.

4.5 Therapeutic Effects

All schools are applicable to the treatment of stroke, cerebral palsy, anxiety, headache, insomnia and other diseases of cerebral origin. According to the literature, Fang's head acupuncture has also treated rheumatic heart disease, Lin's has some clinical effect on central constipation, while Tang's head acupuncture has had experience in treating joint pain in the wind area, and Jiao's has documented documentation about stubborn erratic. In fact, the scope of treatment of each school is extremely broad. With the development of the times, each school of head acupuncture therapy is often combined with other therapies to increase clinical efficacy, and they are quite effective. For example, Zhang Xiaoying [15] et al. demonstrated that Fang's head acupuncture, which is used to treat sudden deafness of the qi stagnation and blood stasis type by combining with acupuncture point injections, and then compared to simply giving the patient methylcobalamin injection. The combination of the two was able to significantly improve the patient's hearing, and improve their tinnitus symptoms. In a clinical study that included 72 patients, Li Wen [16] et al. found that exercise therapy combined with Tang's head acupuncture improved the daily living ability of stroke patients with hemiplegia more than medication. Hong Zhenmei [17] et al. compared the clinical efficacy of Jiao's head acupuncture combined with virtual reality (VR) technology rehabilitation training with VR technology rehabilitation training alone for the treatment of motor dysfunction in Parkinson's disease, and they found that all gait parameters improved in the observation group compared to the pre-treatment period, especially the gait distance and gait speed were better than the control group.

5. Conclusion

Through the above sorting, we can see that the principle of action of each school of head acupuncture, the positioning of head points and operating techniques are different, but they all have the advantages of fewer points, high safety, precise efficacy and easy operation. The development and inheritance of each school is not easy, and it is still in the process of improvement and innovation. From the 1950s to the present, the various schools of medicine have competed with each other, each with its own strengths, and they have continued to expand the scope of treatment of diseases, involving internal and external women and children. However, we cannot ignore that the common shortcoming is the lack of summary and consideration of clinical case studies with large sample sizes, and the exploration of their mechanisms of action. Despite the wide range of treatment, there is a lack of discovery of prominent diseases, and the amount of relevant literature is still lacking, its development still needs time to settle and the efforts of later generations. Therefore, we should gather the strengths of all schools, take their essence and discard their dregs, determine the best protocol for head acupuncture, clarify the effective stimulation zones and specific quantitative acupuncture techniques, standardize and standardize them, reduce blind clinical operations, improve therapeutic efficacy, and promote the application of head acupuncture therapy.

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Author Introduction: Liu Yuanyuan, female, Han nationality, born in Linfen, Shanxi Province, postgraduate student, Research direction:The Mechanism and Clinical study of acupuncture and moxibustion in treating encephalopathy.

Clinical Effect of Lobectomy Under Single-Hole Thoracoscope in Minimally Invasive Surgical Treatment of Non-Small Cell Lung Cancer

Yuting Luo
Department of Cardiothoracic Surgery, The Third Hospital of Jinan, Jinan 250100, China.

Abstract: **Aims:** To explore the effect of single-hole thoracoscopic lobectomy in the treatment of non-small cell lung cancer (NSCLC). **Methods:** A total of 56 patients with NSCLC from the Third People's Hospital of Jinan during May 2020 to May 2022 were selected as the study subjects, which were divided into control group and observation group according to the difference of treatment methods. Three holes thoracoscopic lobectomy was performed in the control group, and single-hole thoracoscopic lobectomy was conducted in the observation group. The operation time, intraoperative bleeding, total number of lymph node dissection, total drainage volume of thoracic duct 3 days after operation, extubation time of thoracic duct, postoperative hospital stays, postoperative pain score (day 1, 3, 7), and postoperative complication rate were compared between the two groups. **Results:** Compared with the control group, the operation time, postoperative decannulation time and postoperative hospital stay of patients in the observation group were significantly shortened ($P<0.05$), the amount of intraoperative bleeding and the total drainage volume of thoracic duct 3 days after operation were significantly reduced ($P<0.05$), and the postoperative pain score and the incidence of postoperative complications were significantly improved ($P<0.05$). **Conclusion:** Single-hole thoracoscopic lobectomy is effective and safe in the treatment of non-small cell lung cancer, which is worthy of clinical promotion.

Keywords: Single-Hole Thoracoscopic Lobectomy; Three Holes Thoracoscopic Lobectomy; Non-Small Cell Lung Cancer (NSCLC); Lobectomy; Curative Effect

Intoduction

Lung cancer is the main cause of cancer related deaths, with an annual death toll of 1.6 million [1]. Non-small cell lung cancer (NSCLC) is the main subtype of lung cancer, accounting for about 85% of lung cancer cases [2]. At present, surgery is still one of the main methods for clinical treatment of NSCLC. With the promotion and application of thoracoscopic technology, thoracoscopic lobectomy has become a common operation for NSCLC patients at this stage due to its minimally invasive and high safety [3]. This study intends to compare the clinical efficacy of single hole thoracoscopic lobectomy with that of three holes thoracoscopic lobectomy in the treatment of NSCLC. The report is as follows.

1. Materials and methods

1.1 General data

56 patients with non-small cell lung cancer admitted to the Third People's Hospital of Jinan from May 2020 to May 2022 were selected as the study subjects. Inclusion criteria：①Patients diagnosed as lung cancer and confirmed as early

NSCLC by biopsy；②Tumor diameter ≤ 4 cm；③Tumor did not accumulate chest wall and large vessels；④No distant metastasis；⑤patients have signed informed consent form in advance. Exclusion criteria：① Patients have a history of chest trauma；②Intolerable lobectomy. According to the difference of treatment methods, the patients were divided into two groups: control group and observation group. The control group consisted of 26 patients who underwent lobectomy under three hole thoracoscope, including 15 males and 11 females, aged 49 to 73 years, with an average age of 60.23±7.51. Location of lesion：9 cases in the upper lobe of the left lung, 7 cases in the lower lobe of the left lung, 7 cases in the upper lobe of the right lung, and 3 cases in the lower lobe of the right lung. In the observation group, 30 patients underwent lobectomy under single hole thoracoscope, including 19 males and 11 females, aged from 51 to 75 years, with an average age of 61.73 ± 7.00. Focus location: left upper lobe 11 cases, left lower lobe 9 cases, right upper lobe 8 cases, right lower lobe 2 cases. There was no significant difference in general information between the two groups, which was comparable。

1.2 Surgical methods

All patients were examined before operation after admission. After admission, they were given general anesthesia with double lumen endotracheal intubation, recumbent position, one lung ventilation, and routine disinfection. In the control group, pulmonary lobectomy under three holes thoracoscope was performed. A 1.5cm incision was made between the 7th intercostal space of the midaxillary line as the observation hole, and a thoracoscope was placed. A 3cm incision was made between the 4th intercostal space of the front axillary line and the 7th intercostal space of the scapular line as the operation hole. For patients with ground glass nodule, the micro spring coil combined with methylene blue localization under CT guidance before operation, while for those who have been diagnosed pathologically before operation, lobectomy was performed directly. If there was no pathological result, the lesion was first removed by wedge and sent for rapid pathology. Lobectomy was performed after lung cancer was identified。All patients underwent systematic lymph node dissection. The left side included groups 4, 5, 6, 7, 9, 10 and intrapulmonary lymph nodes, and the right side included groups 2, 3, 4, 7, 9, 10 and intrapulmonary lymph nodes. The observation group received lobectomy under single hole thoracoscope. The patient was intubated under general anesthesia and placed in a transverse position. After one lung ventilation, an elastic rubber protective sleeve was placed in the fourth to fifth intercostal (about 3 cm long) hole at the front of the axilla as the operation hole, and a trocar was placed at the other end of the seventh intercostal (about 1.5 cm long) of the posterior axillary line as the observation hole. Hilar and mediastinal lymph nodes were completely removed by thoracotomy or thoracoscopic resection. The specimen was then placed in a clean bag, from which it was removed through an operating hole, and a closed thoracic drainage tube was placed.

1.3 Observed indicator

The observation indexes included the operation time (excluding the rapid pathological time during the operation), the amount of bleeding during the operation, the number of lymph node dissection groups, the total number of lymph node dissection, the total drainage volume of the thoracic duct 3 days after the operation, the time of decannulation of the thoracic duct after the operation, the length of hospital stay after the operation, the postoperative pain score (the first, third, seventh days), and the incidence of postoperative complications. Postoperative pain was scored using VAS scale: 0: painless; 1-4 points: mild pain; 5-6 points: moderate pain; 7~9 points: severe pain, which was still tolerable; 10 points: unbearable pain [4]. Postoperative complications include incision infection, pneumothorax, pulmonary infection and atelectasis.

1.4 Statistical analysis

SPSS 26.0 statistical software was used to process the data. The quantitative data （ $\bar{x}\pm s$ ）conforming to the normal distribution were tested by t test, and the qualitative data (%) were analyzed by $\chi 2$ test or Fisher exact test, $P<0.05$ indicates

that the difference is statistically significant.

2. Results

2.1 The surgical conditions were compared between the two groups

The operation time of the observation group was significantly shorter than that of the control group. In addition, the amount of intraoperative bleeding, the volume of drainage 3 days after operation, the time of chest tube extubation and the length of hospital stay after operation in the observation group were significantly higher than those in the control group（P＜0.05）. However, there was no significant difference in the number of lymph node dissection between the two groups (P＞0.05).

Table 1. The operation conditions of the two groups were compared

	operation time（min）	Intraoperative bleeding（ml）	Total lymph node dissection	the volume of drainage 3 days after operation（ml）	the time of chest tube extubation（min）	the length of hospital stay after operation（days）
Control group（n=26）	153.80±24.86	60.73±5.54	11.27±2.77	621.70±38.42	5.92±1.13	7.46±1.33
Observation group（n=30）	192.90±9.94	47.53±4.90	12.07±2.61	453.70±27.44	3.10±0.71	5.73±0.87
t	7.938	9.458	1.109	19.010	11.350	5.820
P	<0.001	<0.001	0.272	<0.001	<0.001	<0.001

2.2 Comparison of VAS pain scores between two groups

The VAS pain scores of patients in the two groups 1, 3 and 7 days after surgery are shown in Table 2. The pain scores in the observation group are significantly lower than those in the control group, with statistically significant differences (P＜0.05).

Table 2. VAS pain score of patients between two groups（ $\bar{x}$±s）

	1 day after operation	3 days after operation	7 days after operation
Control group（n=26）	7.12±1.45	5.27±0.92	3.08±0.80
Observation group（n=30）	6.20±0.71	3.77±1.01	1.60±0.72
t	3.057	5.800	7.269
P	0.0035	<0.001	<0.001

2.3 Comparison of complication rate between two groups

There were 2 patients had incision infection, 1 pneumothorax, 3 pulmonary infections and 2 atelectasis in the control group with the total incidence of complications was 30.77%. Moreover, 1 case of incision infection, 2 cases of lung infection and 1 case of atelectasis occurred were found in observation group with the total incidence of complications was 13.33%. The incidence of complications in the observation group was significantly lower than that in the control group, with statistical significance (P<0.05).

Table 3. Comparison of complication rate between two groups

	Incision infection	Pneumothorax	Pulmonary infection	Atelectasis	Total incidence
Control group（n=26）	2（7.69%）	1（3.85%）	3（11.54%）	2（7.69%）	8（30.77%）
Observation group（n=30）	1（3.33%）	0（0.00%）	0（0.00%）	1（3.33%）	2（6.67%）
χ^2					5.516
P					0.019

3. Discussion

At present, lobectomy is commonly used in clinical treatment of NSCLC. However, the traditional open surgery has great trauma, which is not conducive to the recovery of patients as soon as possible [5]. SALATI M et al. first reported the efficacy of lung wedge resection under single hole thoracoscope in the treatment of spontaneous pneumothorax and interstitial lung disease, and clearly put forward the concept of single-hole thoracoscope [6]. In recent years, with the continuous development of minimally invasive technology, single hole endoscopic surgery is gradually applied to different pneumonectomy [7-9]. However, the safety, difficulty and lymph node dissection of single-hole thoracoscopic surgery are still questioned.

The results of the study showed that the operation time of lobectomy under single-hole thoracoscope was significantly shorter than that of the control group (P<0.05), and the volume of intraoperative bleeding, the total drainage volume of thoracic tube 3 days after operation, the time of removal of thoracic tube after operation, and the length of hospital stay after operation were significantly better than those of the control group (P<0.05). It was suggested that lobectomy under single hole thoracoscope was more effective than lobectomy under three hole thoracoscope, which was consistent with the research results of a large number of scholars [10-12]。 This may be because compared with the three hole operation, the single hole operation has less bleeding, which can save the time for hemostasis and chest closing, so the operation time will not be prolonged; It has less trauma to patients and less bleeding, which can reduce the trauma to patients' bodies caused by surgery, enable patients to recover their incisions and bodies as soon as possible, shorten the time of decannulation and hospitalization after surgery, and thus shorten the recovery time of patients after surgery [13]. In addition, the total number of lymph node dissection in the observation group was more than that in the control group, but the difference was not significant (P<0.05), indicating that single hole thoracoscopic surgery could achieve the same lymph node dissection effect as three holes endoscopic surgery.

The results of this study also showed that the pain scores of the observation group were lower than those of the control group at 1, 3 and 7 days after operation, with a statistically significant difference (P<0.05). Three holes thoracoscopic surgery has many incisions and great damage to the human body, so the postoperative pain is obvious. Single hole surgery has only one operation hole, which has little damage to muscles, blood vessels and nerves, and the patients have little postoperative pain [14]. Therefore, single hole thoracoscopic lobectomy can minimize trauma, improve patient satisfaction, and thus improve their comprehensive quality of life, which is more in line with the minimally invasive concept of modern surgery [11].

Thoracoscopic lobectomy needs to remove 1~2 diseased lung lobes, which can significantly reduce lung volume and pulmonary ventilation. At the same time, postoperative pulmonary infection, atelectasis and other complications can affect pulmonary ventilation function, and reduce the pulmonary function of patients in a short period of time [15]. This study found that the probability of incision infection, pneumothorax, pulmonary infection and atelectasis in the observation group

(6.67%) was significantly lower than that in the control group (30.77%), which further proved the safety of single hole thoracoscopic lobectomy.

To sum up, single-hole thoracoscopic lobectomy has obvious advantages, which could shorten the operation time, the time for decannulation of the thoracic tube after the operation and the hospital stay after the operation, reduce the amount of intraoperative bleeding and the total drainage volume of the thoracic tube 3 days after the operation, improved the quality of life of patients, and could greatly reduce the occurrence of complications. Single-hole thoracoscopic lobectomy was a safe and effective operation method. However, due to the limited sample size, it is still necessary to further explore the exact efficacy of single hole thoracoscopic lobectomy in the future.

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Treating Cartilage Injuries in Young Patients

Feier Ma
Xi'an Physical Education University, Xi'an 710068, China.

Abstract: Young people tend to suffer from cartilage injuries caused by extraneous trauma. There are many treatments for cartilage injuries. This article recommends treatments for different cartilage injuries targeted towards young patients. For young patients with mild or asymptomatic symptoms without cartilage displacement, this article recommends mandatory conservative treatment for young patients. Depending on the recovery condition of conservative treatment, the surgeon can subsequently plan for surgical treatment. Depending on lesion size, this article recommends the following operations. For lesions less than 1 cm2, arthroscopic debridement is recommended. For lesions between 1 and 4 cm2, MACI is recommended. For lesions larger than 4 cm2, OCA is recommended as a priority. If OCA is not feasible, OAT can be considered.

Keywords: Cartilage Injury; Arthroscopic Debridement; MACI; OCA; OAT.

1. Introduction

Cartilage tissues have a limited capacity for self-regeneration (Körner et al., 2021a). This tissue has a few blood vessels, nerves, and lymphatic tissues (Zhou et al., 2021). Slight injuries do not cause dysfunction of cartilage tissues, causing a delay in the diagnosis of slight and acute injuries (Badekas et al., 2013). Cartilage injuries are likely to develop arthritis if a patient does not receive adequate treatment, whether caused by endogenous or exogenous factors (Eichman et al., 2021; Occhetta et al., 2016). Thus, cartilage damages frequently cause joint pain and loss of mobility (Mardones et al., 2020). Young and active patients are more prone to develop potential cartilage damage related to a traumatic injury than older people (Daud et al., 2021; Körner et al., 2021b). For example, 50% of patients develop cartilage defects after an acute ankle sprain (Savage-Elliott et al., 2014). Because inflammatory factors lead to necrosis and apoptosis of chondrocytes after an acute injury (Barakat et al., 2019), their symptoms will deteriorate if patients are not appropriately treated (Cinats et al., 2021). There are many treatment options for cartilage injuries, including conservative and surgical treatments (Dong et al., 2021). Each treatment has its advantages and disadvantages (Versier & Dubrana, 2011). Doctors should balance risks and outcomes when planning treatments for their patients to help them recover better. For young patients, treatments need to consider several factors, such as the recovery of motor function, the success rate of treatment, and long-term treatment outcomes. It is vital to choose practical and suitable treatments to restore motor function for patients. This article will focus on the following two questions to advise patients regarding their treatment:

What is the recommended treatment? What are the current findings of this treatment?

What are the advantages and disadvantages of each treatment? Why is this treatment more suitable for young patients than other treatments?

This article will advise treatment options for young patients in different conditions to help them recover their motor function. This article will explain the reasons for treatment design based on answers to the above questions.

2. Treatment suggestions

This article suggests that young patients select different treatment options depending on their conditions. The detailed treatment protocol is as follows:

Firstly, doctors need to obtain information on patients' situations, such as surgical history and patients' age. These factors affect doctors' decisions on how to treat patients. Doctors should advise children to start with conservative treatment (Reilingh et al., 2014). For obese patients, doctors should advise patients to lose weight, both in conservative treatment and post-operative rehabilitation training (Lopa et al., 2019).

Secondly, doctors should evaluate patients' symptoms. For example, whether there is swelling in joints or patients suffer from pain on movement (Prakash & Learmonth, 2002). After patients get a magnetic resonance imaging (MRI) scan, doctors can determine if there is cartilage displacement in affected areas and the narrowed joint cavity (Thompson & Roukis, 2020). After evaluating patients, conservative treatment is recommended for asymptomatic patients without displacement; patients with symptoms and displacement are recommended for arthroscopy (López-Alcorocho et al., 2021). MRI is suitable for screening soft tissues around joints pre-operatively as a non-invasive test (De Schepper et al., 2000). However, MRI cannot identify lesion size and location (Magnussen et al., 2008). Thus, symptomatic patients with cartilage displacement should proceed with arthroscopy to help surgeons decide on a suitable surgical approach.

Lesion size is determined in arthroscopy. Depending on lesion size, patients are recommended for arthroscopic debridement, matrix-assisted autologous chondrocyte transplantation (MACT), osteochondral allograft (OCA), or osteochondral autograft transplantation (OAT).

After conservative or surgical treatment, patients will be provided rehabilitation training with education treatment to help them restore their daily physical activities. The treatment protocol is shown in Figure 1.

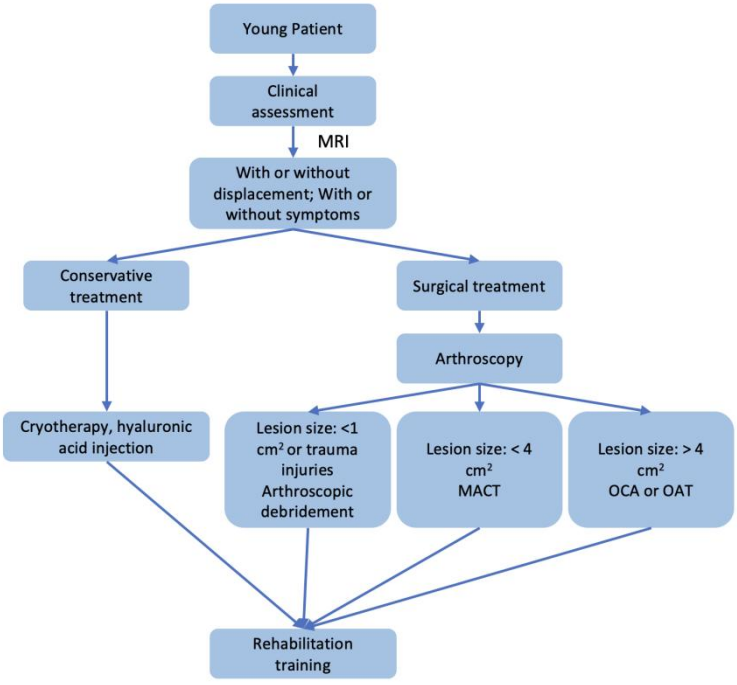

Figure 1 Treatment suggestions for young patients

3. Explanation of treatment options

Patients and doctors should decide the most cost-effective and safest treatment option for their conditions. Whether conservative or surgical treatments, no one treatment option is suitable for all conditions of cartilage defects (Magnussen et al., 2008). Young patients have higher post-operative motor recovery and recovery time requirements than older patients (Di Martino, Silva, et al., 2021). Therefore, doctors should consider young patients' requirements and balance the risks and benefits of treatment when selecting a treatment approach.

3.1 Conservative treatment

Conservative treatment is effective in the short term for patients with mild or acute symptoms. For patients with cartilage defects, conservative treatments include oral non-steroidal anti-inflammatory drugs (NSAID), hyaluronic acid injections, cryotherapy, immobilization, and non-weight bearing. Conservative treatments aim to help cartilage tissues self-recover by reducing oedema surrounding injured joints (Thompson & Roukis, 2020). Although cartilage tissues have a limited ability to self-repair, the recovery rate of conservative treatment is impressive at 45% (Zhang et al., 2022). Conservative treatments provide good results for more stable diseases (Körner et al., 2021b). Conservative treatments usually require 3-9 months for recovery (Eichman et al., 2021). Patients should be treated with cryotherapy at the initial phase of an injury, followed by hyaluronic acid intra-articular injections and oral medications depending on patients' inflammatory status to satisfy young patients' daily activity requirements.

Cryotherapy can effectively help patients with acute injuries to relieve pain, reduce inflammation and improve joint mobility. Cryotherapy is a treatment that uses a topical cold environment such as ice or ice massage to lower tissue temperature and help patients relieve pain, stiffness and joint mobility (Dantas et al., 2019). Cryotherapy is commonly used in patients with acute cartilage trauma and some post-operative swelling (Lieberthal et al., 2015). Low temperature reduces periarticular vasoconstriction and vascular permeability, reducing tissue fluid leakage and joint swelling (Fayyad et al., 2020). Furthermore, low temperature reduces the excitability of periarticular nerves, which reduces pain in patients (Dong et al., 2021). When cartilage is injured, the expression of catabolic genes will increase in vivo, and pro-inflammatory cytokines will promote the breakdown and shedding of chondrocytes (Alexander et al., 2013). Cryotherapy reduces high inflammatory responses and oxidative stress in vivo (Puntel et al., 2013). Riegger et al. (2018) found that hypothermia increased chondrocyte survival after a trauma, and cryotherapy inhibited MMP release and type II collagen breakdown. This study showed that a long-term (7 days) low-temperature environment inhibited MMP gene expression ($P=0.0273$) more than medium-term (24 hours) intervention ($P=0.0371$). Thus, long-term cryotherapy prevents further degradation of chondrocytes. Besides cryotherapy, some physiotherapies also effectively reduce oedema and inflammatory responses (Dong et al., 2021). This article recommends cryotherapy for young patients rather than traditional physiotherapy treatment because most physiotherapies require special equipment and are more expensive. Cryotherapy is more straightforward and more cost-effective. Young patients can be treated more conveniently depending on their schedules.

Hyaluronic acid intra-articular injections are safe and effective in reducing pain and improving joint movement. Abnormal structures cause a release of inflammatory factors after cartilage injuries (Buckwalter, 2012). Thus, acute treatment for cartilage injury aims to inhibit cytokine-induced inflammatory responses (Anderson et al., 2011). Intra-articular injections keep a high concentration of drugs in an articular cavity of damaged cartilage (Bonasia et al., 2005). Thus, intra-articular injections can more rapidly inhibit inflammatory responses than oral NSAIDs. Barakat et al. (2019) studied that patients significantly improved motor function and joint pain after three months of hyaluronic acid injections. But 10% of patients' symptoms got worse. This study had limited participants. And the control group in this trial was without a joint cavity injection rather than a placebo injection. Therefore, the results of this study were subjectively biased. However, the

results of this study provided evidence for the role of hyaluronic acid in the acute phase of inflammation. Studies of joint cavity injections involve hyaluronic acid, mesenchymal stem cells (MSCs), and exosome cell injections. And all three drugs showed significant improvement in joint function and pain management in patients (Centeno et al., 2015; Xia et al., 2021). Each drug has its advantages and disadvantages (Table 1). In recent studies, exosomes showed great advantages and potential (Wu et al., 2019). However, the effects of exosomes on gene expression after injection in vivo still need further investigation (Valadi et al., 2007). Thus, hyaluronic acid injection is very suitable as a treatment for young patients in the acute phase of injury.

	Advantages	Disadvantages
Hyaluronic acid	Safe; effective; cost-effective	Short-term outcomes
MSCs	Promote the regeneration of chondrocytes; Precise number of injected cells	Potential induction of osteoma growth
Exosomes	Reproducible; sustainable; low toxicity than MSCs	Expensive; Uncontrolled gene translation; lack of targeting

Table 1 Advantages and disadvantages of three drugs

This article recommends mandatory conservative treatment for children and adolescents before surgery, as children's chondrocytes have a higher regenerative potential than adults (Salzmann et al., 2018). Patients can start with conservative treatment for six to eight months and decide whether surgery is needed depending on their recovery (Thompson & Roukis, 2020). Every operation has the risk of complications (Harris et al., 2010; Versier & Dubrana, 2011). Therefore, surgical treatment should be carefully chosen for children. The combination of conservative treatment and exercise therapy can be more effective in restoring motor function (Lopa et al., 2019). Thus, young patients should get different rehabilitation training levels to help them to restore joint function, similar to post-surgical rehabilitation training.

3.2 Surgical treatment

Surgery is an effective treatment for patients who have failed conservative treatment or those with severe symptoms, such as free bodies and loose cartilage in patients' joint cavities (Eichman et al., 2021; Zhang et al., 2022). The surgical approaches include arthroscopic debridement, arthroscopic microfracture, MACT, OCA, OAT. According to the international cartilage regeneration & joint preservation society (ICRS), cartilage injuries are classified into four levels according to the defect depth and four levels according to the lesion's continuity. There are various criteria for evaluating cartilage injury, but success rates for different operations depend on lesion size (Chu et al., 2020). There is no single surgical approach suitable for all types of cartilage injury, and there is no gold standard for surgical approaches (Mardones et al., 2020). Different operations have different advantages and disadvantages (Table 2). This article recommends different surgical approaches depending on lesion size. For young patients, the factors to consider are the recovery rate of movement, recovery time, the difficulty of operation, and surgery costs. Based on these factors, this article recommends arthroscopic debridement, MACT, OCA, and OAT for young patients depending on lesion size.

	Advantages	Disadvantages
Arthroscopic debridement	Good Short-term and moderate-term outcomes.	Limited treatment effects
Arthroscopic microfractures	Few pre-operative plans, few surgical types of equipment	The regenerating bone is fibrocartilage. Overgrowth of bone may occur

MACT (the third generation of ACI)	Good clinical outcomes; Precise number of transplanted cells	Two operations are required; expensive
OCA	Only one operation is required; Less fibrocartilage regeneration	Limited Donors; expensive
OAT	Only one operation is required	Expensive; Fibrocartilage regeneration still present

Table 2 Advantages and disadvantages of different surgical approaches

3.2.1 Trauma injuries and lesion size less than 1 cm2

Arthroscopic debridement should be offered for patients with less than 1 cm2 lesion or some acute symptomatic patients. Arthroscopic operations are minimally invasive and high safe (Cohen et al., 2000). Arthroscopic debridement involves debridement of damaged cartilage and removal of free bodies to help improve the function of the damaged joint with minimal tissue damage (Weinstein et al., 2000). Arthroscopic surgeries are characterized by smaller incisions, simpler operations, short operating time, and minor bleeding than other types of surgery (Dong et al., 2021). Although the risk of postoperative complications is low and patients recover quickly after arthroscopic debridement, the overall recovery rate for this operation is not very good (Dervin et al., 2003). For patients with severe symptoms, arthroscopic debridement can buffer a formal operation (Gu et al., 2018), which means that debridement can only partially alleviate symptoms in patients with severe symptoms but cannot replace the final treatment operation. For patients with milder symptoms, arthroscopic debridement can significantly improve their symptoms (Aaron et al., 2006). However, arthroscopic debridement can be adequate to decrease young patients' pain and improve their joint range of motion (Cohen et al., 2000). Rahusen et al. (2006) found that fifteen patients with exfoliated cartilage had a highly significant improvement of elbow function ($p<0.001$) and a highly significant reduction in pain levels ($p<0.001$) after arthroscopic debridement. 80% of patients were recovered within five years, and no patients had postoperative complications. Although this study had a limited number of patients, the recovery ratio was similar to other studies where patients with mild disease were recovered (Aaron et al., 2006; Weinstein et al., 2000). Thus, arthroscopic debridement is well-suited to treating young patients with mild disease.

For patients with minor cartilage injuries, microfracture surgery is a treatment operation with a high recovery rate in the short term. Microfracture is an operation to repair damaged cartilage tissue by causing new damage to the damaged cartilage tissue, destroying subchondral bone tissue, and inducing the proliferation of pluripotent stem cells from the bone marrow to differentiate into fibrocartilage (Magnussen et al., 2008). Microfracture is similar to arthroscopic debridement in advantages. Both operations are suitable for small scale cartilage injuries (Zhou et al., 2021). Also, microfracture is simple, inexpensive, and has an excellent short-term recovery effect (Kon et al., 2021). However, the biggest problem with this operation is that it can cause an overgrowth of subchondral bone and the growth of fibrocartilage (Ibarra et al., 2021). Fibrocartilage is less durable than hyaline cartilage for intra-articular wear (Harris et al., 2010). The instability of fibrocartilage causes patients to deteriorate after two years of surgery (Lolli et al., 2019). Patients who performed microfracture showed decreased motor performance at a 5-year follow-up (Harris et al., 2010). And a failed microfracture operation affect the success of subsequent cartilage revision operations. Lamplot et al. (2018) found that patients who had a history of failed microfracture operation had a lower success rate with ACI operation than patients having their first ACI operation. Thus, this article does not recommend microfracture surgery for young patients. Patients with cartilage defects between 1 and 4 cm2 should be treated with a MACT operation, which offers a high recovery rate.

3.2.2 Lesion size less than 4 cm2

For cartilage defects in 1 to 4 cm2, this article recommends that young patients have a MACI operation. For cartilage repair operations, new cartilage formation requires sufficient chondrocytes, scaffolds to support chondrocyte growth, and adequate mechanical performance of newly implanted cartilage or scaffolds to maintain cartilage function (Shetty et al., 2018). MACI is a third-generation ACI operation (Ibarra et al., 2021), which is a 3-step operation (Versier & Dubrana, 2011):

Firstly, chondrocytes are taken from a non-weight-bearing region at arthroscopic debridement.

Secondly, chondrocytes are transferred on a bio-scaffold after expansion in culture in vitro.

Finally, the bio-scaffold is implanted in the damaged cartilage area.

A sufficient cell density is vital in cartilage repair surgery (Liu et al., 2021), and MACI provides patients with a precise number of cells, making this operation have a high recovery rate for young patients who have not been treated with other cartilage operations (Hamblin et al., 2010). Andriolo et al. (2021) found that 29 patients who completed a MACI operation had a high implant survival rate (87%) over 12 years following the operation. The four failed patients all occurred in the early stages after their operation. Furthermore, 60% of these patients had recovered their pre-injury level of exercise. However, patients who recovered from this surgery are not suitable for high-intensity exercise (Niethammer et al., 2021).

This operation has some drawbacks due to its procedures. First, it is a two-step operation. It is challenging to operate arthroscopically in the second operation and is primarily an open operation (Wang et al., 2017). Secondly, the whole operation is complex and requires a long recovery time (12 months) (Edwards et al., 2013). These factors make the whole operation more costly. One study combined a cell-free bio-scaffold with microfracture surgery to avoid secondary surgery, transplanting the scaffold directly onto defective cartilage tissues (Drobnič et al., 2021). However, the recovery rate for this operation is not high (59%). An innovative technique (Chimutengwende-Gordon et al., 2021) involves extracting stem cells from the bone marrow, culturing them in vitro, transferring them to a bio-scaffold and transplanting them into the body. This approach has significant advantages as it is a one-step operation. However, this study only involved three patients, and there are no mid-term or long-term clinical results to support the recovery rate of this approach, which needs further validation. Considering the long-term recovery outcomes of the MACI operation, this article argues that it is well-suited as a treatment option for young patients with cartilage defects of 1-4 cm2.

3.2.3 Lesion size over 4 cm2

For patients with cartilage defects larger than 4 cm2, only OCA and OAT operations have good outcomes. If a patient has an opportunity to receive an OCA operation, it is recommended as a priority. The OAT operation is an alternative if OCA is not available. The OCA surgery involves placing a fresh and frozen osteochondral allograft in the location of cartilage defects (Versier & Dubrana, 2011), fixed with bioresorbable screws (Eichman et al., 2021). This cartilage repair technique has high cellular viability and no production of fibrocartilage (Bisicchia et al., 2014). A fresh allograft cartilage graft does not cause complications (Merritt et al., 2021), but this approach has a high risk of immunogenicity (Chu et al., 2020). Although fresh and frozen allograft cartilage is less immunogenic, cryogenic temperatures reduce chondrocyte viability (Lattermann & Romine, 2009). Currently, allograft cartilage grafts present an excellent survival rate (Abolghasemian et al., 2019). Daud et al. (2021) found that 38.1% of 244 patients had good grafts survival on average 11 years after surgery, and 43.7% of patients had a 20-year lifespan of their grafts during a long-term follow-up. For patients aged less than 50 years, 80% of patients had good survival with their grafts. Although allograft surgery is ideal for young patients, its availability is limited in most countries for reasons such as the lack or mismatch of grafts (Di Martino, Perdisa, et al., 2021). Therefore, if an OCA operation is unavailable, an OAT operation can be an alternative option.

The OAT operation involves filling defective areas with autologous cartilage derived from non-weight-bearing areas (Baltzer et al., 2016). The advantage of this technique is that it uses mature hyaline cartilage for filling and treats defective cartilage areas very well (Richter et al., 2016). The risk of postoperative complications after OAT operation is not high (Andrade et al., 2016). Patients with OAT surgery recovered more quickly than other surgeries (Krych et al., 2017). However, this operation affects patients' recovery because multiple cartilage plugs are implanted, which lead to potential fibrocartilage production around these plugs (Bisicchia et al., 2014). However, OAT operation is still the best option when OCA is unavailable.

4. Rehabilitation training

Rehabilitation and educational therapy for patients following conservative and surgical treatment are necessary. Patients are educated on postoperative prognostic information, combined with exercise therapy, which effectively manages their pain (Crossley et al., 2015). Pain reduced as training time increased, and a clinically significant improvement needed at least eight weeks to happen (Skou et al., 2017). Postoperative rehabilitation is divided into 3 phases. The first phase is graft protection; the second phase is functional recovery; the third phase is movement recovery. The first rehabilitation phase can be skipped for conservative treatment, and exercise training can be conducted in Phases 2 and 3. The duration and intensity of training should be adjusted to fit patients' conditions. Avoid patients suffering secondary injuries to their cartilage by increasing intensities of exercise.

5. Conclusion

There are many treatment options for cartilage injuries, and this article presents different treatment options for cartilage injuries in young patients. This article recommends conservative and surgical treatments depending on the lesion size of cartilage damage areas to help patients recover. After conservative and surgical treatments, patients should combine exercise therapy and educational therapy to regain mobility of damaged joints more effectively. Cryotherapy and hyaluronic acid injections are recommended for acute or asymptomatic patients without displacement. These two methods are safe and effective to help young patients reduce inflammatory responses in areas of damaged cartilage and reduce the death of chondrocytes to facilitate rapid recovery in young patients. Surgical treatments are divided into three classes depending on lesion size. This article recommends the arthroscopic debridement procedure for patients with lesions smaller than 1 cm^2. In contrast, patients are not advised to have micro-fracture surgery. Microfracture surgery only brings a short-term recovery. Most patients will deteriorate within two years and affect success rates of subsequent cartilage repair surgery. The MACI operation is recommended for patients with lesions between 1 and 4 cm^2. This operation has a high recovery rate and few complications for young patients. And it has shown good outcomes in short-term and medium-term follow-ups. For patients with a lesion size above 4 cm^2, this article recommends that patients give priority to OCA. However, this operation is not always available to all patients due to low graft trapping and donor mismatch. For young patients, the treatment outcomes of this operation can be sustained for ten to twenty years. When OCA surgery is not available, patients may consider OAT surgery. Although this operation can lead to the production of fibrocartilage caused by cartilage plugs, this operation also has a good recovery rate. Thus, it is suitable as an alternative treatment option to OCA surgery.

Patients and doctors can choose different treatment options depending on patients' requirements. This article recommends these treatment methods by comparing the results of existing clinical treatments for young patients. Although there is a subjective bias in selecting treatment methods, these treatments showed good clinical results. For most patients, these treatments can help them to regain their mobility.

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Diagnosis of Dementia and Alzheimer's Disease Based on Classification Algorithms

Ci Song[1], Shuxian Zong[2]

1. School of Resources and Materials, Northeastern University at Qinhuangdao, Qinhuangdao 066004, China.

2. Nanfang College Guangzhou, Guangzhou 510970, China.

Abstract: Alzheimer's disease is currently the most common kind of senile dementia. With the increasing aging degree of the global society, Alzheimer's disease will become an unavoidable social problem in an aging society. In order to improve this situation, artificial intelligence algorithms that are good at mining the internal laws of data are applied in the hope of more effectively diagnose this disease, which should be intervened as early as possible. After briefly restating the current situation of dementia and Alzheimer's disease, the diagnostic model for dementia is built using logistic regression, which achieves great accuracy despite the simplicity of the model. Then, two diagnostic models that can identify if the patient with dementia has Alzheimer's disease based on SVM and Random Forest are tested. Although both the algorithms perform poorly because of the sample imbalance, after processing the original data with SMOTE, their performances are largely improved.

Keywords: Machine Learning; Smote; Dementia Diagnosis

1. Introduction

Alzheimer's disease is a recognized public health problem for the GWHO. The number of Alzheimer's patients worldwide has exceeded 34 million in 2020, and is expected to reach 36.3 million in 2025. At present, the diagnostic method for Alzheimer's disease is mainly exclusion, the challenge of which is that the diseases of most patients are already advanced when explicitly diagnosed. researchers hope that new AI technology can change this situation by strengthening the effective data analysis of AD. Currently, machine learning and deep learning have been widely used in a variety of complex challenges, like medical, financial, industrial, and other fields, which may help improve the reliability, performance, predictability, and accuracy of diagnostic systems for Alzheimer's disease.

The motivation of this paper is that, considering traditional diagnostic methods tend to cause patients to miss out on optimal treatment time, new progress brought to diagnosing diseases by data analysis is crucial. With the development of algorithms that can homogenize samples, machine learning also obtain good accuracy for classification problems with sparse sample sizes such as diseases.

The main contribution of this paper is that, by first building a binary classification model based on logistic regression, an Intelligent diagnostic model for dementia can be obtained. Then, models that can distinguish whether a person with dementia has Alzheimer's disease are built based on SVM and random forest, whose performance are both poor. In order to improve poor accuracy caused by sample imbalance, SMOTE is applied to generate more scarce samples to strike a balance between two categories, which significantly improves the classification performance of SVM and random forest.

2. Overview of dementia

People with dementia and dementia tendencies are divided into several groups, namely cognitive normal elderly (CN), patients with subjective memory complaint (SMC), patients with early mild cognitive impairment (EMCI), patients with late mild cognitive impairment (LMCI) and patients with Alzheimer's disease (AD).

2.1 CN

Cognitive normal elderly can be intervened early on through psychotherapy, behavioral therapy, and drug therapy. The early manifestations of Alzheimer's disease are mainly short-term memory decline, learning ability decline and language ability decline, so for the elderly with normal cognition, prevention is the best choice.

2.2 SMC

For the older population with subjective memory complaint, subjective memory complaints predict an increase in mild cognitive impairment. As one of the manifestations of early and forgotten cognitive impairment in AD, Subjective Memory Complaint is defined as a self-memory impairment arising in the absence of both objective object signs and known pathological conditions. For SMC, the treatment is available through non-drug early intervention, which is a more feasible alternative treatment plan. This scheme can effectively release anxiety, depression and improve subjective memory, delayed memory, and overall cognitive function [1].

2.3 EMCI and LMCI

For EMCI and LMCI, which are the branches of MCI in time, are not easily distinguished from MCI in nature. Early intervention for EMCI and LMCI patients, mainly relies on nursing, and reasonable solutions should be provided for groups of different age.

For youth groups, nursing workers should intervene according to the risk factors in their age group to guide the youth group through the correct health.

In dealing with the intervention problem of MCI in the middle age population, the effective intervention of medical treatment and care are required to maintain MCI in a stable state through screening synchronization and risk factor assessment synchronization and dynamic monitoring, and reduce the tendency to shift to EMCI and LMCI.

The symptom of MCI in the old age stage is mainly reflected in the poor lifestyle, chronic disease, or the previous genetic characteristics, which can aggravate the degree of cognitive impairment. This is more likely to be LMCI, where mainly drug intervention as well as non-drug intervention are used to increase the plasticity of brain function and delay the development of AD. the diagnosis of EMCI and LMCI is like the diagnosis of MCI, which is mainly divided into the following five diagnostic criteria:

1.Relevant information vouchers provided by Informed persons such as family members.

2.Impairment of cognitive functions or other cognitive functions inconsistent with age and education level shown in objective tests.

3.Overall cognitive function is relatively intact.

4.Whether the function of daily life is affected.

4.Whether it meets the diagnostic criteria for dementia [2,3].

2.4 AD

For AD, the early intervention measures are mainly based on the premise of early detection and early treatment through

the careful discovery of community doctors and the close relationship between doctors and patients. As for early intervention, community hospitals are very effective in detecting early AD, based on which early psychosocial intervention promotes a patient-family-centered model transformation to provide or change existing treatment options for patients. Nutritional interventions in the elderly can also reduce the risk of AD. Among the criteria for the diagnosis of AD, the best time to diagnosis is within 1-2 years of the early onset, and the early psychological and pharmacological intervention in AD patients can greatly reduce the morbidity [4].

3. Diagnostic model for dementia based on Logistic Regression

3.1 Data description: Alzheimer Features

The data for this section is collected from Kaggle [5], The dataset contains features, namely Gender, Age, Years of Education, Socioeconomic Status, Mini Mental State Examination, Clinical Dementia Rating, Estimated Total Intracranial Volume, Normalize Whole Brain Volume and Atlas Scaling Factor. The label is Demented or Nondemented, which are represented 1 and 0 in this section. The whole dataset is split into training set and test set by 7:3.

3.2 Diagnostic model based on Logistic Regression

Logistic Regression is a classification model and is commonly used for binary classification, which is popular for its simplicity, parallelizability, and interpretability.

The mathematical model is based on sigmoid function, which is of the form:

$$y = g(x) = \frac{1}{1+e^{x}}, for\ x \in (-\infty, +\infty) \quad (1)$$

The feature of this function is that, when $x \geq 0, y \geq 0.5$. Assume y is a label from 0-1 classification, when $x > 0$, it means the data point is more likely to be classified into the category labeled 1, which gives logistic regression mathematical meaning in classification problems. The logistic regression in this case is defined as:

$$\hat{y} = f(x_1, x_2, ..., x_9) = g(\theta_0 + \theta_1 x_1 + \ldots + \theta_9 x_9) = g(\Theta) \quad (2)$$

The loss function is defined as:

$$J(\Theta) = -\frac{1}{n}\sum_{i=1}^{n} (y_i \ln \hat{y}_i + (1-y_i) \ln (1-\hat{y}_i)) \quad (3)$$

Which can be minimized by Gradient descent, where the update is:

$$\theta_{i+1} = \theta_i - \alpha \frac{\partial J(\Theta)}{\partial \theta} \quad (4)$$

α is the learning rate, which is an empirically set hyperparameters [6]. Use gradient descent to iterate until convergence, then the best decision boundary in binary classification problems is obtained.

To evaluate the performance of the classification model, confusion matrix is first introduced, the form of which is shown in table 1:

Table 1: Confusion matrix in binary classification

TP	*FP*
FN	*TN*

TP and TN are the numbers of positive and negative samples that are predicted correctly, while FP and FN are the other way around. Using confusion matrix, the following indicators can be calculated:

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$

$$\text{Precision} = \frac{TP}{TP + FP}$$

$$\text{Recall} = \frac{TP}{TP + FN}$$

$$F1\ score = 2 \cdot \frac{\text{precision} \cdot \text{recall}}{\text{precision} + \text{recall}}$$

The Intelligent diagnostic model is first trained on the training set and then tested on the test set, the confusion matrices and classification reports achieved by which on both sets are shown below:

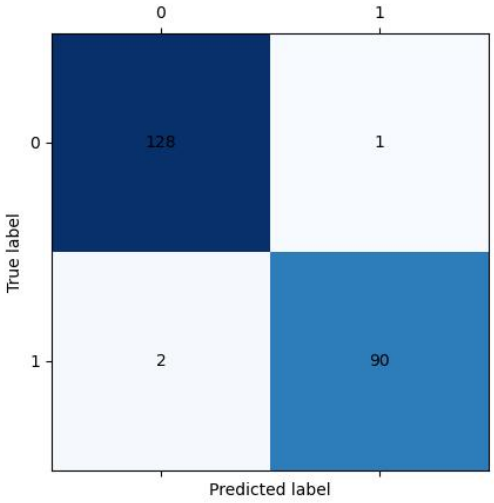

Figure 1: Confusion matrix achieved by logistic regression on training set

Table 2: Classification report of logistic regression on training set

Logistic Regression	0	1
Precision	0.98	0.99
Recall	0.99	0.98
F1-score	0.99	0.98
Accuracy	0.99	

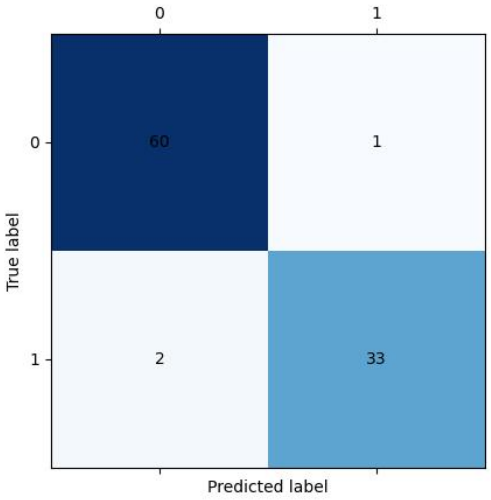

Figure 2: Confusion matrix achieved by logistic regression on test set

Table 3: Classification report of logistic regression on test set

Logistic Regression	0	1
Precision	0.97	0.97
Recall	0.98	0.94
F1-score	0.98	0.96
Accuracy	0.97	

It can be seen from the charts that the indicators obtained by logistic regression on both sets are excellent, which means no overfitting or underfitting occurs and the intelligent diagnostic model has good generalization ability.

3.3 Diagnostic models for Alzheimer's disease based on SVM and Random Forest

In this section, two binary classifier, Support Vector Machine (SVM) and Random Forest are both applied as diagnostic models for Alzheimer's disease.

Data description: Alzheimer's clinical data

The dataset is again from Kaggle [7], which contains only 5 features, namely Gender, Age, MMSE, CDR, Memory level. The labels are Uncertain dementia and Dementia, which are again represented by 0 and 1. The train-test split proportion is still 7:3.

3.4 Diagnostic model based on SVM

SVC is rather popular in binary classification; the core idea is to solve the following optimization problem:

$$minimize \ \frac{\|\vec{w}\|^2}{2}$$

$$subject\ to: g_i(\vec{w}, b) = y_i \cdot (\vec{w} \cdot \vec{x}_i + b) - 1 \geq 0$$

$$for\ i = 1,2, \ldots, n$$

Where $\vec{w}$ is the weight vector of the hyperplane equation that separates two categories and $g_i(\vec{w}, b) \geq 0$ is the constraint. To solve such problem, the following Lagrange equation can be constructed:

$$L(\vec{w}, b, C_i, p_i) = \frac{\|\vec{w}\|^2}{2} - \sum_{i=1}^{n} C_i \left(y_i(\vec{w} \cdot \vec{x} + b) - 1 - p_i^2\right) \quad (5)$$

where C is the penalty factor and p_i is applied to transform constraints into equation. This equation can be solved by KKT conditions:

$$\begin{cases} \vec{w} - \sum_{i=1}^{n} C_i y_i \vec{x}_i = 0 \\ \sum_{i=1}^{n} C_i y_i = 0 \\ y_i(\vec{w} \cdot \vec{x}_i + b) - 1 - p_i = 0 \\ C_i p_i^2 = 0 \\ C_i \geq 0 \end{cases}$$

In addition, SVM classification model must also use Kernel function to map data points to high-dimensional space in order to find the plane of segmentation. This paper chooses Gaussian Radial Kernel Function as the Kernel Function, which is of the form:

$$K(x_i, x_j) = \exp\{-\frac{\|x_i - x_j\|^2}{2\sigma^2}\} \quad (6)$$

where $\gamma = \frac{1}{2\sigma^2}$ is a hyperparameter [8]. Thus, to build an SVC model, the value of C and γ are crucial. After some attempts, it turns out that SVM achieves the best performance when $C = 100$ and $\gamma = 5$, the confusion matrices and classification reports on both training and test set are as follow:

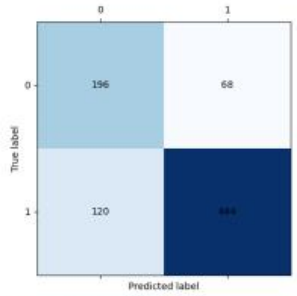

Figure 3: Confusion matrix achieved by SVM on training set

Table 4: Classification report of SVM on training set

SVM	0	1
Precision	0.62	0.87
Recall	0.74	0.79
F1-score	0.68	0.83
Accuracy	0.77	

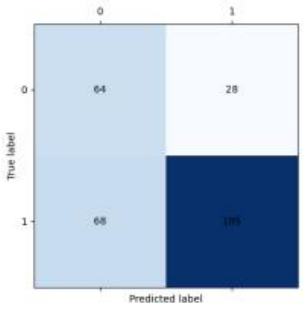

Figure 4: Confusion matrix achieved by SVM on test set

Table 5: Classification report of SVM on test set

SVM	0	1
Precision	0.48	0.87
Recall	0.70	0.74
F1-score	0.57	0.80
Accuracy	0.73	

Obviously, the classification performance achieved by SVM is not ideal enough, especially in terms of the recognition of the samples from the category labeled 0.

3.5 Diagnostic model based on Random Forest

Random forest is an extended variant of the ensemble learning method Bagging. By sampling the original training sample and selecting the feature nodes, many different trees can be obtained. The random forest is the integrated version of the decision tree. It has two main features:

1. randomness: The Bagging algorithm randomly selects n training samples based on the self-service sampling method, and each n training samples is used to train a base learner. A total of t sample sets is sampled to construct t base learner. In addition, in the process of base learner training, the randomness of attribute selection is applied, which is the extension of random forest to Bagging.

2. Forest: The base learner of random forest is CART decision tree, which integrates the learning results of multiple decision trees to determine the result of the model, which is called "forest" [9].

The visual diagram in figure 5 shows the structure of Random Forest

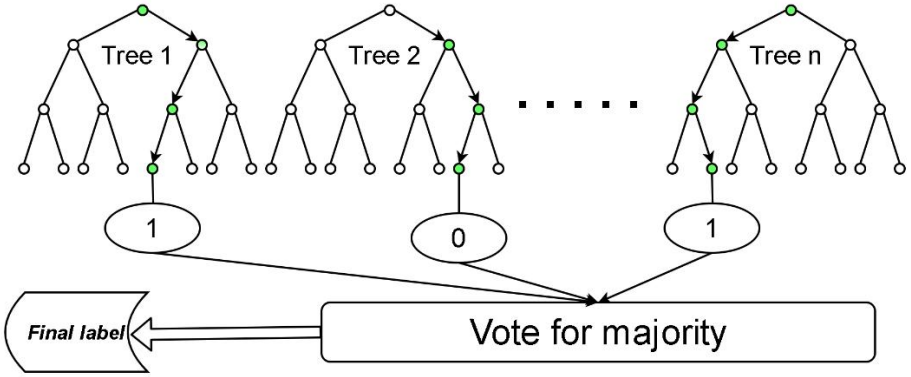

Figure 5: Structure of Random Forest

As can be noticed from the figure, the number of trees is a parameter, which is set as 25 in this case. The confusion matrices and classification reports achieved by Random Forest on training and test are:

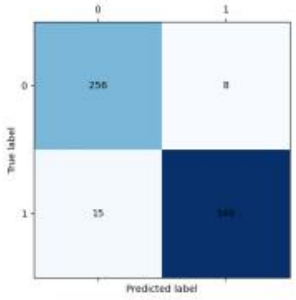

Figure 6: Confusion matrix achieved by random forest on training set

Table 6: Classification report of random forest on training set

Random Forest	0	1
Precision	0.94	0.99
Recall	0.97	0.97
F1-score	0.96	0.98
Accuracy	0.97	

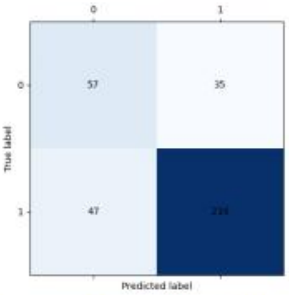

Figure 7: Confusion matrix achieved by random forest on test set

Table 7: Classification report of random forest on training set

Random Forest	0	1
Precision	0.55	0.86
Recall	0.62	0.82
F1-score	0.58	0.84
Accuracy	0.77	

It can be concluded from the charts above that Random Forest performs absolutely well on the training set but far from ideal on test set, which is no better than SVM. Thus, it is likely that the error comes primarily from the distribution of the data rather than models.

3.6 Sample set homogenization using SMOTE

By observing the data, it is easy to acknowledge that the sample is unbalanced, where the size of Category 1 is much larger than Category 0, to solve which an algorithm that can make samples more evenly distributed called SMOTE is now introduced.

Synthetic Minority Over-Sampling Technique (SMOTE) strikes a balance in the entire sample set by artificially

synthesizing minority samples, the process of which is shown in Figure 8.

First, a sample point from a minority class is chosen randomly and it selects another sample point at random from the K points closest to it. Then, a new artificial sample point can be generated randomly at the line segment that connects two points, whose location coordinates can be described as:

$$x_{newly\ generated} = x_1 + \beta \cdot |x_1 - x_2| \quad (7)$$

for $\beta \in (0,1)$, where x_1 and x_2 is the coordinates of the first and second chosen points.

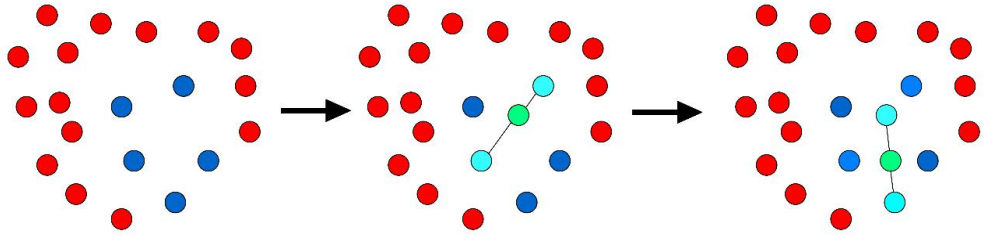

Figure 8: Process of oversampling by SMOTE

After homogenizing the samples using SMOTE, SVM and Random Forest are again deployed to perform classification task, whose results on training and test sets are shown in table 8 and 9 along with the results achieved without SMOTE for comparison.

Table 8: Results on training set

Algorithms		SVM	SVM(SMOTE)	RandomForest	RandomForest(Smote)
Precision	0	0.62	0.72	0.94	0.97
	1	0.87	0.96	0.99	0.99
Recall	0	0.74	0.98	0.97	0.99
	1	0.79	0.62	0.97	0.97
F1 score	0	0.68	0.83	0.96	0.98
	1	0.83	0.76	0.98	0.98
Accuracy		0.77	0.80	0.97	0.98

Table 9: Results on test set

Algorithms		SVM	SVM(SMOTE)	RandomForest	RandomForest(Smote)
Precision	0	0.48	0.72	0.55	0.78
	1	0.87	0.95	0.86	0.81
Recall	0	0.70	0.97	0.62	0.82
	1	0.74	0.64	0.82	0.78
F1 score	0	0.57	0.83	0.58	0.80
	1	0.80	0.76	0.84	0.80
Accuracy		0.73	0.80	0.77	0.80

As is clearly shown in the tables, after SMOTE, the performances achieved by both SVM and Random Forest are both upgraded to a large degree. By comparing the results of SVM and Random Forest, both after SMOTE, it can be found that SVM can accurately identify patients with uncertain dementia and random forests perform equally in the identification of both categories, which are Intuitively visible in their confusion matrix on test set below:

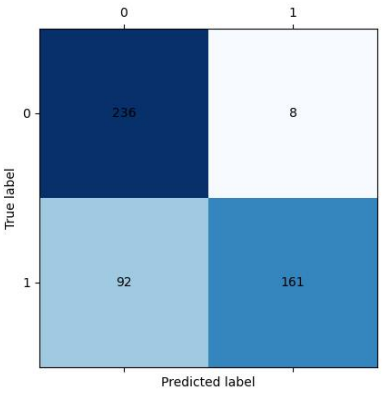

Figure 9: Confusion matrix achieved by Random Forest after SMOTE

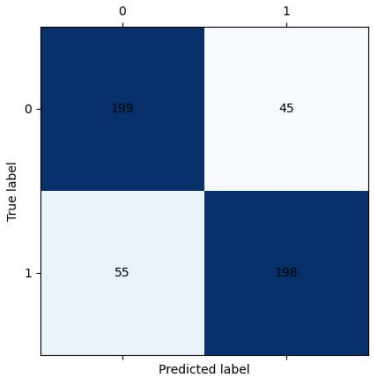

Figure 10: Confusion matrix achieved by SVM after SMOTE

Conclusion

It can be seen by summarizing the early intervention and evaluation criteria for dementia and Alzheimer's disease that it is necessary to use accurate intelligent diagnostic systems to identify the type of disease early. After providing the Gender, Age, Years of Education, Socioeconomic Status, Mini Mental State Examination, Clinical Dementia Rating, Estimated Total Intracranial Volume, Normalize Whole Brain Volume and Atlas Scaling Factor of the patient, the diagnostic model based on logistic regression can precisely diagnose whether a patient has dementia or not. In the case of diagnosing whether the type of dementia is Alzheimer's disease, this paper discusses the diagnostic capabilities of the models based on SVM and Random Forest before and after SMOTE, which turns out SMOTE can significantly improve the diagnostic performance. Also, the difference in SVM and Random Forest shows that each of the algorithm has its own advantages when acting as intelligent diagnostic model for the types of dementia.

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A Review of Nanoparticles in Treatment of Myocardiac Ischemic-Reperfusion Injury

Tszching Sung[1], Peiyang Qin[2]

1. Institute of New Drug Research and Guangdong Province Key Laboratory of Pharmacodynamic Constituents of Traditional Chinese Medicine & New Drug Research, College of Pharmacy, Jinan University, Guangzhou 510632, China.

2. Institute of Biomedicine & Guangdong Provincial Key Laboratory of Bioengineering Medicine, College of Stomatology, Jinan University, Guangzhou 510632, China.

Abstract: Myocardial ischemia-reperfusion injury is a kind of pathologic physiology, clinical refers to, when myocardial or coronary artery in patients with partial completeness of acute obstruction, and leads to ischemia after a period of time, restore blood supply, at this time although the myocardium and coronary ischemia returned to normal perfusion, but they are so tissue level by damage, seriously affecting the prognosis of patients with myocardial infarction. Studies have proved that the injury caused by reperfusion is even more serious than that caused by ischemia itself. The mechanisms leading to myocardial ischemia-reperfusion injury mainly include :(1) calcium overload due to recovery of oxygen supply; (2) cardiac ultrastructural changes; (3) lipid peroxidation; (4) leukocyte infiltration; (5) Increase of free radical reactive oxygen species. Different approaches have been used clinically to reduce ischemia-reperfusion injury, including medication, pretreatment and post-treatment. In recent years, the targeting ability of nano-agents has been used to make drugs highly concentrated at the injury site, thus improving the therapeutic effect of drugs for ischemic-reperfusion injury. This emerging medication method has gradually entered the field of vision of experimental researchers and doctors. This review summarizes the successful development of nanoparticles for the treatment of myocardial ischemia-reperfusion injury.

Keywords:Ischemia-Reperfusion Injury(Iri); Treatment; Myocardial Infarction(Mi); Nanoparticle(Nps); Pharmacodynamics; Targeting; Drug Delivery; Atherosclerosis; Reactive Oxygen Species (Ros); Drug

Introduction

Nanoparticles have been demonstrated to be safe and biocompatible in the treatment of IRI by a variety of preclinical studies. A nanoparticle drug delivery system is a new type of drug delivery system, in which particle size is between 1 and 1000 nm and is usually selected according to the size and thickness required to stay on the target organ. Drugs with nanoparticles can avoid biodegradation during drug administration, expanding drug distribution, prolong action time, and increase drug bioavailability. The outer membrane of the nanoparticle is made of natural polymer materials or polymers, and the active drug is wrapped inside the particle. Different types of nanomedicine preparations that are commonly made for use, including nano-enzyme, nanometer vesicles, nanomedicine, nanoparticle, nanocrystalline, and nanocomposite. An introduction to the m nanoparticles used in the treatment of myocardial ischemia-reperfusion injury so far, including their active components, carrier materials used, and preparation methods.

1.1 Nanocolloidal lipid carriers

This classification includes nanoliposomes, nanocrystals, and nanometer colloids. Their carriers for making nanoparticles are phospholipids or other amphipathic materials that resemble cell membranes. By using a simple stirring precipitation method that always encapsulates biological drugs such as enzymes, DNA, RNA, proteins, and colors. Ruijian L. et al. synthesized polyvinyl alcohol (PVA) coated with 4-vanilanol (VA) by microemulsion method to reduce ROS [1]. Martijn J W Evers et al. prepared modified mRNA liposomes by microfluidic approach. [2]

1.2 Colloidal nanopolymer carrier

Nanopolymer is a technique using a biodegradable macromolecule polymer as a membrane to encapsulate pharmaceuticals, such as polyethylene glycol, and polylactic acid, which are two biodegradable macromolecules. These kinds of nanoparticles are typically generated by the microemulsion method and are frequently used to encapsulate abiotic medicines.

Yabing Z. et al. created polydopamine nanoparticles modified with polyethylene glycol to regulate cellular iron death. Antioxidants are targeted at ROS excess sites in the body through the conventional stirring method. Polydopamine is a family of antioxidants that are used to neutralize excess ROS. Polyethylene glycol modification can enhance the drug's biocompatibility and stability. Fourier transform infrared spectroscopy (FTIR) and transmission electron microscopy was used to analyze the nanoparticles. The nanoparticles were found to be effective in reducing IRI caused by iron death in cardiac cells [3]. This may indicate other anti-iron medicines be acceptable for transport via polyethylene glycol (PEG). Chen-Jie L. et al. created water-soluble nanoparticles with mesoporous silica as the carrier, a high dispersity, and quercetin as the primary active ingredient. The nanoparticles were generated using the solution gel method and characterized using dynamic light scattering (DLS). The results indicated that the nanoparticles might modulate the JAK2/STAT3 pathway and protect cardiomyocytes from oxidative stress-induced damage [4]. As a result, mesoporous silica can be employed to transport water-soluble medicines. Gentaro I. et al. produced nanoparticles using polyethylene glycol/glycolic acid (PLGA) as the carrier material and cyclophilin D as the active ingredient, followed by an emulsion solvent diffusion method and suitable labeling. Experiments were conducted in vitro and in vivo. The nanoparticles decreased mitochondrial permeability conversion pore opening and monocyte-mediated inflammation, as well as reducing IRI produced by verification [5]. The author did not characterize the nanoparticles used in this experiment because they were made similarly to those described in other publications [6][7]. Ju-Rol. et al. produced nanoparticles by using a single emulsion/solvent evaporation method. Polydigestible/Glycolic acid (PLGA) as the carrier material, polyethylene glycol as the aqueous phase, and Bcl2 inhibitor (ABT263) as the active drug. Scanning electron microscopy, nanoparticle tracking analysis, and high-performance liquid chromatography (HPLC) were used to analyze the nanoparticles. The results indicated nanoparticles could minimize apoptosis in cells generated by ischemia-reperfusion injury [8]. Xiaotian S. et al. synthesized nanoparticles with PEG (PEG) and lactoferrin (LF) modified mesoporous ferric oxide as carriers, hexadiene trisulfide (DATS) as the primary active component. PEG was used to extend the activity period of nanoparticles, whereas lactoferrin was used to transform nanoparticles into typical blood-brain barriers. Characterization was carried out using scanning electron microscopy. The results indicated the nanoparticles mitigated hypoxia-induced neuronal and myocardial injury [9]. Thus, distinct modified pieces can be placed on the surface of nanoparticles to alter their properties and render them selective. Mengying Hou et al. investigated the co-delivery of VCAM-1 siRNA (SiVCAM-1) and dexamethasone (DXM) to central granulocytes using PLGA nanoparticles modified with CrGD-polyethylene glycol (PEG)crosslinked PEI (RPPT). 13 C NMR, 1 H NMR, and Fourier transform infrared spectroscopy was used to analyze it (FT-IR). The results indicated that the nanoparticles could mitigate inflammatory cell-induced cardiac injury [10].

Discussion

Nanoparticles can be prepared in many ways and materials and should be suitable carrier materials according to the quality and target of drugs. However, no articles compared the biochemical changes and long-term therapeutic effects of different vectors on the same type of drugs. In the case of the same sample size and environment, it is difficult to determine which carrier material has the best effect. That is a feature worth considering and the main research direction of future nanotechnology for the same disease or topic. The selection of suitable nanoparticle preparation technology according to the properties of drugs is also a key index for the safe and effective use of nanomaterials in clinical treatment.

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Making Foreign Aid Work: A Case Study of China-UK-Tanzania Pilot Project on Malaria Control

Jiawei Tian[1], Mengjie Ma[2]

1. China Europe International Business School, Shanghai 201206, China.

2. Guangzhou Xinhua University, Guangzhou 510520, China.

Abstract: Foreign aid is a topic with a long history. However, after so many years of practice, the effect of foreign aid is still controversial. This paper takes the China UK Tanzania malaria control pilot project as an example to understand the conditions under which foreign aid is effective by analyzing the reasons for the success of the project. This paper finds that there are several reasons that make foreign aid effective, including adjusting measures to local conditions, obtaining local people's support and participation, and having multilateral partners participate in projects.

Keywords: Foreign Aid; Effectiveness; Pilot Project; Multilateral Cooperation

Introduction

This essay will discuss the China-UK-Tanzania Pilot Project on Malaria Control. It was the first pilot project of its kind for the Chinese government in Africa. It was supported by the China-UK Global Health Support Program and funded by the UK Department for International Development (DFID), implemented from April 2015 to June 2018.

The pilot project was an operational research project with two communities receiving the proposed interventions and two comparable communities serving as control sites. The goal of the project was to explore an appropriate model and mechanism on how Chinese models and strategies could be used effectively to reduce the disease burden of malaria based on the existing local system, which could then be scaled up and applied in other similar settings of Africa. The results of this pilot project were encouraging, it demonstrated that the malaria burden could be reduced by 81% when China's experience with malaria control was shared in Tanzania through interactions between health officials from these two countries.

Foreign aid is a topic with a long history. However, after so many years of practice, the effect of foreign aid is still controversial. Although the impact of the China-UK-Tanzania Pilot Project on Malaria Control still needs further evaluation, the effectiveness of this project in the short term has been verified. Based on the previous study on the effects of foreign aid, this paper will analyze the possible reasons for the success of this project. It is hoped that through analysis, we can better understand under what condition aid works. In this way lessons and experience can be drawn to provide useful insights for future foreign aid projects.

Literature review

Due to the mixed empirical evidence on foreign aid`s benefits, there has been a longstanding academic and policy debate regarding the effectiveness of foreign aid among leading experts on economic development around the world(Toseef et al., 2019). Debates about aid effectiveness over the past two decades have been characterized by three schools of thought, which we characterize as "more aid," "problem aid," and "conditional aid."(Tierney et al., 2011) For instance, Sachs（2005）

argued that through carefully planned development aid, extreme poverty—defined by the World Bank as incomes of less than one dollar per day—can be eliminated globally by the year 2025.

Collier and Dehn (2001) introduce export shocks into the growth-aid regression to find that controlling for GDP levels, foreign aid can help mitigate the adverse effects of negative export shocks for a panel of 113 developing countries during 1957-1997.

However, there are many critics who argue that aid does very little impact. One academic review of the evidence of aid's impact over the course of a few months in 2005 maintained that aid has neither increased welfare nor enhanced growth in poor countries, and thus it should be reduced rather than increased (Erixon 2005).

Some even find that aid does harm to recipient countries. Djankov et al (2008) study ODA from OECD countries using a panel of 108 countries during 1960-1999 and institutional quality data from the Polity IV database. The authors measure foreign aid with variables such as the initial level of income of the population and find that aid reduces democracy for the top quartile of recipients.

There are also those in the "middle ground" who believe that aid works under some conditions. For example, Dollar and Burnside (2000) provide a case study and cross country evidence from 56 countries during 1970-1993 that multilateral aid can promote growth if given to countries with good economic policies, which they measure as a function of the budget surplus, inflation, and trade openness.

Regarding under which conditions foreign aid can work, Qian (2015) argued several reasons contribute to the different results of different studies. Whether aid works depends on the type of aid and the outcome under consideration. One key difficulty comes from the fact that much of the existing literature examines aggregate ODA, which is a bundle of many different types of aid. She argued that the effectiveness of aid depends on whether the donor is a country or a multilateral agency, designated as humanitarian or non-humanitarian, transferred as cash or in-kind, or spent in the donor or the recipient country. Each aspect can influence how aid affects the recipient country.

Mawdsley (2012) argued that development effectiveness is influenced by various factors, beginning with the quality of project design and ending with the relevance and sustainability of desired results.Sumner and Glennie (2015) argued that there is a set of broad areas where the evidence reviewed shows signs of convergence that have direct relevance for policy decisions on aid and aid-effectiveness discussions. These areas are aid levels (meaning if the level of aid is too low or too high); domestic political institutions (including political stability and the extent of decentralization); the composition of aid (including sectors, modalities, objectives, and time horizons); and the volatility and fragmentation of aid.

Compared to foreign aid overall impact, there is less research on whether foreign aid improves population health in recipient countries. Increasingly, research has examined whether foreign aid has been effective in improving human development or the health of citizens in recipient nations since the establishment of the Millennium Development Goals (MDGs) in 2000.

With regard to the effectiveness of health aid, current research has focused on the following topics: what factors influence the impact of foreign aid on health, and under what conditions foreign aid is effective.

Concerning the effectiveness of health aid, current research has focused on the following topics: what factors influence the impact of foreign aid on health, and under what conditions foreign aid is effective. The main topics covered in the current study are: relationship between health aid and main health indicators (e.g. infant mortality), the impact of health aid on a certain group of people (e.g. Maternal health, women, children under 5), the relationship between certain sector (e.g. Water and sanitation) aid and health etc. Most studies use published data and mainly focus on the long-term impact of health aid to many countries.

For instance, Mishra and Newhouse (2009) examines the relationship between health aid and infant mortality, using data from 118 countries between 1973 and 2004; Pickbourn and Ndikumana (2019) examines the impact of foreign aid to the

health sector on diarrhea mortality in children under five in 47 sub-Saharan African countries, using panel data on the sectoral allocation of official development assistance in conjunction with country-level data on health outcomes. Bandhani and Swiss (2019) used data from the Organization for Economic Cooperation and Development, the World Development Indicators, and the Institute of Health Metrics and Evaluation, this study analyzes the effects of aid on maternal health in a sample of 130 LMICs from 1996 through 2015. The most commonly used approach is the Difference–Differences approach.

Case study

As mentioned above, this paper will focus on the China-UK-Tanzania malaria control pilot project as a way to discuss the impact of foreign aid. While the long-term impact of this project is still under debate and still needs to be observed and evaluated. According to the independent evaluation body, there is a high degree of certainty about the short-term impact.

The intervention approach in the pilot areas significantly reduced the malaria burden in rural high transmission areas in southern Tanzania. This locally tailored approach can accelerate malaria control and elimination efforts. These results provide an impetus for further evaluation of the effectiveness of this approach and its replication in other high malaria burden states in Africa, including Tanzania (Mlacha et al., 2020).

“Randomized control trials” adopted

China provides at least nine kinds of aid to Africa (Brautigam, 2011). Of these, medical assistance began earlier, mainly in the form of medical teams. China deployed its first medical team in 1964 at the invitation of the Algerian government, since then it has cumulatively sent over 15,000 doctors to more than 47 African countries and treated approximately 180 million African patients. (Xinhua, December 16, 2004). Chinese doctors that are part of the medical teams, known as yiliaodui, normally spend up to two years in-country (Thompson, 2005).

After more than half a century of implementation, the organizational and operational flaws of the medical team program have become increasingly apparent and are in dire need of reform(Chen et al., 2019). Besides, the Chinese government has accelerated the training component of its foreign aid, focusing in part on transferring information about China’s own experience with urbanization, economic growth, and poverty alleviation since 2000(Brautigam, 2011). It is therefore worth considering how to reform the form of China's medical aid to Africa and whether China's experience in eradicating certain diseases can be adopted by Africa.

Malaria, a disease almost eradicated in China but still rampant in Africa, raises concerns in this context. Over the last 60 years, Chinese national malaria elimination program implemented a set of control strategies and measures in different local settings successfully with a low cost of investment. It is expected that Chinese experience may benefit malaria control in Africa (Xia et al., 2014).

In Tanzania as it is the case with the rest of sub-Saharan Africa, malaria is a major cause of morbidity and mortality especially among children less than five years and pregnant women (WHO: World malaria report 2013. Geneva: World Health Organization; 2013). The elimination of malaria is Tanzania`s long-term goal and mission. However, there are many challenges to reaching and sustaining the universal coverage policy by effective curative and preventive services, the health system in Tanzania is still weak, effective treatment is undermined by the capacity of the health system to deliver appropriate care, shortages of essential medical products for malaria and other diseases are prominent. (Wang et al., 2019).

Against this background, China implemented this project in Tanzania, the first of its kind in continental Africa. As an intervention study and operational research, this project adopted “randomized control trials (RCTs)”, it chose two separate representative pilot communities receiving the proposed interventions and two comparable communities serving as control sites.

The use of experimental methodologies has emerged as a central means of evaluating international aid interventions in recent years, It has become a crucial epistemic practice today, and has been adopted throughout academia and by NGOs, the World Bank, and governments (Donovan, 2018).

As pioneers in the use of RCTs within international development, the MIT economists Banerjee and Duflo (2011) argued that a radical rethinking of the way to fight global poverty is premised on the use of experimentation to assess the effectiveness of international aid programs. They argued that the use of RCTs may help devise effective and specific aid programs in the war against poverty and underdevelopment.

Indeed, we can see from this project that the adoption of RCTs have many advantages. Previous Chinese medical teams have undergone little internal or external evaluation since their inception more than fifty years ago (Chen et al., 2019). By using RCTs, this project can test the effectiveness of new and existing interventions and variations thereof, and therefore can learn what is working and what is not and to adopt policies so that they steadily improve and evolve both in terms of quality and effectiveness (Haynes et al., 2012).

As many critics argued, RCTs also has many problems. The most common example of this problem is that of participation rates. Many interventions suffer from low participation rates, that is, intended beneficiaries are not terribly interested in the intervention (White, 2013).

To avoid this problem, during the implementation of this project, onsite staff tried different ways to encourage all participants to seek treatment at a dedicated health facility for any febrile illness followed the national guidelines for malaria treatment. Any participant in the home diagnosed with malaria or anemia during the screening was treated accordingly (Wang et al., 2019).

Although the RCTs have improved the pertinence and flexibility of foreign aid, its limitations cannot be ignored. As Glennie and Sumner (2014) argued, compared to other types of aid, “program” aid and project aid given for real sector investments are likely to be more effective for growth, but aid in sectors like health and education may only affect growth after a long period of time and thus may be difficult to detect rather than be non-existent.

This argument applies to this project, which has reduced the incidence of malaria in the short term, but the long-term impact on the Tanzanian economy and society remains to be observed and evaluated over time.

Participatory development theory applied

Participatory methodologies have now been used in a diverse range of projects and programs, by NGOs, international agencies, and multilateral organizations. Though the results of participatory methodologies have been mixed, they generally support the contention that participation in terms of structures for beneficiary involvement can enhance project effectiveness (Manikutty, 1997).

However, not all foreign aid projects that adopt participatory theory end up improving efficiency. There is little doubt that aid has become more participative, and has been geared towards smaller projects and programs (Edwards, 2015). Besides this, to improve efficiency, appropriate strategies must be adopted. For example, during the course of this project, the implementers developed rigorous strategies that increased the effectiveness of the project and were key to its success.

First, as a project that required a high degree of public participation, the project team members realized the importance of seeking permission from community leaders and motivating community members.

While aid may contribute to positive development outcomes, it may also contribute to rights violations committed by Donor governments (Dasandi and Erez, 2019). Therefore, firstly, this project tried to make collaborative efforts to gain community consent.

Before the study began, the project team held community meetings at the district level and at specific ward level where the study was conducted to inform the community leaders, key informants, and District Medical Officer's (DMO's) office staff of the purpose, design, objectives, and methods of the study (Wang et al., 2019).

The next step is community mobilization. To maximize project acceptance after a village had been identified as a hotspot, weekly social mobilizations were initiated, i.e., the field supervisor and village community leaders held meetings to discuss the logistics. Upon deciding on the locations, village leaders and CHCWs informed the rest of the community members about the presence of cases, emphasizing that testing and treatment were free (Mlacha et al., 2020).

In addition to community involvement, finding the right local partners at the project implementation sites to cooperate with is also very important. The most important local partner for this project is the Ifakara Health Institute (IHI). IHI is an independent non-profit organization, also one of Africa's most eminent health research organizations, with a history of more than 50 years. It has done a lot of research on the malaria situation in Tanzania and has participated in many foreign aid projects before. During the implementation of the project, onsite Chinese staff for technical support was paired with local staff from IHI to do work plan designing, local staff training, field implementation, and supervision (Mlacha et al., 2020).

The participation of local people and local institutions made a big difference. Problems with aid arise because of poor decision-making, often as a result of insufficient understanding of what is needed, and how aid may help (Riddell, 2008). Therefore, by listening to local people and letting them know that their ideas and judgments are valued, the relationship between aid providers and aid recipients has been fundamentally shifted (Anderson et al., 2012).

Besides, by offering a place for beneficiaries in some aspects of project implementation and design, community involvement reduced costs for donors, contributing to the effectiveness of cost "sharing" and recovery, and longer-term sustainability (Oakley, 1991). Involving civil society and local NGOs also affected accountability and has helped reduced–although not eliminate – corruption and malfeasance (Edwards, 2015).

Foreign aid form localized

During the past six decades, remarkable success in malaria control has been made in China. This experience could be shared with other malaria-endemic countries including Tanzania with high malaria burden. Especially, China's "1–3-7 model" for malaria elimination is one of the most important sources of experience after many years' in practice and key innovation measures for malaria elimination in China. "1–3-7 model" stands for reporting of malaria cases within 1 day, their confirmation and investigation within 3 days, and the appropriate public health response to prevent further transmission within 7 days(Zhou et al., 2015).

While 1-3-7 is best suited for very low transmission areas with a relatively very low number of cases, the pilot project was to be implemented in a moderate transmission site with a huge burden of malaria. Given this reality, Chinese and Tanzanian teams have developed a locally-tailored malaria control approach screening for febrile cases in endemic villages on Day 1 followed by focal treatment of holoendemic villages within 7 days to stop transmission at the same phase of the plasmodium life-cycle.

This 1,7-Reactive Community-based Testing and Response (1,7-mRCT) model ensures the smooth progress of the project. It utilized existing health facility data and locally trained community-based health workers to conduct community-level testing and treatment (Mlacha et al., 2020).

Community-based health workers are important participants in the project and are also the result of localization of Chinese experience. Village doctors have made great contributions to malaria control by providing primary health care to malaria patients in rural areas at relatively low costs in a door-to-door manner. Here, China`s village-doctor model was localized according to local conditions.

In Tanzania, many people do not go to health facilities due to a lack of awareness of malaria illness, and a lack of accessible health services. Therefore, this project recruited and did capacity building for community health workers (CHWs). It cultivated a local team of 35 CHWs, who were trained and supervised and ensured the success of the implementation process. The training included case management, vector control, and health education.

As a result, by sharing China's village-doctor model in such a way that CHWs could provide basic malaria diagnosis, drug treatment, and primary health education to members of the community, even reaching previously under-served patients. Their door-to-door healthcare services helped ensure the primary health of community members and served as an extension of the services provided by local health facilities. (Ma et al., 2020).

Just as Sauri, 2005 argued, by using the original mechanism that existed in the projects, aid can be well used. Projects that empower village-based community organizations can be highly successful (Sachs, 2005).

In conclusion, what we learn from this project is: development interventions should aim to solve particular problems in local contexts, involving active, ongoing, and experiential learning and the iterative feedback of lessons into new solutions, and engaging broad sets of agents to ensure that reforms are viable, legitimate, and relevant—i.e., politically supportable and practically implementable(Andrews et al., 2013).

Multi-cooperation for "public goods"

In addition to the features mentioned above, this project has another great feature, that is, it is a multi-cooperation project. It represents a new trend in the field of international development: cooperation is expected to increase the effectiveness of foreign aid.

The old aid architecture is being replaced by a more complex and diverse landscape of development cooperation in which there are new actors, new approaches, and attempts to create an overarching architecture which, by embracing all, is expected to be more developmentally effective (Gore, 2013).

Over the past decade and in particular, since 2008, there has been an intensification and diversification in the ways that Northern donors engage with South-South cooperation (Abdenur and Da Fonseca, 2013). China and the UK are pioneers of so-called "trilateral development cooperation", which involves OECD donors like the UK working together with Southern donors such as China on development initiatives in third countries.

Chinese government agencies and international philanthropic organizations/ communities have recognized that the best practices and lessons learned from China's health development over the past six decades could be relevant and very useful in supporting the achievement of health-related Millennium Development Goals and post-2015 Sustainable Development Goals in the low and middle-income countries.

Against this background, the Ministry of Commerce of China, in collaboration with the Department for International Development (DFID) of the UK, has launched the "Global Health Support Programme (GHSP)" in 2011, which is a China-UK partnership contributing to improved global health policy and outcomes. This pilot program aimed at promoting China's experiences, and exploring the new model of tripartite cooperation through conducting a malaria control pilot project in Tanzania, financially supported by DFID. Multi-cooperation can ensure the complementary strengths of all sides, and bring a win-win-win situation.

For China, providing affordable experience/technologies that are suited to the needs of Tanzania created chances for commercial investment. Also, In 2017, for the first time, zero indigenous cases were reported in China, with only 7 imported cases (Feng et al., 2018). If there are fewer imported cases from Africa, it will consolidate the achievement of the elimination of malaria in China.

To the UK, which brings relatively deep pockets and experienced project management, the success of this project will create new opportunities for long-term global health aid. To the aid recipient Tanzania, the successful implementation of this

project can reduce the burden of disease in the country, thereby improving productivity and indirectly promoting economic and social development.

From a longer-term perspective, China and the UK have established a good model for North-South Cooperation in the GHSP, and the program facilitated the 2030 Agenda for Sustainable Development by building a new type of bilateral partnership and carrying out trilateral cooperation practices. This model has demonstrated huge potential for cooperation through partnership and can also be referred to by other countries developing bilateral partnerships (Wang et al., 2020).

With faster and cheaper transportation and communication, health innovations in one country have almost instantaneous implications for health in the rest of the world (Deaton, 2013). Growing amounts of aid have been channeled through international institutions and used to expand international “public goods”, such as controlling the spread of infectious diseases worldwide or reducing environmental degradation ((Lancaster, 2008)).

Conclusion

While the impact of foreign aid on health is still debated, the China-UK-Tanzania Pilot Project on Malaria Control does show that foreign aid that aims at tackling a certain disease in a certain area is relatively easily monitored and evaluated in regards to the short-term impact.

As analyzed above, several possible reasons contributed to the success of the project. The foreign aid project discussed in this paper adopted RCTs, it successfully validated in a short period of time that the Chinese experience in treating malaria is feasible in Africa; moreover, the project's success in engaging the local community was due to the adoption of appropriate strategies, including mobilizing community leadership, motivating community members and cooperating with local institutions that have experience in malaria research. Furthermore, this approach allows for the adjustment of responses to local conditions and the localizing the Chinese experience as the project progresses. Finally, the project is a model for multilateral cooperation in which developed and developing countries play to their respective strengths, creating a synergistic effect that maximizes the efficiency of the project. The Sino-British cooperation in the fight against malaria in Tanzania also represents a new trend in global development cooperation, namely, North-South cooperation to address global public health issues of common concern.

Of course, as some critics have pointed out, there are many limitations to randomized controlled experimental projects. For example, it is still controversial how variables can be effectively controlled during the course of the project and how the long-term validity of the project can be evaluated. The extent to which the Chinese experience is localized also needs to be further explored. Besides, as a multi-stakeholder project, how to solve the communication problems during the collaboration process and how to form an effective cooperation mechanism is a topic that needs continuous attention in the future.

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Reflections on the Use of Blood Activation and Stasis Removal in the Treatment of Lung Cancer

Junhui Wang, Kai Wang*
Shaanxi University of Chinese Medicine, Xiangyang 712046, China.

Abstract: According to Chinese medicine, lung cancer is a malignant tumour with cough, haemoptysis, chest pain, fever and shortness of breath as its main manifestations. Its causes are: deficiency of positive qi, external invasion of evil toxins, internal accumulation of phlegm, stagnation of qi and blood, obstruction in the lung and loss of suction and descent of the lung. Blood stasis is the main cause of lung cancer, therefore, activating blood circulation and removing blood stasis is an important principle in the treatment of lung cancer. In recent years, the anti-cancer mechanism of traditional Chinese medicine and its extracts has gradually received academic attention, and the herbs that invigorate blood circulation and remove blood stasis have been widely used in clinical practice. This article introduces the mechanism of the action of Chinese medicine to invigorate blood circulation and remove blood stasis in the treatment of lung cancer in recent years, which provides a reference for clinical treatment and new drug development.

Keywords: Lung Cancer; Blood Circulation and Blood Stasis Activation; Overview

1. Introduction

Lung cancer is currently the most common malignant tumour in clinical practice, and its incidence and mortality rate are increasing year by year. 2010, lung cancer ranked first in China in terms of morbidity and mortality, and both mortality and morbidity rates are increasing. Therefore, the search for new anti-tumour drugs has become a hot spot for medical research.

2. Basic Principles and Historical Origins of Chinese Medicine

The treatment method based on activating blood circulation and removing blood stasis works by regulating blood, activating blood circulation and removing blood stasis. The method of activating blood circulation and resolving blood stasis is commonly used in clinical practice, and is combined with other methods of treatment depending on the situation. Common clinical treatments include: warming the meridians and invigorating the Blood, detoxifying and invigorating the Blood, cooling the Blood and removing stasis, moving Qi and invigorating the Blood, attacking and expelling stasis, benefiting Qi and invigorating the Blood, nourishing the Blood and invigorating the Blood, nourishing Yin and invigorating the Blood, and warming Yang and invigorating the Blood. In recent years, modern scientific knowledge and methods have been used to discuss the theory of "invigorating Blood and resolving Blood stasis", which has deepened people's understanding of "Blood stasis" and enriched the connotation of "Blood stasis". Clinical practice has proven that Blood Stasis can be used in the treatment of various diseases in Western medicine, especially malignant tumours, and that it can effectively destroy cancer cells, enhance the antigenicity of tumours and strengthen the body's immunity to tumours [1]. At present, many Chinese scholars believe that the etiology of tumor is mainly caused by empty fire phlegm stasis, which is not only a factor of pathology, but also the result of pathology. Lung cancer is a common malignant tumor, also known as "lung accumulation"

and "lung fistula" in traditional Chinese medicine, but its pathogenesis is related to "blood stasis", so it can be treated by "activating blood circulation and removing blood stasis" method.

3. Study on the Relationship Between Lung Carcinogenesis and Blood Stasis

According to TCM, those with blood fetishes are closely related to lung deficiency evidence. Stasis of blood can induce tumours, while redness can promote blood deficiency, and the two have a synergistic effect. According to the "Guidelines for Clinical Research on New Chinese Medicines" issued by the Ministry of Health of the People's Republic of China in 1993, the TCM typing of lung cancer, the "Clinical Chinese Medical Oncology" lung cancer typing in 2003, and the "Tenth Five-Year Plan" Key Specialties Cooperation Group of the State Administration of Traditional Chinese Medicine in 2011 Professor Liu Jiaxiang's TCM lung cancer typology includes "blood stasis", which is considered to be the main cause of lung cancer; a study was conducted on 120 patients with advanced NSCLC. The results showed that more than 60% of the patients had signs of blood stasis [2]. At the same time, the treatment with traditional Chinese medicine could reduce the metastasis of the tumor. The results showed as follows: Among the 68 NSCLC patients, 24 patients mainly had Qi-stasis and blood stasis, mainly stage IV NSCLC, indicating that Qi-stasis and blood stasis were related to the development of lung cancer to a certain extent. The TCM syndromes after NSCLC surgery were analyzed. The results showed that the proportion of blood stasis evidence was basically the same before and after surgery, indicating that although surgery removed the tumour, it did not change its TCM evidence; on the contrary, it suggests that blood stasis evidence is an important cause of lung cancer development. 2) Tumour-blood stasis: as stated in Wang Qingren's "Medical Lin Correction", "Insufficient qi and blood, when the qi and blood are not smooth, they stagnate in the blood "Lung cancer is a disease of "accumulation", and over time, it will lead to "blood stasis".

The modern medical dimension: 1) Blood stasis - tumour: In modern medicine, "blood stasis" is a different phenomenon from "hypercoagulable state", which is caused by abnormalities of certain prothrombin time, fibrinogen, D-dimer and platelets in cells. The mechanisms by which hypercoagulability can also lead to tumour development are: Platelet activation directly stimulates tumour cell activation and leads to tumour development: tumour cells cause damage to endothelial cells, leading to active aggregation of vascular endothelial cells. FW is produced by the liver and is closely related to tumor angiogenesis, which has certain influence on tumor growth, differentiation, invasion, and metastasis. Tumor-blood stasis: Because tumor cells can cause vascular endothelial damage, hemodynamic abnormalities and blood hypercoagulation, hemorheological examination shows that the blood coagulation of lung cancer increases, and with the deepening of blood agglutination, the chance of metastasis of lung cancer will also increase, which may cause tumor metastasis.Pathological hypercoagulability often occurs in patients with malignant tumor due to abnormal bleeding function, which is generally believed to be related to the condition and prognosis of the tumor, and has important clinical significance [3].

4. Experience in the Treatment of Lung Cancer by Promoting Blood Circulation and Removing Stasis

Lung cancer is the "lung accumulation" and "Ben" of traditional Chinese medicine. Although there is no direct corresponding disease name in traditional Chinese medicine books, there are descriptions of "rock" and "accumulation" in ancient literature, accompanied by cough, phlegm, blood coughing, labile breathing and other diseases. The descriptions of these diseases are the same, which is likely to be of the same type. The name of TCM lung cancer was first published in

Practical TCM Internal Medicine in the editor-in-chief of Prescription. Since then, the name has been used in both the Catalogue of Diseases of Traditional Chinese and Western Medicine and the sixth edition of the Internal Medicine of Traditional Chinese Medicine, because modern medicine has many diagnoses of diseases, so most of them can be confirmed. However, clinically, some patients' lungs occupy a large space and have the above symptoms, but due to some special reasons, the etiology cannot be determined. It can be referred to that these patients are typical representatives of TCM lung cancer, and the syndrome differentiation treatment is of great help to the treatment of TCM lung cancer. In the literature, the pathogenesis of tumor is mainly phlegm, deficiency, poison and stasis, and the same is true for lung cancer. Lung cancer is caused by a variety of causes, not a single cause [4].

"Blood stasis" is a kind of self-defense response of the body. When the body organs are dysfunctional, the internal organs fail to function properly, and the body will spontaneously make a defense response due to its own lesions, thus forming a protective response of "blood stasis", which is similar to the self-immune response of modern medicine. Scholars believe that this kind of defense response is beneficial. It's not true that you can prevent the development of disease and you can prevent the development of cancer. In recent years, Bi Liangyan et al. investigated the effects of blood-stasis activating drugs, such as Salvia miltiorrhiza, Radix Paeoniae, Rhizoma saffroni, Corydalis, Sodium ferulic acid and Chuanxiongzine, on the lung metastasis of liver cells in mice in more than 300 cases of blood-stasis malignant tumours treated with radiotherapy and chemotherapy combined with the method of activating blood stasis. The results showed that most of the drugs had the effect of promoting tumor metastasis; Fu Naiwu et al. found that Salvia miltiorrhiza had a significant promotion effect on intravascular hematological diffusion and metastasis in W256 rats; Ding Gang et al. reported that Salvia miltiorrhiza and Paeonia lactiflora had a significant promotion effect on VEGF expression in rats and promoted angiogenesis in rat tumors, thus increasing their chances of infiltration and metastasis. Therefore, we should be cautious in the treatment of tumours. We should conduct individual analysis and identification of the causes of blood stasis according to the time of tumour onset, the time of blood stasis, the tumour patient's constitution, the Chinese medical evidence, the tongue, the pulse and other factors, and try to find out the cause of blood stasis, whether it is an "etiological cause" or a "defensive reaction". It is important to find out the cause of blood stasis, whether it is the "cause of the disease" or a "defensive reaction", which plays a crucial role in the treatment of tumour patients and may even affect the prognosis of the tumour. Although it is still debated, it is still beneficial to the treatment of tumour patients, provided it is correctly identified and used appropriately [5].

In addition, a study by HeitJA et al. showed that the proportion of blood stasis evidence was the same in pre- and post-operative NSCLC, suggesting that surgical treatment did not change the patient's TCM symptoms, which suggests that "blood stasis" is highly relevant to lung cancer. In modern medicine, "blood stasis" can be interpreted as blood hypercoagulation, which is a common, highly morbid and dangerous disease in lung cancer patients and is closely related to their prognosis. It is mainly manifested as increased D-dimer or abnormal coagulation function. Panax notoginseng has the effect of activating blood circulation and resolving blood stasis. A study by Wu Yan et al. on Panax notoginseng wall-broken tablets showed that Panax notoginseng has some effect on coagulation and blood clotting, but there is a significant relationship with the use of the drug, when higher doses are used, the effect of Panax notoginseng can vary greatly, so clinicians can choose Panax notoginseng according to the actual situation. Also, this trial measured the D-dimer content at 0, 14 and 28 days. The results showed that the level of D-dimer in the control group of the lotus model gradually increased over time, while the level of D-dimer decreased significantly after TSPN gavage, and the degree of reduction of D-dimer was positively correlated with TSPN concentration. The results showed that TSPN could not only inhibit the expression of histone B, but also reduce the concentration of D-dimer, thus changing the blood viscosity, improving the prognosis and prolonging the survival rate of the patients. Therefore, although TSPN has the risk of activating blood circulation, promoting swelling and pain, and metastasis, it can still be used clinically as long as the evidence is correctly identified and varied from person to person.

5. Conclusion

"Stasis" is a state of the body, "stasis" is a disease mechanism, and blood stasis is a pathological product of "stasis". In the early stage of "stasis" syndrome, there is only Qi machine obstruction without blood stasis. In the stage of Qi machine obstruction, it will lead to blood hypercoagulation, abnormal blood rheology, slow blood flow rate and increase of D dimer, etc. With the deepening of the degree of Qi machine obstruction, Qi machine obstruction forms the stage of Qi stagnation and blood stasis, which is a kind of substantial blood stasis damage, mainly manifested by the formation of thromboembolus, the formation of vascular plaque, the thickening of blood vessel wall, the decrease of blood vessel elasticity, and the formation of local mass. Therefore, further breakthroughs can be made in the fields of molecular biology, pharmacology, drug extraction and drug research and development through the extraction and separation of active ingredients and the study of their anti-tumor action mechanism.

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Review of Tumor Suppressor Gene P53

Xin Wang, Ruowen Zhang*
Beihua University, Jilin 132000, China.

Abstract: **Background:** During tumorigenesis, cells proliferate unchecked, altering tissue homeostasis and leading to subsequent hyperplasia. This process parallels the recovery of cell cycle, abnormal DNA repair, and the passivation of apoptotic programs in response to DNA damage. In most human cancers, these processes are associated with dysfunctions of the tumor suppressor p53. As a key transcription factor, the evolutionarily conserved tumor suppressor p53 (encoded by TP53) plays a central role in response to various cellular stresses. A variety of biological processes are regulated by p53 such as cell cycle arrest, apoptosis, senescence and metabolism. Besides these well-known roles of p53, accumulating evidence show that p53 also regulates innate immune and adaptive immune responses. p53 influences the innate immune system by secreted factors that modulate macrophage function to suppress tumourigenesis. Dysfunction of p53 in cancer affects the activity and recruitment of T and myeloid cells, resulting in immune evasion. p53 can also activate key regulators in immune signaling pathways which support or impede tumor development[1]. Hence, it seems that the tumor suppressor p53 exerts its tumor suppressive effect to a considerable extent by modulating the immune response. In this review, we concisely discuss the emerging connections between p53 and immune responses, and their impact on tumor progression. Understanding the role of p53 in regulation of immunity will help to developing more effective anti-tumor immunotherapies for patients with TP53 mutation or depletion.

Keywords: P53; Tumor Suppressor Genes; Tumor; Cancer

1. Introduction

As a well-studied protein, p53's reputation largely stems from its role as a tumor suppressor, which is activated in response to stress signals such as genotoxic injury or nutrient deprivation [2]. Mutations in p53 are always accompanied by dysregulation of metabolism, migration and invasion, all of which ultimately lead to the development of clinical tumors and more aggressive malignancies [3]. Cancer cells can be recognized and destroyed by innate and adaptive immune effector cells, a process known as cancer immune surveillance [4]. In recent years, various studies have shown that p53 can also control tumor-immune system crosstalk. Loss of p53 in tumors causes changes in myeloid and T cell responses. Specifically, p53 deletion increases myeloid infiltration by enhancing cytokine secretion [5]. Furthermore, p53 dysfunction in some cases reprograms components of the tumor microenvironment, leading to changes in the immune milieu that exacerbate tumor progression. In addition to its ability to control cellular homeostasis to suppress tumorigenesis, accumulating observations suggest that p53 also plays a role in the inflammatory response [6]. Chronic inflammation creates potentially cancer-promoting conditions. In inflamed tissues, cytokines or inflammatory mediators can activate a variety of transcription factors, such as NF-κB and signal transducer and activator of transcription 3, which are critical for the promotion of cancer. Activation of NF-κB and STAT pathways leads to the enrichment of ROS in the TME, ultimately leading to chronic inflammation [7]. Growing evidence strongly suggests that p53 dysfunction in tumors enhances chronic inflammation, which in turn promotes tumor progression.

2. P53 and signal sensors and activators of transcriptional pathways

The signal sensors and activators of the transcription family are a group of transcription factors that regulate cytokine-dependent inflammation and immunity. Constitutive activation of STATs, especially STAT3, induces and maintains the primary inflammatory microenvironment to stimulate the initiation and survival of malignant cells. p53 regulates inflammatory responses through STAT3 activated by the inflammatory factor IL-6. Furthermore, loss of p53 in pancreatic cancer resulted in activated STAT3 phosphorylation, which was initiated by IL-6. Like NF-κB, STAT3 directly binds to the p53 promoter to repress p53 transcription, limiting its typical tumor suppressor function. Blocking STAT3 activates p53 expression, resulting in p53-dependent tumor cell apoptosis [8]. Studies have shown that tumor cells that rely on long-term STAT3 signaling are more sensitive to STAT3 inhibitors than normal cells. Therefore, STAT3 protein can be used as a new type of cancer treatment drug, and more effective and selective STAT inhibitors are expected to be developed in the future. Emerging studies have shown that the tumor microenvironment (TME) significantly affects tumor cell growth and invasion. The TME contains not only cells but also signaling molecules, extracellular matrix and mechanical signals. The immune landscape of the TME is composed of all these cells and molecules that support tumor transformation, protect cancer cells from host immunity, and provide a niche for metastasis. In addition to the cell-autonomous effects of p53, emerging evidence suggests that p53 can also exert effects on neighboring cells, namely the non-cell-autonomous activities of p53. Therefore, a better understanding of the function of p53 in the TME may be helpful for those with p53 mutations of cancer patients tailor-made personalized treatment.

3. Mutant p53 as a tumor antigen

Cancer cells are always accompanied by unstable genetic changes and produce new antigens to differentiate cancer cells from normal cells. The accumulation of p53 hotspot mutations in tumors is considered an immunocompetent neoantigen for immunotherapy. However, progress in this field has been limited by the efficiency of p53 mutant antigen recognition in cells [9]. A recent clinical trial in metastatic ovarian cancer showed that p53 hotspot mutations lead to infiltration of mutation-reactive T cells into ovarian cancer metastases. TIL and TCR genetically engineered T cells recognize tumor cell lines that endogenously express these p53 neoantigens. These results highlight the potential of p53 mutations as targets for T-cell immunity and gene therapy. Furthermore, increased p53 protein levels associated with p53 mutations were associated with the production of anti-p53 autoantibodies, reinforcing the potential role of p53 in regulating tumor antigenicity. While mutant p53 has shown promise in the field of immunotherapy, in some cases induction of specific antitumor responses can trigger immune evasion. Recent studies have shown that broad-spectrum vaccines generated from dendritic cell/tumor cell fusions can potentially prevent adaptive immune escape [10].

As a tumor suppressor, p53 has been extensively studied for its cell-autonomous inhibition of malignant tumors. Recently, increasing evidence has suggested a potential link between p53 and immune function, and p53 dysfunction is also associated with inflammation. Dysfunction of p53 in tumors not only regulates immune recognition, but also affects the interstitial compartment and plays an important role in controlling tumor progression. There are still many uncharacterized issues that may have broad implications for immunity and inflammation, which may ultimately lead to tumor development. For example, how exactly p53 dysregulation affects the immune response to various external or internal stimuli, and the role of p53 in immune cell development. Furthermore, loss or mutation of p53 may reprogram the microenvironment, especially the extracellular components of tumors, but the molecular regulatory mechanisms involved remain largely unknown. P53 mutations can promote tumor cell metastasis. During this process, how immune regulation and responses are altered, and in particular which immune cell functions are altered. In addition, the role of p53 in remote regulation and communication between different tissues or organs will also be a highly anticipated research direction.

4. P53 as a tumor suppressor

Genetic instability is one of the most prominent features of malignant tumors. There are very sophisticated systems for detecting DNA damage and repairing the genome. P53 plays an important role in this "guardian" system. When p53 responds to DNA damage, it causes cell cycle arrest or apoptosis [11]. A study in 1991 showed that wild-type p53 induced apoptosis in leukemia cells [12]. MDM2 is an E3 ubiquitin ligase that controls the degradation of p53. Many tumors overexpress MDM2, even those without p53 mutations. Targeting MDM2 to stabilize p53 seems promising, so many reports on targeting MDM2 or MDM2-p53 have been published. MI-219 is a small molecule that inhibits the MDM2-p53 interaction. MI-219 can also activate the p53 pathway in wild-type p53 cells. Apoptosis and cell cycle arrest were observed in xenograft tumors, resulting in tumor regression. However, MDM2 inhibition and p53 activation in normal tissues may be detrimental. Ringshausen et al. found that p53 is spontaneously activated in many tissues of mdm2-deficient mice. Furthermore, p53 triggers lethal lesions, including ablation of typically radiosensitive tissues [13].

5. P53 Cancer Treatment

Inhibition of p53 protects normal cells during genotoxic chemotherapy or radiotherapy. The side effects of genotoxic treatment of cancer are mainly caused by p53-mediated apoptosis. Small molecules can block p53-dependent transcriptional activity and protect mice from lethal side effects associated with anticancer treatments. If we can avoid the dose-limiting genotoxic pressure on normal cells during cancer chemotherapy or radiotherapy, higher doses may be available for those patients who have an inadequate response to conventional chemotherapy [14].

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Author's brief introduction: Wang Xin (1998-), Female, Han Nationality, born in Qiqihar City, Heilongjiang Province, studying for a master's degree, majoring in pathogenic biology. Her research direction is prostate cancer.

Corresponding author: Zhang Ruowen, Researcher at Beihua University

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Analysis of Clinical Efficacy of Single-Port Endoscopic Breast-Conserving Surgery and Modified Radical Mastectomy in the Treatment of Early Breast Cancer

Zhu Wu[1], Zhuo Wang[2], Qingqing Ye[3], Rong Fan[*]
Jingzhou First People's Hospital, Jingzhou 434000, China.

Abstract: **Objective:** To analyze the effect of single-port endoscopic breast-conserving surgery and modified radical mastectomy in the treatment of early breast cancer. **Methods:** The research subjects included in this study were 52 patients with early breast cancer who were admitted to our hospital from February 2020 to February 2021. They were divided into control group and experimental group by random number table method. The control group received modified radical mastectomy(26 cases), and the experimental group received single-port endoscopic breast-conserving surgery (26 cases). The treatment effects of the two groups were compared. **Results:** The blood loss, incision length and hospital stay in the experimental group were lower than those in the control group (P<0.05), but the operation time was significantly longer than that in the control group (P<0.05). There were significant differences in breast beauty between the two groups, and the experimental group was better (P<0.05). **Conclusion:** Single-port endoscopic breast-conserving surgery and modified radical mastectomy are used in the treatment of early breast cancer, and the treatment effect of the former is significantly better than that of the latter. This treatment method can be promoted.

Keywords: Single-Port Laparoscopic Breast-Conserving Surgery; Modified Radical Mastectomy; Early Breast Cancer; Surgery-Related Indicators; Aesthetics

Introduction

Breast cancer is one of the most common malignant tumors in clinical practice, and it is one of the most common cancers that cause death in women. Effective treatment in the early stage of breast cancer can better control the patient's condition and improve the quality of life. In the treatment of this disease, modified radical mastectomy is often used, which can effectively remove the lesion tissue. However, this type of surgery is very traumatic and can have a great impact on the aesthetics of the patient's breasts, so as to cause psychological trauma to the patient, and then affect postoperative recovery. Single-port laparoscopic breast-conserving surgery has been used in clinical practice in recent years with minimal trauma and can ensure the beauty of the breasts. It is favored by the majority of patients with early breast cancer [1]. To this end, the effect of single-port endoscopic breast-conserving surgery and modified radical mastectomy in the treatment of early breast cancer was analyzed. The results of the study are detailed below.

1. Materials and methods

1.7 Basic information

The subjects included in this study were patients with early breast cancer who were admitted to our hospital from

February 2020 to February 2021, with a total of 52 cases. They were divided into control group and experimental group by random number table method. The control group received modified radical mastectomy (26 cases), and the experimental group received single-port endoscopic breast-conserving surgery (26 cases). The age of the experimental group was 32-51 years old, with an average of (35.65±2.43) years old. The age of the control group was 33-50 years old, with an average of (35.43±2.43) years old. The analysis of the basic data of the two groups of patients showed that there was no significant difference in the age of the patients (P>0.05).

1.8 Methods

1.8.1 Control group

Modified radical mastectomy was performed in this group, and the patients were treated with anesthesia. A 20 cm transverse fusiform incision was made on the nipple and areola as the center points. The skin flap is freed between the subcutaneous and superficial fascia, up to the lower clavicle to the anterior sheath of the rectus abdominis, inside to the outer border of the sternum, outside to the anterior border of the latissimus dorsi, the thickness of the skin flap is 0.5 cm, and the breast and basal thorax are sharply dissected. The myofascia major reaches the outer edge of the pectoralis major muscle, the coracoclavicular fascia is incised, the axillary adipose lymph node tissue is removed, the axillary lymph node is dissected preventively according to the direction of the axillary vein, the breast tissue is excised, and the axillary lymph node dissection is followed by hemostasis , the incision is sutured layer by layer, followed by compression bandaging.

1.8.2 Experimental group

In this group, single-port laparoscopic breast-conserving surgery was performed. The patients were injected with methylene blue 0.5 ml circumferentially at a position 1 cm outside the tumor edge 15 minutes before surgery to mark the pre-resection margin and establish a laparoscopic surgery space. A 2 cm incision was made on the outer edge of the pectoralis major muscle, and the skin flap and the superficial glandular space were bluntly separated with a tunnel device. A single-hole laparoscopic Trocar and surgical instruments were placed through the hole, and the tumor lesions were excised laparoscopically for pathological diagnosis. For patients with negative margins, the axillary incision should be made along the dermatoglyphics, and lymph nodes should be dissected. For patients with positive margins, the scope of resection should be increased, and lymph node dissection should be performed after negative margins. After the operation was determined whether there was active bleeding, a negative pressure drainage tube was placed, which was drawn out through a single-hole incision, and the remaining glands were sutured with a barbed thread under the laparoscope, followed by pressure bandaging.

1.9 Performance criteria

(1) To observe and record the relevant indicators (operation time, intraoperative blood loss, incision length, hospitalization time) during the two groups, and make a comparative analysis.

(2) Observe the beauty of the breasts of the patients after surgery, and judge by their appearance and feel. Criteria: no difference between the appearance and feel of the breast and preoperative is excellent; there is a certain difference between the appearance and feeling of the breast and the preoperative difference, and the detection difference is between 0.8 and 1.5 cm, which is good; the difference between the appearance and feeling of the breast is obviously poor.

1.10 Statistical methods

The data obtained in the study were processed by SPSS 23.0 software. ($\bar{x}$ ±s) is used to represent measurement data,

using t test; (%) is used to represent count data, using (x^2) test. When the calculated P<0.05, it was suggested that there was a significant difference between the compared subjects.

2. Results

2.1 Comparative analysis of surgery-related indicators between the two groups

The intraoperative blood loss, incision length and hospital stay in the experimental group were lower than those in the control group (P<0.05), but the operation time was significantly longer than that in the control group (P<0.05). See Table 1 for details.

Table 1 Comparative analysis of surgery-related indicators between the two groups（$\bar{x} \pm s$）

Groups	Number of cases	Operation time（min）	Intraoperative blood loss（ml）	Incision length（cm）	Hospital stay（d）
Experimental group	26	125.43±12.32	32.43±11.32	6.76±0.43	11.65±1.54
Control group	26	96.54±11.54	55.43±12.54	3.24±0.45	16.76±1.67
t	-	8.726	6.942	28.837	11.470
P	-	0.001	0.001	0.001	0.001

2.2 Comparative analysis of postoperative breast aesthetics between two groups

There were significant differences in breast beauty between the two groups, and the experimental group was better (P<0.05). See Table 2 for details.

Table 2 Comparative analysis of postoperative breast aesthetics between the two groups [n, (%)]

Groups	Number of cases	Excellent	Good	Poor
Experimental group	26	20（76.92%）	5（19.23%）	1（3.85%）
Control group	26	10（38.46%）	10（38.46%）	6（23.08%）
χ^2	-	7.879	2.342	4.127
P	-	0.005	0.126	0.042

3. Discussion

Breast cancer is one of the most common malignant tumors in the clinic. The disease can be caused by many factors, and its incidence is relatively high, which can pose a greater threat to the life of patients, so the early diagnosis and treatment of the disease are of great importance. significance. In clinical treatment of this disease, surgery is often used to control the patient's condition and improve its life cycle. With the increasing improvement of people's living standards, their health concepts and aesthetic concepts have also improved. Female patients also pay more attention to aesthetics when they need

effective treatment effects.

Modified radical mastectomy is a common surgical method for the treatment of early breast cancer, which can preserve the breast of patients. However, this method can produce large scars on the breast surface, which cannot meet the aesthetic needs of patients. At the same time, the large incision and high intraoperative blood loss are not conducive to the postoperative recovery of patients. Single-port laparoscopic breast-conserving surgery requires a small incision and low intraoperative blood loss, which will not affect the aesthetics of the breast [2]. The results of this study showed that the intraoperative blood loss, incision length and hospital stay in the experimental group were lower than those in the control group ($P<0.05$), and the operation time was significantly longer than that in the control group ($P<0.05$). It is suggested that single-port endoscopic breast-conserving surgery can reduce the amount of blood loss and the incision is small, but its operation time is longer. Marks are removed, and laparoscopy is required to establish an operating area during the operation, which prolongs the operation time. There were significant differences in breast beauty between the two groups, and the experimental group was better ($P<0.05$). It is suggested that single-port laparoscopic breast-conserving surgery can ensure the aesthetics of the patient's breasts, because the incision required by the operation is small and will not cause major trauma.

In conclusion, single-port laparoscopic breast-conserving surgery and modified radical mastectomy are used in the treatment of early breast cancer, and the treatment effect of the former is significantly better than that of the latter. This treatment method can be promoted.

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Evaluation of the Effect of PETCT in the Examination and Diagnosis of Lymphoma Patients

Bingqiang Xu, Mingqing Kou* ***Corresponding authors: Dr. Mingqing Kou**
Shaanxi Provincial People's Hospital, Xi'an 710068, China.

Abstract: Objective: To analyze the effect of PET in the diagnosis of lymphoma. Methods: 42 patients with lymphoma admitted to our hospital from January 2018 to December 2019 were selected as the study subjects. All patients were examined by ultrasound and PETCT, and the examination results were observed and analyzed. Results: The positive rate of ultrasonic examination was 69.05% (29/42), and the positive rate of PET examination was 78.57% (33/42). There was significant difference between groups (P<0.05); The sensitivity, specificity and accuracy of PETCT in lymphoma patients were 91.67%, 83.33% and 90.48%, respectively. There was significant difference between the two groups (P<0.05). Conclusion: PETCT examination of lymphoma patients has high positive detection rate, sensitivity, specificity and accuracy, and can make accurate diagnosis of the disease.

Keywords: Lymphoma; PETCT; Diagnosis

Introduction

Lymphoma is a malignant tumor disease originating from the lymphohematopoietic system, which has a high incidence rate in China [1]. Lymphoma patients often have clinical symptoms such as night sweating, fever, emaciation and itching after the onset, which will affect the physical and mental health and quality of life of patients. If the patients cannot be properly treated, the disease will endanger the life safety of patients. Before clinical treatment for lymphoma patients, it is necessary to check and diagnose the patient's condition, and carry out targeted treatment for patients according to the inspection results. Therefore, a reasonable inspection and diagnosis mode plays a very important role. This article mainly studies the effect of PET in the examination and diagnosis of lymphoma patients, as shown below.[2]

1. Data and methods

1.1 Data

42 lymphoma patients admitted by Hohhot First Hospital from January 2018 to December 2019 were selected as the subjects of this study. Among all the selected patients, there were 28 male patients and 14 female patients, the minimum age was 26 years old, the maximum age was 71 years old, with an average of 48.53 ± 4.66 years old.

1.2 Methods

All patients received ultrasonic examination and PETCT examination. The ultrasonic examination method is: use the PhillipHD11 color Doppler ultrasound diagnostic instrument produced by Phillip Company in the Netherlands for examination and diagnosis. The probe frequency is 5.0 ～ 7.5MHz. Use the fan scanning probe and the abdominal probe to jointly scan the pelvic cavity of all patients. At the same time, pay attention to the location, scope, size, echo Blood flow

signal, etc., send the examination results to the attending physician to provide targeted treatment for patients. PETCT examination method: use Biograph16HRPET-CT scanner produced by Siemens in Germany to examine and diagnose the patient, instruct the patient to fast for 6 hours before examination, and control the patient's blood glucose level below 7.0 mmol/L to improve the quality of examination; Then, the patient was given intravenous injection of F-FDG with a dose of 3.70 ～ 5.55 MBq/kg to keep the patient quiet for 60 minutes, and then PET was performed. The slice thickness was controlled at about 5.0 mm, and transverse, sagittal and coronal images were obtained to diagnose the patient's condition.[3]

1.3 Observations

The positive detection of lymphoma patients and the sensitivity, specificity and accuracy of the two methods were observed and compared.

1.4 Data processing

SPSS22.0 software was used to process the data in the paper. For counting data $\chi 2$ Inspection and percentage (%) statement. $P < 0.05$ indicates statistically significant.

2. Results

2.1 Positive detection of lymphoma patients

The positive rate of patients with lymphoma was 69.05% (29/42) after ultrasonic examination and 78.57% (33/42) after PETCT examination, with significant difference between groups ($P<0.05$).

2.2 Comparison of sensitivity, specificity and accuracy of the two methods

The sensitivity, specificity and accuracy of PETCT in lymphoma patients were 91.67%, 83.33% and 90.48% respectively. There was significant difference between the two groups ($P<0.05$).

3. Discussion

Lymphoma is a kind of tumor disease that has a certain impact on the health of patients in clinic. If we do not do a good job in the diagnosis and treatment of the disease, it will not only affect the normal life of patients, leading to the continuous deterioration of the patient's condition, and even lead to the death of patients. Therefore, in order to ensure the smooth progress of the patient's disease treatment, it is necessary for the detection personnel to carry out strict detection of the patient's disease.[4]

In the past, ultrasonic diagnosis, as a common diagnostic measure used by inspectors during disease diagnosis, can provide more help for patients' disease treatment. However, with the continuous improvement of medical technology in China, in order to promote the quality of patient diagnosis, PETCT diagnostic measures are more and more widely used in the actual diagnosis work. PETCT examination is a new examination method, which can check the proliferation of tumor cells, organ functions and body blood perfusion of patients. It is not only conducive to the diagnosis of patients' diseases, but also can help medical staff to judge the tumor stages of patients, improve the accuracy of patients' disease diagnosis, and actively help patients to continue to promote disease treatment, It is an important means to improve the relationship between doctors and patients.[5]

Lymphoma is a common malignant tumor disease in clinic. It originates from the lymphohematopoietic system and is related to virus, pathogen infection, gene mutation and other factors . Most patients with lymphoma will have painless lymph node enlargement, as well as fever, itching, emaciation and other clinical symptoms, which pose a serious threat to the health

and life safety of patients. [6] In clinical practice, before the treatment of lymphoma patients, it is necessary to check and diagnose the patients' diseases to determine their specific pathological conditions, and then formulate targeted treatment for patients to improve the treatment effect. In the past, ultrasonic examination was mainly performed on patients in clinical practice. This method can play a better diagnostic effect, but it is still prone to misdiagnosis and missed diagnosis. PETCT can check the growth of tumor cells, organ function, body blood perfusion, etc., and can significantly improve the accuracy of diagnosis. The results showed that the positive rate of patients with lymphoma was 69.05% (29/42) after ultrasonic examination and 78.57 (33/42) after PETCT examination, with significant difference between groups ($P<0.05$); The sensitivity, specificity and accuracy of PETCT in lymphoma patients were 91.67%, 83.33% and 90.48% respectively. There was significant difference between the two groups ($P<0.05$). To sum up, PETCT examination for lymphoma patients can significantly improve the positive detection rate of the disease and the diagnostic accuracy of the disease, with high application value.[7]

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The Relationships of the Type of Needle and the Flushing of the Needle with the Satisfactory Rate of Thyroid Nodule Fine Needle Biopsy

Chonman Ieong, MeiLeng Ieong
Radiology Department of Centro Hospitalar Conde de S. Januário, Macao 999078, China.

Abstract: **Objective**: To explore the factors that affect the satisfactory rate of fine needle aspiration biospy(FBAB)sampling of thyroid nodules and the effects of different needle types and needle flushing methods on the satisfactory rate of FNAB sampling. **Methods**: The clinical data of 190 patients with thyroid nodules (200 nodules in total) who underwent FNAB from June 2020 to December 2020 were analyzed. The relationship of the satisfaction rate of sampling with the type of puncture needle and the flushing method of the puncture needle was analyzed. **Results**: In 200 thyroid nodules, we found that the nondiagnostic rate (37%) with a larger needle (22G) was lower than that with a smaller needle (25G) (55%), and the difference was statistically significant ($P < 0.05$). In the analysis of the comparison of the satisfaction rate of the flushing of the puncture needle, it was found that the nondiagnostic rate of the flushing method was lower (24%) than that of the nonflushing method (68%), with a statistically significant difference (< 0.05). In the randomized test according to the size of the puncture needle and the flushing method, the nondiagnostic rates of the four groups (25G needle with flushing group, 25G needle without flushing group, 22G needle with flushing group and 22G needle without flushing group) were 34%, 76%, 14% and 60%, respectively. Moreover, there was no significant change in the diagnosis rate of benign and malignant lesions in the obtained samples ($p=0.912$). **Conclusion**: In fine-needle biopsy of thyroid nodules, a larger needle should be used in combination with the flushing method to reduce the nondiagnostic rate and improve the pathological diagnosis rate.

Keywords: Thyroid Nodules; Fine Needle Biopsy; Needle Flushing

Introduction

Thyroid nodules are common thyroid diseases, with a prevalence of 4-7%. Malignant nodules account for approximately 5 ~ 15% of the total number of thyroid nodules [1]. It is the primary purpose of thyroid nodule diagnosis to identify benign and malignant thyroid nodules, which can not only reduce the economic and mental burden of patients but also be particularly important for disease treatment and prognosis. At present, fine needle aspiration biopsy (FNAB) is considered the most convenient, safe and effective method to detect benign and malignant thyroid nodules [2]. However, when using FNAB as a clinical examination means, misdiagnosis and missed diagnosis are inevitable [3]. It is reported in the literature that approximately 1/5 of thyroid nodules cannot be clearly diagnosed by pathology [4]. It is considered that dissatisfaction with specimens is the most common reason for the low positive rate. At present, some studies have found that the diameter and type of puncture needle are the factors affecting the dissatisfaction of nodule puncture specimens [5-6], and some studies have reported that the flushing of the puncture needle may have an impact on the satisfaction rate of puncture specimens [7]. This study combines these two factors to analyze whether they have an impact on the nondiagnostic rate of specimens.

Methods

A total of 190 patients with thyroid nodules who underwent FNAB in our department from June 2020 to December 2020 were enrolled, with a total of 200 nodules. All patients were informed before the operation and signed informed consent to undergo FNAB. We randomly divided the patients into four groups according to the use of different sizes of puncture needles and whether the puncture needles were rinsed: the group using 25G needles with flushing, the group using 25G needles without flushing, the group using 22G needles with flushing, and the group using 22G needles without flushing. Inclusion criteria: We first used ti-rads (ACR ti-rads) published by the American Society of Radiology in 2017 for classification. According to the ACR ti-rads guidelines, nodules that were rated above TR3 with a size reaching the puncture index were all included in this study. Exclusion criteria: nodules rated as TR2 or below and nonthyroid origin nodules.

All punctures were performed by the same interventional radiologist with technical experience (more than 5 years). The puncture process was as follows: the patient reclined on his or her back, Betadine iodine solution ®) was applied on the skin over the nodule, and a 22G or 25G needle was connected with a specimen aspirator (CYTOMAT) for puncture. Under the guidance of ultrasound, the puncture successfully entered the nodule and began to aspirate samples. Three to five back-and-forth suctioning motions were performed in different directions, and then the sample was injected into a solution containing 10 ml of normal saline by a puncture needle without repeated flushing. Then, Papanicolaou technology was used to stain the cells.

In patients in the flushing group, in addition to the described process, the puncture needle was injected into a solution containing 10 ml of normal saline for 5-10 repeated flushes. Then, Papanicolaou technology was used to stain the cells.

The cytological and pathological classification of thyroid nodules referred to the Bethesda system classification standard, and the diagnosis of thyroid nodules by cell smear was divided into I ~ VI: class I, the samples are unsatisfactory or the samples cannot be used for pathological diagnosis; class II, considered benign lesions; class III, atypical cell lesions with ambiguous meaning or follicular lesions with ambiguous meaning (AUS/flu); and class IV, follicular tumors or suspected follicular tumors. Class I is regarded as unsatisfactory for needle aspiration cytology samples, and classes II to VI are regarded as satisfactory for needle aspiration cytology samples.

SPSS 22.0 statistical software was used to analyze and process the data. The measurement data are expressed as the means ± standard deviations ($x \pm s$). The chi square test was used for the comparison of the count data, and the four grid table method was used for the comparison between and within the measurement data groups. $P < 0.05$ indicates significance.

Results

A total of 200 thyroid nodules were included in this study. Table 1 shows the basic characteristics of the patients studied. We found that there was no significant difference in age, sex, TSH, plasma concentration of free T3 or free T4, thyroid nodule grade or nodule size.

In different study groups (Table 2), we found that the nondiagnostic rates of the four groups of samples were 14%, 36%, 60% and 74%. The sample nondiagnostic rate of the group using 25G needle without flushing was the highest(74%). Moreover, it was found that the group using a thicker needle, 22G, plus flushing had the lowest nondiagnostic rate of 14%. There was a significant difference ($P < 0.05$). Among the groups using different sizes of puncture needles(Table 4), the nondiagnostic rates of 22G and 25G puncture needles were 37% and 55%, respectively, and there was a significant difference ($p=0.01$). In the comparison of the flushing method(Table 5), the nondiagnostic rates of the group using puncture needle flushing and the group without flushing were 24% and 68%, respectively, which were significantly different ($p<0.05$). Among the groups with pathological diagnosis(Table 3), the malignant diagnosis rate was 4 - 10%, which was not statistically significant. This indicates that the use of different sizes of puncture needles and lavage or not had no effect on

the differentiation of tumor properties.

Table 1 Demographic characteristics of the selected patients

Case(s)	200
Age (year)	47.28± 17.03
Sex	Male-69 Female-131
TSH level (normal range: 0.5 to 5.0 mIU/L)	2.89±1.2
Free T3 (normal range: 0.9-2.8 nmol/L)	1.96 ± 0.59
Free T4 (normal range: 0.7-1.53 ng/dL)	1.14 ± 0.41
ACR TI-RADS classification	
TR3	137
TR4	49
TR5	14
The size of nodule(cm)	3.54 ± 1.23 cm

Table 2 Comparison of basic data of each group

	25G with needle flushing group	25G without needle flushing group	22G with needle flushing	22G without needle flushing	P value
Case(s)	50	50	50	50	
Age (years)	48.62±17.62	47.80±17.19	44.74±15.67	47.96±17.56	0.727
Sex	F-39, M-11	F-38, M-12	F-33, M-17	F-30, M-20	0.163
TSH level(mIU/L)	2.92±1.27	3.01±1.30	2.99±1.11	2.63±1.1	0.398
Free T3 (nmol/L)	2±0.57	1.93±0.55	1.95±0.59	1.96±0.66	0.951
Free T4 (ng/dL)	1.14±0.4	1.19±0.43	1.07±0.46	1.16±0.43	0.557
ACR TI-RADS classification					0.881
TR3	33	35	33	36	
TR4	13	12	13	11	
TR5	4	3	4	3	
The size of lesion(cm)	3.62±1.29	3.61±1.37	3.34±1.14	3.59±1.14	0.527

Table 3 Comparison of nondiagnostic rate and nodule results after puncture in each group

	25G with needle flushing group	25G without needle flushing group	22G with needle flushing group	22G without needle flushing group	P value
Nondiagnostic(cases)	17 (34%)	38 (76%)	7 (14%)	30 (60%)	0.000
Benign	30 (60%)	10 (20%)	38 (76%)	13 (26%)	0.912
Malignant	3 (6%)	2 (4%)	5 (10%)	2 (4%)	0.912

Table 4 Comparison of the nondiagnostic rate of puncture needles with different sizes

	22G needle group	25G needle group	P value

Nondiagnostic(cases)	37(37%)	55(55%)	0.01

Table 5 Comparison of nondiagnostic rates between the groups with and without flushing puncture needles

	Needle flushing group	No needle flushing group	P value
Nondiagnostic(cases)	24 (24%)	68 (68%)	0.00

Discussion

Thyroid cancer is the most common malignant tumor of the endocrine system in the clinical setting [8]. Although high-frequency ultrasound is the first choice for screening thyroid nodules and differentiating benign and malignant thyroid nodules, it can only give a clear diagnosis of benign and malignant thyroid nodules. Puncture biopsy has become an inspection technique to further judge the benign and malignant nature of nodules. However, due to the associated tissue damage, relatively weak controllability, and strict requirements for puncture target nodules, puncture biopsy has limited clinical application. In contrast, as a minimally invasive and relatively controllable inspection method, fine-needle puncture can be performed on an outpatient basis. Moreover, the sensitivity and specificity of ultrasound-guided FNAB in the diagnosis of thyroid cancer can be as high as 98% and 100%, respectively [9].

To improve the diagnostic efficiency of puncture cytology specimens, the Bethesda reporting system was proposed by the American Cancer Institute in 2007 [10]. It is reported in the literature that according to the Bethesda report system classification that if FNAB puncture results are undiagnosed or unsatisfactory, approximately 4% of nodules may still be malignant tumors [11]. Therefore, improving the satisfaction rate of cytological specimens with diagnostic significance is of great significance to the clinical diagnosis and treatment of thyroid nodules. Obtaining satisfactory cytological specimens is not only a prerequisite for reducing false negative diagnoses of FNAB in thyroid nodules but can also significantly increase the sensitivity and specificity of FNAB [12-13].

In this study, we found that the nondiagnostic rates of using 22G and 25G puncture needles were 37% and 55%, respectively. The difference was statistically significant (p-0.01). The diameter of the 22G needle is larger than that of the 25G needle, so the 22G fine needle has more tissue cells than the 25G needle, less interference of blood cells, and more sufficient tissue cells for smear. It is easier to obtain a better sample successful rate for 22G fine needles than 25G fine needles when puncturing thyroid nodules. The nondiagnostic rates of the samples in the different groups with and without flushing the puncture needle were 24% and 68%, respectively. When the puncture needle enters the nodule to suck up cells, some of the cells will remain in the puncture needle. When flushing repeatedly, the cells remaining in the puncture needle can be washed into the test tube to increase the number of cell samples and improve the probability of diagnosis, increasing sensitivity and specificity. Therefore, in the group using 22G needles with rinsing, the sample nondiagnostic rate was the lowest(14%). Therefore, this study indicates that the use of a larger puncture needle with flushing can improve the sample satisfaction rate of fine-needle puncture and increase the pathological diagnosis rate.

There are some limitations in this study. The number of specimens in this study was small (200 cases), and this study was a single-center study. More research is needed in the future.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Preparation and Characterization of Epitope-Based Ratiometric Fluorescent Molecularly Imprinted Polymers

Xicheng Yang[1], Hongjuan Zhang[2], Hongliang Xin[2] , Yankun Gao[2*]
1.Jinling High School, Nanjing 210029, China.
2. Nanjing Medical University, Nanjing 211166, China.

Abstract: In order to solve the problem of difficult detection of neuronal nitric oxide synthase in the screening of neuronal nitric oxide synthase-postsynaptic density95 (nNOS-PSD95) uncoupling agent, this study used 133 amino acids ($nNOS_{1-133}$) at the nitrogen terminal of nNOS as template molecules, carbon dots and quantum dots as ratio fluorescence recognition elements, SiO_2 as matrix for the first time, combined with surface molecular imprinting technology and antigen-determining principle, to prepare ratiometric flurescent molecularly imprinted polymers (RFMIPs). The resulting RFMIPs were characterized by fourier transform infrared spectroscopy, scanning electron microscopy, transmission electron microscopy and thermogravimetric analysis，exhibiting uniform spherical morphology, which unambiguously confirmed the successful formation of the nanosensor. The result indicates that the synthesized sensors have promising potential for the assay of trace peptides in complex matrices.

Keywords: Fluorescent Nanosensor; Molecularly Imprinted Polymers; Preparation; Characterization

1. Introduction

Molecular imprinting simulates the reaction between antigens and antibodies in living organisms, which can memorize the size and shape of template molecules and interact with the coordination groups of template molecules [1]. The technology using small molecule compounds as templates, has been widely applied in environmental monitoring, food testing and drug separation [2-4]. However, the preparation of molecularly imprinted polymers (MIPs) using biological macromolecules such as peptides and proteins as templates is still challenging [5]. The exposure fragment of the target protein (epitope) with small structure is used as the template molecule to identify the target protein according to the cavity generated by the epitope, which can greatly reduce the uncertainty of the imprinting process and has a broad application prospect in protein detection [6,7].

In order to improve the sensitivity of MIPs detection, fluorescent materials have been introduced into molecular imprinting technology as sensitive sensors [8]. Quantum dots (QDs), a traditional nano-fluorescent material, has been widely used in the field of molecular imprinting, especially in the detection of proteins due to its wide excitation spectrum and narrow symmetric emission spectrum [9]. Carbon dots (CDs), a new type of fluorescent nanomaterial which has attracted great attention from biologists, show good stability and low toxicity in aqueous solution. Therefore, studies on the combination of CDs and molecularly imprinted technology in the field of proteins are also emerging [10]. However, if only the intensity of a single emission wavelength is used to quantitatively detect the target protein, the accuracy of the detection result is lower, because the fluorescence intensity of a single wavelength may be disturbed by light scattering, changes in the microenvironment near the probe, differences in the stability of excitation light source, and changes in protein concentration around the probe. In order to minimize these interference factors, ratiometric fluorescence is introduced into molecular

imprinting, and the concentration of the target protein is determined based on the ratio of the two emitted light intensities, which can improve the accuracy of the detection results.

In addition, QDs are often combined with SiO_2 to prepare fluorescent nanocomposites compatible with water systems and organic systems, which can be used in biological and chemical fields. The commonly used method is to directly wrap the QDs in SiO_2, but this will greatly reduce the fluorescence efficiency of the QDs, and at the same time loss the complete protection of QDs. In order to reduce the fluorescence quenching of QDs, the CdTe QDs were first fixed on the surface of SiO_2 sphere and then coated with a layer of silicon to form a nanocomposite fluorescent sphere with electrostatic interaction between positive and negative particles [11]. Hundreds of CdTe QDs particles were assembled on the surface of the same silicon sphere, which can play the role of amplifying the fluorescence signal layer by layer and improve the efficiency of fluorescence detection.

Considering the above, we have successfully constructed a biomimetic fluorescent nanosensor based on molecularly imprinted polymers modified with CDs and QDs which is also capable of rapid, highly sensitive and selective detection of nNOS in biological samples, where CDs were used as transducer elements and MIPs were used as recognition. The schematic illustration of the procedure is given in Fig. 1.

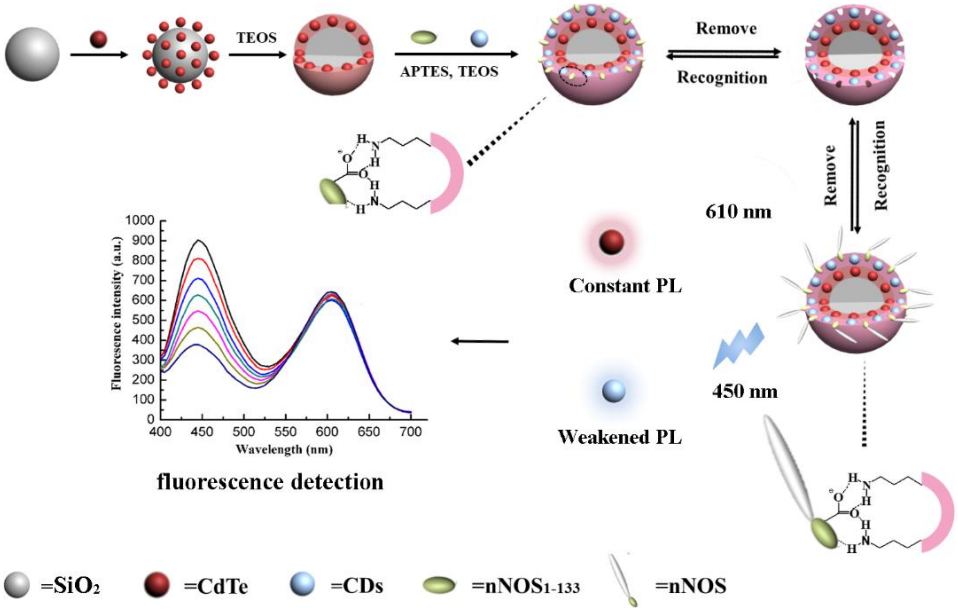

Fig. 1 Scheme of the preparation and the recognition process of RFMIPs

2. Experimental

2.1 Materials and Apparatus

Tellurium power, cadmium acetate ($CdAc_2 \cdot 2H_2O$), 3-mercaptopropionic acid (MPA), 3-aminopropyltriethoxysilane (APTES) and tetraethoxysilane (TEOS) were purchased from Aladdin (Shanghai, China). Sodium borohydride ($NaBH_4$) and ammonia ($NH_3 \cdot H_2O$) were obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). A shake culture box (ZHLY-180, China) and temperature magnetic mixer of C-MAG HS 7 (IKA Processing Equipment, Germany) were used during the experiment.

2.2 Preparation of SiO_2-NH_2, CdTe QDs and functionalized CDs

Monodisperse amino-functional SiO_2 nanoparticles were prepared according to the Stöber method. 15 mL $NH_3 \cdot H_2O$,

2.5 mL TEOS and 250 mL ethanol were added into a three-necked bottle, stirred magnetically at 40 °C for 12 h. Afterwards, 1.3 mL TEOS/APTES (12:1, v/v) was added dropwise and then the reaction was kept for 12 h. Finally, the product was washed with ethanol and water to neutrality, and then freeze-dried for later use.

The preparation of red fluorescent CdTe QDs is as follows: The reaction system was strictly controlled without oxygen. 1 mM tellurium powder and 10 mM $NaBH_4$ were added into 10 mL water, and continuously stirred until Te was completely reacted, resulting in colorless or pale pink transparent liquid, namely NaHTe solution. Afterwards, 2 mM $CdAc_2 \cdot 2H_2O$ was dissolved in 150 mL ultrapure water, mixed with 4.8 mM MPA, and the pH of the system was adjusted to about 10 with NaOH (1 M) solution. Then the NaHTe solution prepared above was stirred magnetically at 95 °C for 8 h. The product was purified by ethanol and then dried for later use.

Aminosilane-modified CDs were synthesized by a one-step hydrothermal method. 0.8 g sodium citrate was completely dissolved in 16 mL ultrapure water, then 4 mL APTES was added and continuously stirred magnetically for 20 min to mix well. The mixture was then transferred to a 50 mL polytetrafluoroethylene reactor and reacted in an oven at 200 °C for 2 h. Then, the obtained product was dialyzed in a 500 KDa dialysis bag for 24 h and concentrated to 10 mL for later use.

2.3 reparation of SiO_2@CdTe@SiO_2

First, 80 mg SiO_2-NH_2 nanoparticles were added in 20 mL ultrapure water, after ultrasonic dispersion, 1 mg CdTe QDs and 1 mL phosphate buffered saline (PBS, pH 5.5) were added successively. After being magnetically stirred for several minutes, the CdTe QDs were assembled on the surface of SiO_2-NH_2 by electrostatic interaction to generate SiO_2@CdTe. Afterwards, the resulting SiO_2@CdTe were centrifuged, washed with ultrapure water, and dispersed again in 6 mL water. The Stböer method was still used to wrap SiO_2 layer in the outer layer of SiO_2@CdTe. 48 mL anhydrous ethanol and 210 μL APTES were added to the above solution and stirred at 40°C for 3 hours. Then 480 μL $NH_3 \cdot H_2O$ and 240 μL TEOS were added dropwise and reacted for 6 h to form SiO_2@CdTe@SiO_2 (SS). The resulting product SS was centrifuged, washed with anhydrous ethanol to remove impurities, then washed with water to neutrality, and freeze-dried for use.

2.4 Preparation of RFMIPs

2 mg $nNOS_{1-133}$ and 160 μL APTES were added into 20 mL PBS, magnetically stirred and then reacted for 1 h in the dark to form pre-polymerization solution. Afterwards, 10 mL PBS solution was added in which CDs and 20 mg SS were dispersed, and magnetically stirred for 1 h, then 200 μL $NH_3 \cdot H_2O$ and 200 μL TEOS were added, and reacted at 40 °C in the dark for 12 h. The reaction product was eluted with methanol/0.1 M sodium hydroxide (9/1, v/v) to remove $nNOS_{1-133}$, and the remaining methanol and sodium hydroxide were removed with ultrapure water, and then freeze-dried to obtain RFMIPs. The template protein $nNOS_{1-133}$ was not added during the preparation of ratiometric fluorescent molecularly non-imprinted polymers (RFNIPs). The rest of the preparation was the same as RFMIPs.

2.5 Characterization of RFMIPs

The characteristic absorption peaks of the infrared spectrum (FT-IR) in the range of 4000-500 cm^{-1} were investigated and analyzed. Scanning electron microscopy (SEM), transmission electron microscopy (TEM) and high-resolution scanning electron microscopy (HESEM) recorded the morphology and structure of the synthesized nanoparticles, and thermogravimetric analysis (TGA) detected the thermal stability of the polymer.

3. Results and discussion

3.1 Preparation of RFMIPs

The preparation of RFMIPs was shown in Fig. 1. In this experiment, SiO_2 with an amino functional group was first prepared. As shown in Table 1, the amino functional group would be protonated under slightly acidic conditions, making SiO_2-NH_2 positively charged. SiO_2-NH_2 and CdTe had a zeta potential of 11 and -33 mv in buffer solution (pH 5.5) respectively. After the formation of SiO_2@CdTe through electrostatic assembly, it was found that the zeta potential changed to -21. The decrease of the zeta potential indicated that CdTe was adsorbed on the surface of SiO_2-NH_2. In order to protect the CdTe on the surface of SiO_2@CdTe, the surface layer of silica was further modified to form SS. After the modification was completed, it was found that the Zeta potential level was equivalent to SiO_2-NH_2.

Table 1 Diameter distribution and Zeta potential of particles

Particles	Diameter/nm	Zeta potential/mv (pH=5.5)
SiO_2	88	-18
SiO_2-NH_2	101	11
CdTe	10	-33
SiO_2@CdTe	122	-21
SS	151	8

3.2 Characterization of RFMIPs

3.2.1 Electron microscope analysis

In this experiment, TEM and SEM were used to analyze the morphology of the nanoparticles synthesized at each step. Fig. 2A and 2B are high-resolution scanning electron microscope images of CDs and CdTe respectively. From the figure, it can be seen that the edges of the two were not clear and the shape was irregular. The particle size of CDs and CdTe was about 11 nm and 10 nm respectively. Fig. 2C-F and Fig. 2c-f were SEM and TEM of SiO_2-NH_2, SiO_2@CdTe, SS, and RFMIPs, respectively. Fig. 2C and Fig. 2c showed that SiO_2-NH_2 was a round shape with smooth surface and the hydrated particle size was about 100 nm. Due to the small particle size of CdTe, the morphology of SiO_2@CdTe was not significantly different from that of SiO_2-NH_2 in the SEM, but it can be clearly seen from the TEM that a large number of black spots were adsorbed on the surface of the silicon sphere, indicating that the connection of CdTe by static electricity was successful. Compared with SiO_2-NH_2, the hydration particle size of SiO_2@CdTe increased by about 22 nm. After further modification of a layer of silicon, the shape of SS was similar to that of SiO_2-NH_2, and it remained a relatively round sphere. No wrapped CdTe was observed from TEM, and the hydrated particle size was about 150 nm. After the preparation of the imprinted layer, the surface of the RFMIPs became rough, the particle size further increased, and the hydrated particle size was about 220 nm. The observation of the electron micrograph showed that each step in the experiment was successfully synthesized.

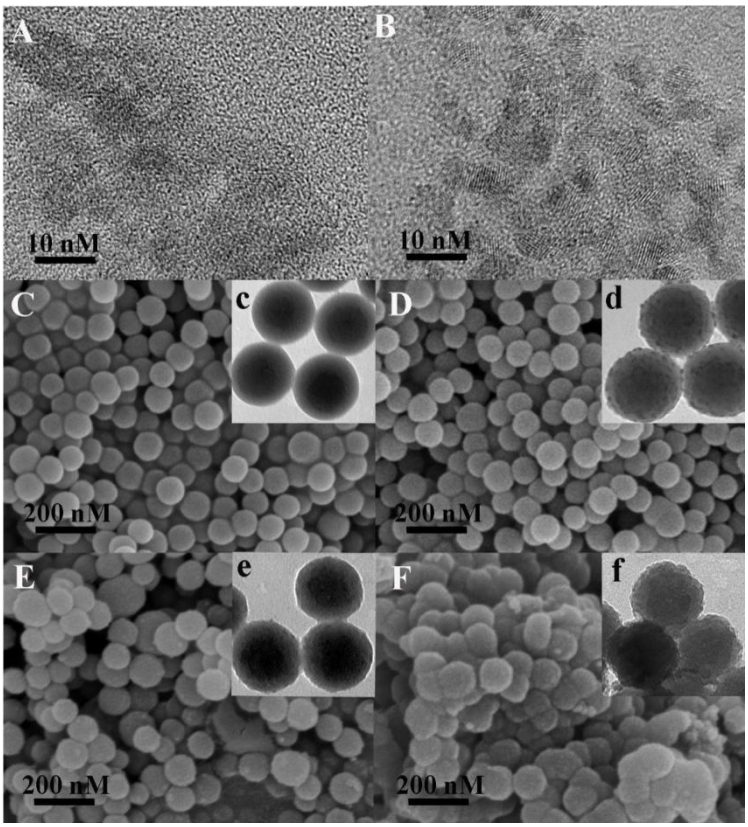

Fig.2 High resolution SEM images of (A) CDs and (B) CdTe; SEM images of (C) SiO_2-NH_2、(D) SiO_2@CdTe、(E) SS and (F) RFMIPs; TEM images of (c) SiO_2-NH_2、(d) SiO_2@CdTe、(e) SS and (f) RFMIPs

3.2.2 Infrared analysis

To verify the successful preparation of RFMIPs, FT-IR scanning was performed on the prepared CDs, CdTe, SiO_2-NH_2, SiO_2@CdTe, SS, and RFMIPs. As shown in Fig. 3A (a), the stretching vibration peaks of the carboxylate on MPA appeared at 1560 cm^{-1} and 1408 cm^{-1}, indicating that the MPA-modified CdTe were successfully synthesized. The absorption at 799 cm^{-1} and 1096 cm^{-1} was caused by the vibration of Si-O-Si. Compared with the infrared curve (3A (b)) of SiO_2-NH_2, the characteristic absorption of MPA was added on the SiO_2@CdTe curve (3A (c)), indicating that CdTe was electrostatically assembled on the surface of SiO_2-NH_2. In 3B (a), the absorption of amino-functionalized CDs at 2800-3000 cm^{-1} and 1403 cm^{-1} was attributed to the stretching vibration and in-plane bending vibration of C-H. The absorption at 1595 cm^{-1} was due to the out-of-plane bending vibration of N-H. SS (3B (b)) only contained the characteristic peaks of Si-O-Si. After the synthesis of RFMIPs (3B(c)), the characteristic peak of CDs can be clearly observed, which indicated the successful preparation of RFMIPs.

3.2.3 Thermogravimetric analysis

TGA evaluates the thermal stability of RFMIPs between 25-800 °C. As shown in Fig. 3C, when the temperature reached 200 °C, RFMIPs had a weight loss of about 6.3% in the first stage, which may be caused by evaporation of some organic solvents and physically adsorbed water. When the temperature exceeded 400 °C, the weight loss in the second stage started to accelerate, which may be because the imprinted lay er of RFMIPs started to degrade and reached stability at 600 °C, and the weight loss at this stage was about 10.4%. The experiments showed that SMMIPs had good thermal stability and usability in the range of 25-200°C.

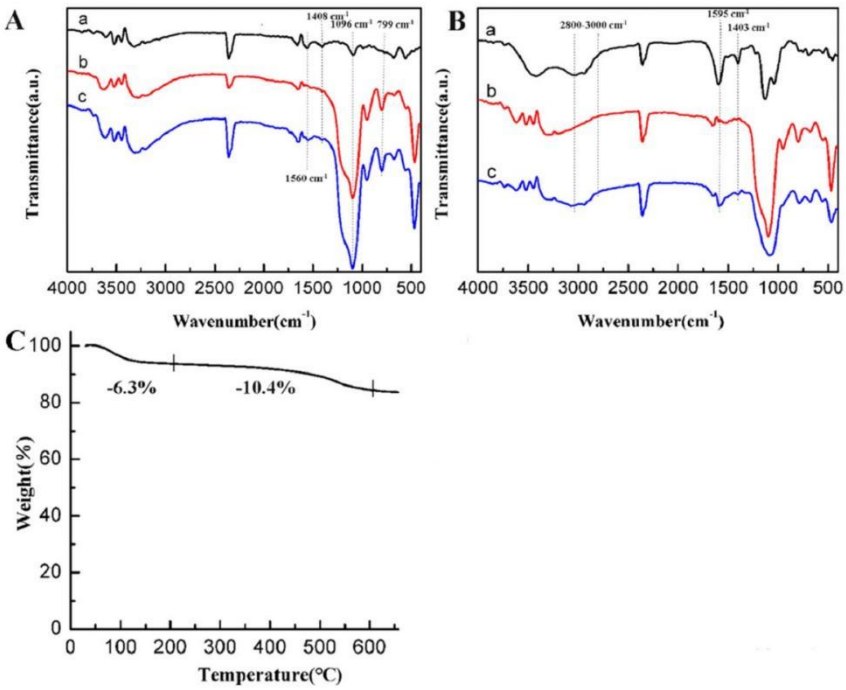

Fig. 3 (A) FT-IR spectrum of (a) CdTe, (b) SiO_2-NH_2 and (c) SiO_2@CdTe, (B) FT-IR spectrum of (a) CDs, (b) SS and (c) RFMIPs, (C) the thermogravimetric weight loss curve of RFMIPs

4. Conclusion

In this experiment, a combination of molecularly imprinted technology, epitope imprinting and nano-fluorescent materials was used to prepare RFMIPs, which was used for sensitive detection of nNOS. This method combines the selectivity and stability of an epitope-imprinted polymer with the sensitivity of ratio fluorescence. It could specifically recognize the template molecule nNOS.

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Analysis of Metabolic Factors Associated with Hyperuricemia in Diabetes Mellitus

Min Zhang, Yanming Ren
Qinghai University, Xining 810016, China.

Abstract: After the occurrence of diabetes in patients, with the increase of the course of disease and the increase of the age of patients, the incidence of other combined diseases in patients is also increasing. Diabetes combined with hyperuricemia is a common clinical disease, and 40% of patients with diabetes will develop hyperuricemia and other complications, which not only makes the treatment of the disease more difficult, but also increases the burden of the hospital. Therefore, to analyze the metabolic factors related to hyperfatemia, and to provide a reference for the clinical exploration of active and effective treatment.

Keywords: Diabetes Mellitus; Hyperuricemia; Metabolic Factors

Introduction

Diabetes mellitus is a common chronic disease in clinical practice, and patients are often complicated with hyperglycemia, hyperuricemia and other complications. Related studies have shown that there is a certain relationship between hyperuricemia and diabetes[1]. This paper studies the internal pathogenesis and rules of diabetes combined with hyperuricemia, providing a new basis for the clinical prevention and treatment of diabetes combined with hyperuricemia.

1. Overview of the correlation between hyperuricemia and diabetes mellitus

Hyperuricemia refers to the hypersaturated state of urate in the extracellular fluid. It is characterized by the disorder of purine metabolism and the increase of uric acid in the body. It is generally believed that hyperuricemia should be considered when blood uric acid ≥420umol/L(7mg/L) in males and ≥360umol/L(6mg/L) in females.

Uric acid (UA) is the end product of purine metabolism in the human body. One third of purines in the body come from food breakdown, two thirds are synthesized by the body itself, and most purines are oxidized and metabolized by the liver into uric acid. The daily production is approximately equal to the excretion, 1/3 is excreted by the intestine, and 2/3 is excreted by the kidney. The kidney is the main way of uric acid excretion. After blood uric acid is filtered from the glomeruli, 98% of uric acid is reabsorbed by the proximal tubules, and finally, less than 10% of uric acid is excreted into the urine by the distal convoluted tubules. Blood uric acid (SUA) concentration depends on the balance between the amount of purine synthesis, the amount of ingested and the amount of uric acid excreted. If uric acid is generated too much or excreted too little, uric acid metabolism will lose balance, and uric acid will accumulate in the body, leading to elevated blood uric acid, hyperuricemia (HUA), and a series of pathophysiological changes.

With the rapid development of economy in recent years, the occurrence of hyperuricemia not only gradually increases, but also tends to occur at an earlier age. At present, it is clinically found that the age of 30 to 39 years old is prone to hyperuricemia, which may be related to genetic factors, mental factors, lifestyle (diet, alcohol consumption, physical

exercise). After puberty, serum uric acid levels increase more rapidly in men than in women and peak at age 50. The serum uric acid level of females does not rise significantly after puberty, but rapidly rises to a level similar to that of males after menopause, possibly because estrogen can promote the excretion of uric acid by the kidney. In the 40 to 59 age group, hyperuricemia is associated with a cluster of diseases, such as hyperuricemia with hyperuricemia, hypertension, obesity, and diabetes. This is mainly related to metabolic risk factors such as renal excretory dysfunction and insulin resistance. It is worth exploring the relationship between diabetes mellitus combined with hyperuricemia and these metabolic diseases.

2. Analysis of metabolic factors related to hyperuricemia in diabetes mellitus

Uric acid is the end product of purine metabolism in the body. In the body, uric acid is mainly degraded by urate oxidase (uricase) in the liver to produce allantoin, and then excreted by the kidney. Uric acid levels in the body is mainly affected by two aspects, on the one hand is to make increased uric acid to produce factors (10%), such as high purine or protein diet is taken, alcohol consumption, the high level of cell metabolism, and the shortcomings of the purine metabolic enzymes, etc., on the other hand is reduce uric acid excretion factor (90%), two-thirds of renal excretion by the blood uric acid, a third by the bowels, After glomerular filtration, 98% of uric acid is reabsorbed by proximal tubules, and less than 10% is finally excreted into urine by distal convoluted tubules[3]. For example, the renal excretion capacity decreases, the glomerular filtration rate decreases, the renal tubular reabsorption increases (such as the use of thiazide diuretics), and the blood uric acid increases.

The occurrence of hyperuricemia in diabetic patients is the result of increased production or decreased excretion. The reasons may be as follows :① Microangiopaplasia is common in diabetic patients, and renal microangiopaplasia leads to renal ischemia and decreased renal blood flow, while uric acid excretion is directly proportional to renal blood flow, so blood uric acid increases. ② Uric acid, as one of the most widely distributed water-soluble antioxidants in the human body, has the property of iron as a mixture, which can reduce the incidence of lipid peroxidation and stabilize the serum ascorbic acid from oxidation. In some patients, oxidative stress is aggravated and large blood vessels are damaged. Uric acid compensatively increases to counter this oxidative reaction, resulting in hyperuricemia. ③ Elevated serum uric acid can further damage islet B cells. Hyperuricemia is also one of the clinical manifestations of metabolic syndrome. The pathogenesis of diabetic hyperuricemia is also related to hyperinsulinemia caused by insulin resistance. Because it increases urinary sodium excretion in proximal convoluted tubules, it competitively inhibits uric acid excretion. It is known that glucose and uric acid are competitively reabsorbed in the proximal convoluted tubules of the kidney. Increased excretion of urine sugar will competitively inhibit uric acid reabsorption, resulting in a decrease in blood uric acid level. When blood glucose is well controlled, urine sugar decreases, uric acid reabsorption increases, and blood uric acid increases. It is suggested that the decrease of renal function can increase the serum uric acid level, 8 but the blood glucose level is not the cause of the abnormal uric acid metabolism. Studies have shown that body weight is an independent risk factor for diabetes mellitus complicated with hyperuricemia. The mechanism of association between obesity and hyperuricemia may be the decreased expression or clearance of leptin gene in serum of patients with hyperuricemia. Atherosclerosis induced by high level of serum uric acid in patients with diabetes may be deposited directly in the arteriolar wall through uric acid stones, and then damage the intima through purine metabolism and lipid metabolism. Hyperuric acid, hyperglycemia and hyperlipidemia have superposed pathogenic effects to accelerate the process of atherosclerosis, while hypertension can also cause renal microvascular sclerosis, increase the concentration of angiotensin and catecholamines, reduce renal blood flow, and accumulate hypoxic lactic acid in local tissues, which compete with blood uric acid for excretion, and increase blood uric acid[4].

On the other hand, uric acid crystals in diabetes can promote blood pressure by stimulating renin angiotensin system

and inhibiting nitric oxide synthesis[5]. At the same time, uric acid crystals are deposited in the vessel wall, which promote lipid peroxidation, increase the generation of oxygen free radicals, and participate in the inflammatory reaction. Recent studies have also found that hypertension is related to genes related to vascular proliferation and sclerosis, such as upregulation of uric acid transporter I and cyclooxygenase-2 genes on vascular wall. It can be seen that hyperuricemia is closely related to hypertension and its atherosclerotic complications. Stepwise regression analysis showed that Ccr, body weight and LDL-C were independent risk factors for diabetes mellitus complicated with hyperuricemia. These results indicated that the increase of serum uric acid level in diabetes mellitus was closely related to obesity, lipid metabolism disorder, elevated blood pressure, IR and metabolic syndrome. Elevated serum uric acid level is an important characteristic of insulin resistance syndrome.

3. The prevention of hyperuricemia

For asymptomatic hyperuricemia patients with family history of gout or blood uric acid >535umol/L and 24h urine uric acid >5.9mmol/L, drugs should be used to reduce uric acid. At present, drugs to reduce uric acid are mainly divided into two kinds: uric acid excreting drugs (benbromarone) and uric acid inhibiting drugs (allopurinol), the former can inhibit uric acid. Reabsorption of uric acid by renal tubules increases uric acid excretion. Generally applicable to the type of uric acid excretion reduction, taking method :50mg, once a day. Allopurinol can inhibit the activity of xanthine oxidase, thereby reducing the biosynthesis of uric acid and decreasing the concentration of blood uric acid. Allopurinol is commonly used in patients with increased uric acid production. How to take: Starting dose 50mg, 3 times a day, gradually increased to 300-600mg/d. It is worth pointing out that the above two types of drugs must be used after the control of acute inflammation in gouty arthritis (2 weeks after the acute attack). Colchicine or non-steroidal anti-inflammatory drugs should be used in acute gout attacks.

4. Summary

To sum up, high uric acid hematic disease is common complications of diabetes, are caused by lipid metabolism disorders in body, is in patients with atherosclerosis, stroke and other chronic cardiovascular disease risk factors, treatment and prevention of diabetic high blood uric acid is an important content of current medical research, is of great significance to reduce chronic cardiovascular disease clinically. Since hyperuric acid, hyperglycemia, dyslipidemia and hypertension complement each other and promote the formation of atherosclerosis and the aggravation of insulin resistance, it is necessary to not only control fasting blood glucose, blood pressure, blood lipids and obesity, but also pay attention to the risk factor of hyperuric acid in patients with T2DM and give timely treatment relevant interventions.

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The Mechanism and Some Controversies of SGLT2 Inhibitor Protects the Cardiovascular System

Shuo Zhang
The School of Public Health, Xiamen University, Xiamen 361102, China.

Abstract: SGLT2 inhibitor, a kind of hypoglycemic drug, whose mechanism is to suppress glucose reabsorption in proximal renal tubules in the kidney to promote the excretion of glucose, has been demonstrated to have a positive effect on our cardiovascular system and reduce the risk of suffering from cardiovascular events. In this review, we will focus on four aspects to elaborate on its mechanism. First: diuresis and electrolytes, second: blood pressure, hormone, and nerve, third: regulating lipid metabolism, and the last: the direct effect on cardiomyocytes. This paper presents some puzzles of different mechanisms, aiming for waiting to be answered in later research.

Keywords: Sglt2 Inhibitor; Cardiovascular Event; Heart Failure; Metabolization

Introduction

SGLT2 inhibitor is a new kind of oral antihyperglycemic drug. It has been confirmed that making some differences to the cardiovascular system, whether accompanied by type 2 diabetes. There have been many clinical trials that discovered the drug can improve the outcomes of heart failure patients, reducing the risk of hospitalization. There are many possible mechanisms existing, such as reversing myocardial remodeling, improving water-sodium retention, inhibiting inflammatory response, regulating lipid metabolism, and so on. In this paper, we want to explain the different functions and potential benefits of SGLT2 inhibitors to people suffering from cardiovascular disease, making guidance for future clinical usage.

1. Natriuretic diuresis and electrolyte regulation

The diuresis effect of the SGLT2 inhibitor is still in debate. We think its diuretic effect may be mainly caused by the natriuretic effect. It can only increase urine output for a short period. It can prompt the excretion of glucose for a long time, which is the primary pharmacological action. Its effect on sodium excretion is complex. Though it suppresses the function of sodium-dependent glucose transporters 2, its natriuretic effect is not as significant as we thought.[1] Scientists speculate that the ability of other parts of renal tubules and collecting ducts to reabsorb sodium and water increases compensatory over time. [1] This may lead to changes in other electrolytes in the urine and blood. Sodium-potassium transporter or sodium hydrogen transporter or other transporters may be activated secondarily and bring some unpredictable changes in ion distribution in the body. So far, it has not been found that it will bring severe fluctuations of electrolytes in the human body after taking the drugs for a long period.[2] But there have been studies showing that taking these drugs can affect the blood concentration of magnesium, chloride, and sulfate,[3] also SGLT2 inhibitors will increase serum phosphorus and PTH without affecting serum calcium.[4] Both of them can be explained by the activation of other channels in the kidney partly. In future clinical use, we need to be more careful when giving drugs to patients with electrolyte disorders, for it may have unexpected harm.

2. Improve volume load and pressure in neurohumoral aspects

This mechanism has a strong connection with diuresis. The renin-angiotensin- aldosterone system will be activated due to the sodium excretion effect in the early stage of medication, which will bring a short fluctuation of blood pressure. With the long-term use of the drug, the patient's blood pressure was observed to decrease notably. [5] For now, some idea has been presented. First, SGLT2 inhibitors can improve hematocrit, meaning that blood is concentrated and less body fluid.[6] Second, there is evidence showing that it can inhibit sympathetic activity and increase parasympathetic activity, which will bring slower heart rate and smaller contractions.[7] Now these two points are widely accepted.

The drug will also bring some changes to pulmonary circulation. Experiments have shown that the long-term application of dapagliflozin can effectively improve lung fluid volumes.[8] Empagliflozin can produce rapid reductions in pulmonary artery (PA) pressures that were amplified over time. The symptoms of heart failure have improved a lot. [9] However, these views are contradictory to the diuretic ability mentioned above, for its diuretic effect can't last for a long-time. Will changes in electrolyte concentration or blood glucose lead to the redistribution of body fluids within or outside cells or do SGLT2 inhibitors have the effect of dilating blood vessels related to the releasing of vasodilator? The specific mechanism is still waiting to be explored. In clinical application, this will effectively alleviate the symptoms of heart failure, especially left heart failure accompanied by pulmonary congestion.

3. Regulating lipid metabolism

With the further study of SGLT2 inhibitor, researchers found that it can regulate blood lipid profile. The evidence-based medicine has already confirmed that TC, HDL-L, and LDL-L increase significantly after taking that drug, and TG decreases. If we only focus on lipid profile, it is difficult to find its relationship with coronary atherosclerosis, because its control of different risk factors is contradictory.

The regulatory capacity of this lipoprotein is generally considered to be promoted the lipid efflux of macrophages by ameliorating insulin resistance, reducing the absorption of lipids, and accelerating their metabolism. [10] This can improve the fat metabolism of the liver, promote the degradation of VLDL and chylomicrons, and promote their conversion to HDL.

Its influence on LDL is still in huge debate. Some experiments still can't find a significant difference in the level of LDL after taking that drug. It brings more subtle changes, sdLDL-c decreases, and IbLDL-C increases, [11] which has little to do with AS. The mechanism of affecting LDL-C is not clear now. We can hypothesize that it may be caused by the ketogenic effect caused by the massive excretion of glucose. The liver transports cholesterol to various organs of the body using LDL to meet energy needs. But this can't explain the change of subspecies of LDL-C, which is a fascinating but puzzling alteration that needs further research. We predict that though the total amount of LDL increases, the risk of suffering from AS still decreases.

SGLT2 inhibitor will bring no reversion to the atherosclerotic or fat accumulation that has already occurred, however, the preventive effect brought by lipid regulation should be paid attention to, which may become a valuable role in clinical application.

4. Changes in myocardial metabolism

The function that regulating lipid metabolism will also bring some subsequent metabolic changes, especially in the myocardium. Due to the obvious ketogenic effect, we speculate that the ability of the myocardium to use the ketone body (KB) to provide energy will increase. Noteworthy, the high level of KB is a protection factor for our hearts. When suffering from acute myocardial infarction, KB will inhibit the inflammatory reaction, reduce necrotic area and effectively maintain mitochondrial function. [12] This is also equivalent to providing another layer of protection for our heart. The second

biomarker is uric acid. Experts think that a higher level of uric acid means a worse state of cardiac function. [13] Fortunately, experiments have confirmed that this medicine can reduce the concertation of uric acid which shows a better condition of the myocardium. [14] Except for KB and uric acid, SGLT2 inhibitor will also decrease myocardial blood flow (MBF). [15] The load on the heart is improved and may also have an impact on oxygen consumption. Both of these alterations may be the potential to safeguard our hearts. The harm of acute ischemia and hypoxia will be less because cells are more adaptive to that environment.

Conclusion

SGLT2 inhibitor was regarded as an oral hypoglycemic drug. The most amazing thing is that SGLT2 inhibitors can benefit all patients, whether accompanied by type 2 diabetes. It brings changes in the energy metabolism of the whole body. With more and more cardiovascular benefits being demonstrated, some scholars have recommended adding these drugs to the guidelines for the treatment of heart failure, although the specific mechanism is still waiting for us to explore. What surprises will SGLT2 inhibitor bring to us in the future? We look forward to it with complete confidence.

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Application of Nanotechnology in Oral Implantation Based on Exercise-Induced Tooth Injury

Yuxian Zhang*, Yao Huang*, Yekun Deng, Xinyi Chen, Jingchen Zhang, Jiayi Gao, Yibo Wang
Suzhou University, Suzhou 215031, China.

Abstract: With the development of sports in various countries, more and more people participate in sports, and the rate of sports injuries to the oral and maxillofacial system also increases, especially the dental injuries caused by boxing are more common. At the same time, with the improvement of modern production, people's basic needs have been continuously met, and more and more people have begun to pay attention to their physical health and appearance characteristics. Among them, dental plastic correction and restoration have received great attention. In addition, with the application of nanotechnology in various fields in recent years, scholars at home and abroad have also tried or have continued to introduce nanomaterials into oral clinics, in order to improve and develop the application of oral materials, so that the oral clinic can be continuously improved and developed. Therefore, this paper reviews the current situation of sports injury of the oral and maxillofacial system, the mechanical analysis of tooth injury, the current situation of tooth restoration and the application of nanotechnology in the field of oral implantation.

Keywords: Sports; Alveolar Bone Injury; Nanotechnology; Oral Implantation

1. Introduction

In maxillofacial injuries, the injury to the teeth caused by boxing is more common . According to the author's statistics, among the 770 maxillofacial injuries, 174 (22.60%) were dental injuries. Oral soft tissue injury is easy to bleed, and it is necessary to stop the bleeding in time. Tooth fractures are common in clinical practice, and different degrees of damage are difficult to repair, and the results are also different. Common restoration methods include removable dentures, fixed bridge braces and dental implants, among which dental implants are currently the most popular and suitable treatment for broken teeth. Tooth damage is mainly reflected in oral soft tissue damage, tooth fracture, alveolar bone fracture and tooth dislocation. The alveolar bone is a part of the skeleton of the whole body. The decrease in the bone density of the alveolar bone can weaken the structure of the jawbone and cause fractures easily. When oral and maxillofacial trauma is caused by sports and other reasons, the risk of anterior tooth loosening, dislocation and alveolar bone injury increases, and it is more common in clinical practice. However, due to insufficient bone mass during the treatment, the replantation in the operation area is often unsuccessful, or the denture repair in the later defect area is difficult to obtain effective support, resulting in decreased occlusal function and damaged appearance. If artificial bone can be used to repair the defect in time after trauma, it is expected to improve the height and fullness of the alveolar bone, establish a bony support structure, and create conditions for later denture repair or dental implantation .

1.1 Current status of oral and maxillofacial movement injuries

The oral cavity and maxillofacial region are the beginning of the respiratory tract and digestive tract, connected to the skull above and the neck below. The upper and lower jaws are the main skeleton, with teeth and tongue, rich blood supply,

and the trigeminal nerve and facial nerve are distributed in it. These special anatomical and physiological structures are the important basis for the injury characteristics of this part.Oral and maxillofacial injuries are also common in clinical practice, mainly including soft tissue injuries, pressure groove injuries, jaw fractures and other comprehensive fractures. Injuries to the oral cavity and maxillofacial area have a small fatality rate, but are extremely destructive to the face and function, and their treatment has become one of the directions that medical care has paid more and more attention to in recent years. Among the many sports injuries, oral and maxillofacial injuries have long received attention due to their high incidence, long treatment time, high treatment costs, and greater psychological impact on athletes, and have been recognized in many countries for a long time. are the most common sports injuries. A survey of 409 athletes showed that the sport with the highest injury rate was wrestling (83.3%), followed by boxing (73.7%), basketball (70.6%) and karate (60%) . Most of these injuries occur in the maxilla, especially the maxillary anterior teeth are the most vulnerable.

1.2 Mechanical analysis of tooth damage

Teeth can maintain firmness, mainly relying on the support of gingiva, cementum, periodontal ligament and alveolar bone. At the same time, due to the point-like contact between the teeth, the teeth are arched to form a dental arch, which increases the overall stability of the teeth. resistance. Under the action of severe external force, the gums, periodontal ligament fibers, and alveolar bone of the tooth are damaged, and the connection between the tooth and the alveolar bone is interrupted and falls off. Healthy teeth can withstand large vertical forces, but have poor tolerance to horizontal forces and rotational forces. These two external forces can cause horizontal displacement of teeth, loosening of teeth, and finally tooth dislocation. Some scholars believe that: the ratio of the tooth's resistance to vertical external force to that of horizontal external force is 62:1. Some people have tested that the vertical force that a tooth can accept is 485.7kg, while the horizontal force can only be tolerated. Tolerate 7.5kg. According to the determination: the world's top level boxer punching power can reach 500kg. Boxing feet can cause displacement or dislocation of teeth.

1.3 Current status of tooth restoration

The oral and maxillofacial area is a prominent and exposed part of the human body, and its trauma is often accompanied by alveolar trauma.If the alveolar bone defect combined with alveolar trauma is not repaired in time, the teeth on both sides will be displaced to the missing side, and the maxillary teeth will be displaced to the opposite side, which will lead to the reduction of the interdental space and the narrowing of the alveolar bone to a certain extent. Low and flat, it is not conducive to the restoration of implant dentures and traditional dentures, and affects the occlusal function and appearance. The traditional treatment method is to first perform debridement and suture for alveolar trauma, arch splint fixation and root extraction, etc., and the denture is restored after the alveolar bone and mucosal damage has healed [3]. However, with the gradual improvement of people's requirements for the quality of life, people pay more attention to the appearance and image, so they also have higher requirements for the aesthetics of teeth when restoring teeth. Dental implants are widely used in dental restorations because of their high aesthetics, comfort, and chewing rate, meeting people's requirements for aesthetics. The basis of dental implant restoration is sufficient alveolar bone volume, but the problem of insufficient dental implant bone volume often occurs in dental implant restoration, which brings difficulties to dental implant restoration. Therefore, the development of ideal artificial bone materials to repair bone defects has become the focus of research in the fields of medicine and biomaterials.

2. Technology and application

2.1 Surface Nanotechnology

With the development of nanomaterials and nanotechnology, surface nanotechnology has become an important direction in the development of surface technology, and it is also one of the important contents of today's nanotechnology.Surface nanotechnology is to prepare some materials into nano-scale powders by modern surface preparation technology and fix them on the surface of objects, so that the materials can obtain new functions and structures, such as high hardness, wear resistance, corrosion resistance, etc. Using nano-surface technology Karksson Met al. formed a nanoporous alumina coating on the surface of titanium alloy implants, and co-cultured with human osteoblasts in vitro. The results were detected by biochemical and morphological methods. Osteocytes showed a normal growth pattern, the number of cells increased continuously, and the phenotype of osteoblasts was normal. Polyacrylamide gel electrophoresis and Western blotting showed that the nanoporous alumina coating could adsorb fibronectin, which was beneficial to bone-implantation. Early healing of the body interface. The long-term stability of implants is not only dependent on osseointegration, but also affected by the healing of soft tissue around the implants. Areva Set al. applied the sol-gel method to form a nano-scale porous titanium dioxide coating on the surface of pure titanium implants and implanted them into the body. After two days of implantation, the adhesion between the coating material and the surrounding soft tissue was observed. The nano-coated implants quickly made contact with connective tissue, while the pure titanium control group formed a fibrocystic encapsulation on the implant surface. This good soft tissue attachment may be due to the titania coating initiating the nucleation and growth of calcium phosphate on the coating surface.

2.2 Nano-artificial bone materials

Nano-scale bone material is a new type of artificially synthesized bone repair material, which has no toxic and side effects, and can be absorbed, degraded and vascularized. The preliminary clinical use of nano-artificial bone shows that it has good biocompatibility with the human body, no immune rejection, and good healing . It is true that sufficient bone mass in the implantation area is the key to the success of oral implantation. Studies have shown that if the bone defect is greater than 1 mm, bone grafting should be sought to facilitate the growth of new bone and the early retention of the implant. nHAC is a new type of nano-hydroxyapatite material independently developed by my country. It imitates the natural bone structure by compounding collagen and hydroxyapatite, and modifies it with polylactic acid, so that the nanostructure is very close to natural bone and has better porosity and biocompatibility. Compared with the previously prepared mineralized collagen composite materials, the mineralized collagen matrix material has more similar characteristics to natural bone tissue in terms of composition and microstructure. Collagen-based nanobone porous framework materials have a three-dimensional pore network structure similar to that of natural cancellous bone, which is beneficial to the transport of nutrients, the migration and growth of cells, and the subsequent formation of new bone tissue after implantation in vivo . Zhu Fei et al. used it to repair mandibular defects in rabbits, and the results confirmed that nHAC has good biocompatibility, and has obvious effects on promoting and accelerating the healing of bone wounds, and the osteogenesis process matches the resorption process of the implant.

3. Conclusion

In a word, in this world where sports are developing and people value self-image, people's attention to teeth is gradually increasing, and clinical medical care also attaches great importance to dental restoration technology and materials used,expect to find more complete methods and more suitable materials. . The birth of nanotechnology and the excellent

properties of nanomaterials that are different from other ordinary materials will determine that it will play an increasingly important role in the study of sports injuries, and provide certain methods for the treatment of sports injuries. practical basis. Nanotechnology in stomatology will also promote the further development of prosthodontics, expanding the indications of prosthodontics, improving the biomechanical properties of prostheses, prolonging the service life of dentures, and improving the success rate of implant restorations. In this regard, it plays an irreplaceable role.

About the author: Yuxian Zhang 1998.10, Han, Zhijin County, Bijie City, Guizhou Province, Suzhou University, Cells, Bone development.

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Progress of Autophagy Related Research in the Treatment of Ophthalmic Diseases

Zuyan Zhang[1], Xueqing Deng[1], Ying Su2*, Feng Wang[1*]

1. Department of Ophthalmology, the Fourth Affiliated Hospital of Harbin Medical University, Harbin 150001, China.

2. Department of Ophthalmology, the First Affiliated Hospital of Harbin Medical University, Harbin 150000, China.

Abstract: Autophagy is a process in which some organelles and proteins are wrapped by cells into specific membranes and then transported to lysosomes to degrade these membranes, ultimately degrading small molecules and energy. Autophagy can make cells have a certain tolerance to starvation, and remove damaged organelles and protein structure dislocation caused by cell aging, so as to balance the intracellular environment. Autophagy includes autophagy molecules, microactive autophagy and macrophage autophagy. The mechanism characteristics of autophagy itself have aroused the upsurge of relevant application research, and more and more diseases are related to it. This paper reviews the research progress of autophagy in novel clinical application of autophagy.

Keywords: Autophagy; Keratopathy; Retinal Diseases; RPE Degeneration; Glaucoma; RGCs Apoptosis

1. Instruction

Cell autophagy process mainly occurs in eukaryotic cells, make the cell without ribosome connected ER generate bilayer membrane, and these membrane structures will be to be cleared proteins, organelles to form autophagomes [1], these autophagy experience to lysosome, make the autophagy material to degradation, and then generate autophysosomes, complete the intracellular organelle update and cell metabolism process [2], is essential for maintaining cellular homeostasis under stressful conditions [3].

2. Discovery and application of autophagy characteristics in multiple domains

IL-13 in chronic inflammatory airway disease activates autophagy in epithelial cells of respiratory system and directly induces the cellular secretion of mucin and oxidative stress in chronic asthma and COPD. This finding is particularly important when analyzing an defined state of autophagy viability in epithelial cells of airway of asthma. The association of autophagy with AMPK and MTOR [4], the crucial molecules in the process of immune metabolism, serves as a promoting factor or inhibitor of inflammation of tumor and act on tumor developing, vascular growth, grade malignancy, and the likelihood of metastasis. Autopophagy-associated secretion can affect the tumor microenvironment, and plasma and possible monitoring of proteins that mediate autophagy in tumors can be treated as surrogate indicators of autophagy activity within tumor cells. In the field of neurodegeneration, although plenty of number of studies linking autophagy to neurodegenerative diseases[5], lacks convincing clues to link inflammation through autophagy[6]. Furthermore, Atg5-induced epithelial

autophagy prevents renal fibrosis by blocking G2/M resistance, which is an important host defense mechanism [7].

3. Discovery and application of autophagy in keratopathy

To effectively maintain the stability of corneal epithelial cells, the cilia generation and autophagy process play an unnegligible role and coordinate molecular involvement through E phA2. In order to strengthen the autophagy effect, rapamycin suppresses the negative regulator rapamycin target protein, thus alleviating the degree of TGFβI mutation, which shows that if the autophagy is insufficient, it is easy to cause the problem of corneal undernutrition. Some substances with toxic toxicity such as lithium metal and rapamycin can promote cellular autophagy in the form of substrate, which have significant effect in relieving and healing degenerative neurological diseases (8). In herpeskeratitis, autophagy is controlled by the rapid induction of HSV-1 infection through an innate immune response. In echanthamoeba keratitis, it was found that low concentrations (0.00125%) autophagy inhibitors can fully remove echanthamoeba cells while ensuring the relatively safe state of epithelial cells, which also provides a new way in the fields related to treating eye diseases.

4. Discovery and application of autophagy in retinal diseases

In treating retinal diseases, cell autophagy is important,and the regulation of autophagy is able to create an alternative therapeutic strategy for retinoid disorders. Targeted autophagy can prevent retinal cell death by inhibiting the process of apoptosis, to recover denatured proteins and organelles to rebuild the retina, increased clearance of denatured mitochondria, decreased oxidative stress induced by ROS, and decreased activity of retinal microglia has found that in diabetic retinal (DR) lesions, The density of RGCs decreased gradually with the prolongation of the disease. High glucose can cause autophagy in RPE. Age-related dysfunction in RPEs is noted to be a cause of retinal diseases. The inflammatory response to amyloid B induced RPE dysfunction may be mediated by SIRT6. Autopophagy regulated by SIRT6 may be a pro-inflammatory mechanism of amyloid-b induced RPE dysfunction. SIRT6 causes inflammation mainly by promoting macrophage.

Studies have shown that a significant number of mirnas targeting autophagy, small RNA molecules and epigenetic regulators have been found in AMD patients and in experiments. It opens up prospects for the application of autophagy targets in AMD therapy. The results also showed that autophagy was involved in the protective effect of H2S on apoptosis of retinal ARPE-19 cells induced by oxidative stress. These findings led us to discover the possibility of exogenous H_2S in treating AMD.

In addition, studies that upregulate basal autophagy by targeting the protein factor Rubicon could help to prevent RPE damage caused by aging and inflammation caused by photoinduced cell stress, oxidative stress under intermittent high-glucose conditions, induced RPE damage, and autophagy could be important in mitigating this process. Protein HMGB1 mediates signaling in both ways.

5. Progress of autophagy in the trabecular meshwork

Autopophagy promotes the antioxidant process of trabecular mesh cells and opens new ideas for the treatment of open-angle glaucoma. Autophagy functions in regulating fibroblast formation in TM cells through BAMBI and Smad2/3 signaling. The significance of autophagy in inducing fibrotic responses opens up a new field for studying therapeutic targets to improve TM fibrosis. Dysregulates the autophagy in trabecular mesh sheets and retinal structure as the old, and suggests that this abnormal autophagy regulation helps with nerve damage in glaucoma.

RGCs death has been related with a variety of visual disease. Oxidative stress damages mitochondria through a variety of mechanismsand induce cell apoptosis. The structural functional features of long axons and long lives of RGC make them sensitive to lack of energy, they are more susceptible to dysmitochondria and more sensitive to oxidative stress. When undernutrition, hypoxia, ischemia and other stress reactions occur,oxidative stress and intracellular ROS accumulation is

very important in stimulating autophagy. Other studies have shown that apoptosis in RGC cells caused by the E50K mutation (OPTNE50KNTG) of the OPTN gene also has some therapeutic basis.

6. Role of autophagy in RGCs

Long axonal neurons with myelinated structures within the central nervous system constitute retinal ganglion cells, the axon through which the optic nerve can deliver retinal captured signals to the CNS of the brain. Compared to other neurons, the blood supply to the cell body and to the RGC axons is different, resulting in neurons being extremely sensitive to differential stress damage. Autopagy is an adaptive response to various stress conditions. It has been found that autophagy within the dendrites with gradually increasing IOP in RGCs is activated in the first time, starting to exert its protective role on the cells. Immediately thereafter, partial autophagy occurs in the cytoplasm that ultimately causes apoptosis. Relevant studies speculate that neuronal axons are rich in mitochondria, which can therefore detect the body's chronic ischemia in time, thus first triggering autophagy to maintain cellular homeostasis, and terminating apoptosis by eliminating damaged mitochondria and releasing energy to prevent cell necrosis by catabolism. However, as IOP increases gradually, autophagy in neurons is also activated, homeostasis is disrupted, and cell viability may be reduced. If the intraocular pressure increases dramatically,the autophagy of the retina is unbalanced, and the autophagy activity in the retinal ganglion cell layer (retinal ganglion cell, GCL) increases immediately, mainly in the cell body and in a short time. The progression of various optic neuropathy is influenced by individual differences and environmental factors, making the degree of oxidative stress and autophagy vary in the RGC. If we increase autophagy in the early stages of neuropathy,the death of RGCs might be reduced in axons, pending further investigation.

7. Enhanced autophagy to reduce RGC apoptosis due to mutations in the OPTN gene-associated glaucoma

OPTN (Optiineurin) is involved in cell signal transduction, vesicle transport and autophagy. The E50K mutation (OPTNE50KNTG) in OPTN gene leads to the increase of Optineurin (OPTN) in pluripotent stem cells in normal intraocular glaucoma (NTG) patients. NTG induces OPTNE50K cell aggregation, astrocyte activation, decreased RGC number, and increased apoptotic cell death. Timolol reduces OPTNE50K-positive regions and reduces insoluble OPTNE50K, so we predict that timolol has the potential to reduce OPTNE50K increasing. It can also increase ath5-positive cells, resulting in a reduced number of tunel-positive cells, and increased LC3B-II/LC3B-I values, and thus reduced p62 expression levels. These results suggest that timolol may increase autophagy intensity and decrease OPTNE50K. It is a potential therapeutic agent for OPTNE50KNTG because it can reduce the increase of OPTNE50K in RGC by enhancing autophagy and neural protection. TBK1 protein kinase may be used in the treatment of e50K-OPTN and M98K-OPTN-induced glaucoma in the future because TBK1 inhibitors strongly inhibit M98K-OPTN apoptosis induced in retinal cells. Given the role of OPTN in the immune signaling pathway, the immune effect of OPTN in glaucoma needs further study.

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About author: Zuyan Zhang (1997.2.14), female, Han, from Da'an, Jilin Province, education, master, unit, Harbin Medical University, research direction: ophthalmology.

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Design and Study of a Wearable Non-Invasive Photoacoustic Glucose Monitor

Yongshi Zhao
Enlight Technology, Yuncheng 044000, China.

Abstract: This paper relates to a wearable non-invasive photoacoustic blood glucose monitor with a display, control buttons, controller, battery and measurement box in a wearable housing. The wearable case is fitted with a strap that is worn on the wrist of the person being tested. The photoacoustic excitation source and the optical lens system produce a focused laser beam that passes through the hollow multi-ring array sensor and is directed towards the blood vessels in the wrist to achieve continuous A-shaped dynamic focus scanning photoacoustic glucose detection, providing photoacoustic glucose results at multiple sites in the depth direction of the wrist. This paper has the advantages of being compact, portable, easy to operate, enabling real-time monitoring of photoacoustic glucose, non-invasive during testing, eliminating the need to extract blood and provide test strips, and avoiding cross-contamination and environmental effects.

Keywords: Blood Glucose Monitoring; Non-Invasive; Wearable; Photoacoustic; Instrumentation

1. Introduction

At present, blood glucose testing is still commonly performed by invasive or minimally invasive interventional methods, which require minute amounts of peripheral blood and corresponding test strips. The future direction of development should be non-invasive non-invasive blood glucose testing techniques, such as photoacoustic analysis, spectroscopy, Raman spectroscopy, light scattering spectroscopy and optical polarisation spectroscopy. There are still many difficulties with current photoacoustic analysis methods, such as the need to achieve non-destructive detection, the energy of the incident laser cannot exceed the threshold value, so effectively improving the excitation efficiency of photoacoustics is an urgent problem to be solved. In addition, photoacoustic detection also mostly uses solid-state lasers as the excitation source, and there are certain difficulties in the integration and miniaturisation of the system.

Due to the single detector as the sensing part, photoacoustic excitation and sensing can not achieve coaxial confocal structure, so the efficiency of photoacoustic excitation and detection is not high, need a larger power solid-state laser to provide photoacoustic excitation energy, or need thousands of signal averaging to improve the signal-to-noise ratio, and the large volume of solid-state laser can not achieve the integration of excitation and sensing and miniaturization, multiple signal averaging greatly reduces the The large size of the solid-state laser does not allow for the integration and miniaturisation of excitation and sensing, multiple signal averaging greatly reduces the temporal resolution of the system, and both forward and lateral detection modes lack practical ease of operation, limiting the prospects for practical application.

2. Wearable non-invasive photoacoustic glucose monitor design

The technical problem to be solved in this paper is to design a wearable non-invasive blood glucose monitor with compact structure, easy portability and simple operation, which can provide simultaneous photoacoustic blood glucose monitoring results at multiple loci in the wrist depth direction. The overall framework of the specific design is shown in

Figure 1.

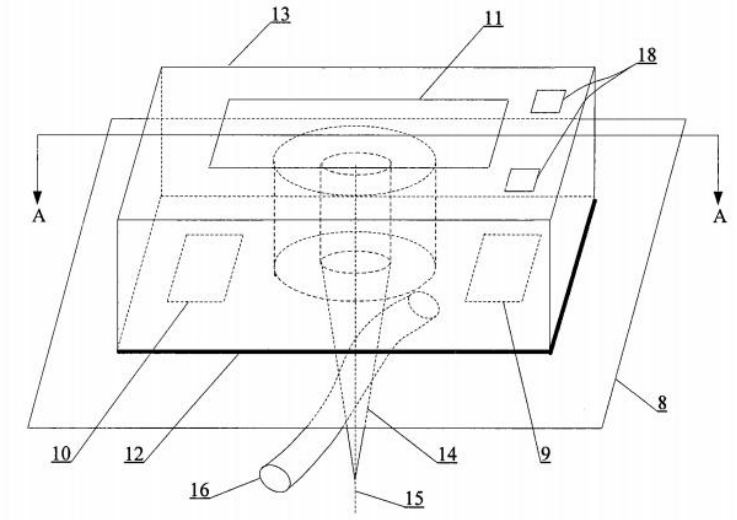

Figure 1 Overall framework of the wearable non-invasive photoacoustic glucose monitor

This paper designs a wearable non-invasive photoacoustic blood glucose monitor, characterized in that the surface of the housing is provided with a display and control buttons, the bottom surface of the housing is a multi-layer bonding plate, the measurement box is placed on the multi-layer bonding plate, the measurement box is provided with a hollow acoustic insulation layer and an acoustic liner; on top of the acoustic insulation layer is a semiconductor laser tube, below the semiconductor laser tube is a Fourier lens, the Fourier lens The centre of the semiconductor laser tube, the Fourier lens, the light-transmitting protective film and the hollow multi-loop array sensor are all located on the same central axis and are integrated in the measurement box, forming an integrated coaxial confocal structure, which can effectively reduce the laser energy requirement while increasing the detection depth; the side of the measurement box is equipped with a controller and a battery. The hollow multi-ring array sensor is connected to the terminal block of the controller through the wires of each ring. The housing is of a wearable type, fitted with a strap to be worn on the wrist of the person being tested. Said semiconductor laser tube is a semiconductor pulsed laser diode, operating at one or more wavelengths in the ultraviolet to infrared range. Said semiconductor laser tube and Fourier lens form a photoacoustic excitation source and optical path lens system to produce a focused laser beam that passes through the light-transmitting protective film and the hollow inner ring of the hollow multi-ring array sensor and is directed at the blood vessels within the wrist. Said hollow multi-ring array sensor is a hollow planar or concave-convex array made of piezoelectric materials, including lithium niobate, composite materials, piezoelectric ceramics or PVDF films; the hollow multi-ring array sensor uses serial or parallel real-time reception of photoacoustic signals in backward mode to achieve continuous A-shaped dynamic focus scanning of photoacoustic glucose detection, providing photoacoustic glucose results at multiple loci in the depth direction of the wrist.

3. Workflow of the wearable non-invasive photoacoustic glucose monitor

Under the trigger of the controller, the semiconductor laser tube is excited to produce a pulsed laser whose wavelength, pulse width and repetition frequency can be selected as required.

Laser energy is collimated and focused through the optical lens and radiated through the protective film to the blood vessels under the skin of the wrist, blood sugar and other functional groups absorb the light energy to excite the photoacoustic signal; the controller simultaneously triggers the multi-ring array sensor backward mode to detect the photoacoustic signal to achieve the excitation and sensing of the photoacoustic signal.

By processing the collected photoacoustic data through certain algorithms, the continuous A-shaped dynamic focus

scanning detection of photoacoustic blood glucose in the depth direction can be achieved, and the photoacoustic blood glucose results of multiple loci in the depth direction of the wrist can be obtained.

4. Summary

The method in this paper integrates the backward receiving mode of photoacoustic, excitation and sensing processing, effectively realising a miniaturised and practical wearable system structure, with the advantages of compact structure, easy portability, simple operation, enabling real-time monitoring of photoacoustic blood glucose, non-invasive detection, no need to extract blood and provide test strips, avoiding cross infection and environmental impact. In addition, this paper combines the photoacoustic excitation source, the optical path lens system and the multi-ring array sensor to form a coaxial confocal structure, which can greatly improve the photoacoustic excitation and sensing efficiency, effectively reduce the laser energy requirement while increasing the detection depth, achieve continuous A-type dynamic focus scanning detection of photoacoustic glucose, and provide photoacoustic glucose results at multiple loci in the wrist depth direction.

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Author Biography

Zhao Yongshi (27 March 1983), Male, Han Nationality, Xia County, Yuncheng City, Shanxi Province, College, Engineer.

Research interests: monitoring and intervention of blood glucose by smart wearable devices, engaged in smart manufacturing.

Music Analgesia Used in Delivery of Pregnant Women

ZiXiang Zou[1,2], Yan Liu[3]

1. Graduate School of Jiangxi University of Traditional Chinese Medicine, Nanchang 330103, China.

2. Jiangxi College of Traditional Chinese Medicine, Nanchang 330103, China.

3. School of Humanities, Jiangxi University of Traditional Chinese Medicine, Nanchang 330103, China.

Abstract: Music therapy is one of the non-drug labor analgesia methods advocated during labor, which can relieve labor pain and anxiety and promote natural childbirth. The author here from the definition of music therapy, physiological principles, for labor analgesia on maternal and neonatal effects, as well as music therapy and doula accompany childbirth combined application effect were reviewed.

Keywords: Music Therapy; Childbirth; Non-Drug Analgesia

Introduction

Labor pain is the most severe pain experienced by most women in their lives [1]. Pregnant women are often accompanied by strong physiological and psychological stress during childbirth, such as tension, anxiety, fear, dystocia, postpartum hemorrhage, neonatal asphyxia and other adverse outcomes, which seriously threaten maternal and child health and life safety [2]. How to effectively alleviate the fear and tension of parturients in childbirth and improve the rate of natural delivery as much as possible is one of the focuses of current obstetric work[3]. Reducing childbirth pain is the main factor to relieve the anxiety of pregnant women. The American College of Obstetricians and Gynecologists (ACOG) believes that medical staff should reduce maternal labor pain as much as possible. Non-drug analgesic side effects of small, by domestic and foreign scholars respected [4]. In the article "Study on the Relieving Effect of Music on Analgesia". The experimental results of the subjects showed that under the condition of music stimulation, the pain threshold of the subjects increased by 20.23 % on average ($p < 0.01$). The pain tolerance threshold increased by 11.84 % ($p < 0.01$). In addition, the study found that the use of music and noise in dental surgery, a combination of methods, 65 % of patients with pain completely disappeared. In clinical trials, music is widely used in surgery to reduce the dose of anesthetics by 50 %. In addition, music can completely or mostly replace analgesic drugs in the postoperative recovery period to avoid the harm of analgesic drugs to the brain[5-6].

1. Definition of music therapy

Music therapy is the application and development of music beyond the traditional field of art appreciation and aesthetics. Music therapy is a systematic intervention process. In this process, the therapist uses music to experience various forms, as well as the therapeutic relationship developed in the course of treatment, as the driving force of treatment to help the treated achieve health.

2. Physiological Principle of Music Analgesia

2.1 Neural pathway of sound analgesia

Scientists have found that sounds 5 decibels larger than environmental sounds have analgesic effects in mice. To explore the brain circuits behind the pain-alleviation effect of this 5-decibel low-intensity sound, the team used adeno-associated virus combined with fluorescent proteins to track connections between brain regions, monitoring neuronal activity in different brain regions of awake mice in real time. Researchers found that 5 decibels of low-intensity sound blocked glutamatergic neurons in the auditory cortex from releasing glutamate into the posterior thalamic nucleus and ventral postmedial nucleus, inhibiting activation of downstream neural pathways. In the absence of sound, inhibition of this thalamus pathway by optogenetics or chemical genetics can simulate the effect of low-intensity sound on pain relief, and activation of this pathway restores sensitivity to pain. Finally, scientists determined the route from the auditory cortex to the thalamus, which receives and processes information about sounds, and the thalamus acts as a relay station for sensory signals from the body.

2.2 Maternal music analgesia

Music analgesia delivery can effectively relieve maternal childbirth pain. The reason is that in the human cerebral cortex, when a nerve center is excited, it inhibits other nerve centers around it. Human auditory center and pain center are located in the temporal lobe of the brain. Therefore, when music stimulates the maternal auditory nerve, the surrounding pain nerve center is inhibited. It may also be because the maternal after receiving music stimulation will secrete endorphin, and endorphin has a strong analgesic effect, thus receiving music analgesia childbirth maternal pain feeling reduced [7]. In addition, when stimulated by soothing music, the mother 's attention is diverted from the birth event, reducing the focus on pain, which in turn reduces pain sensation [8].

3. Music painless childbirth method

Music is widely used during childbirth Although the main purpose of using music during childbirth is still to reduce labor pain, the method is relatively complex.

Music painless childbirth method consists of three parts music-lamaz relaxation training music imagination training music labor analgesia. The entire musical intervention usually begins the week before the due date. The first stage of music-lamaz relaxation training can use the rhythm of music to help pregnant women breathe and relax so that pregnant women can relax after entering the labor process, breathe correctly, save physical strength, and cooperate with medical staff correctly when the baby is delivered. The second stage of the musical imagination can help pregnant women in the heart to establish a positive psychological expectation during childbirth to eliminate tension and fear. During the third stage of childbirth, the use of music, especially familiar music, can help reduce and eliminate pain during childbirth.

4. The effect of music therapy on maternal

4.1 Relieved pain

Studies have shown that music therapy as a non-drug adjuvant intervention has a good effect on reducing pain, anxiety, enhancing comfort and promoting recovery. Simavli et al. [9] also showed that listening to music during childbirth had a positive effect on labor pain and anxiety, and met the analgesic needs of pregnant women. Liu et al [10] found that music can effectively reduce the labor pain in the latent period (2 ~ 4 cm). Domestic Dong Qiuping et al. [11]

4.2 Relieve maternal stress and anxiety

Domestic and foreign studies have shown that music therapy can reduce maternal stress and relieve anxiety. The study of Liu et al. [11] suggested that music therapy can alleviate the anxiety of maternal latency. Zhang Yan [12] By detecting maternal stress during the second stage of labor, it can be seen that the observation group collected peripheral blood to detect renin (R), epinephrine (E), norepinephrine (NE) and angiotensin II. The level of ATII was significantly lower than that of the control group, indicating that music therapy and motivational psychotherapy were helpful to alleviate the stress state during childbirth and had a positive effect on alleviating negative emotions.

4.3 Increase natural birth rate

Music therapy can promote natural childbirth. Qian Hong et al [13] showed that music intervention had a good effect on the psychology of maternal childbirth, accelerated the progress of labor, and promoted natural childbirth. He et al. [14] Studies have shown that music therapy can significantly shorten the first and second stages of labor. Dong Qiuping et al. [11] also showed that music therapy significantly shortened the active period and the second stage of labor.

5. Combined Application of Music Therapy and Other Methods

5.1 Combined Application of Music Therapy and Doula Accompanying Childbirth

Clinically, the effect of doula delivery combined with music therapy is ideal in the process of maternal delivery. The two play a role in different ways, effectively reducing the degree of labor pain and relieving fear. The performer massaged the abdomen of the parturient, communicated and communicated with it, diverted their attention, and played soft music for the parturient, controlling the volume below 70 dB until the cervix of the parturient was completely opened.[15]

6. Nodule

Music analgesia delivery is a new type of natural analgesia delivery without side effects and drug intervention. Based on the different stages of labor and maternal various physical and psychological needs and feelings, the scientific use of music, combined with breathing, relaxation, free position, guided music accompaniment, delivery ball, touch, massage and other methods for a series of services, can effectively relieve labor pain, shorten the labor time, improve the success rate of natural childbirth. In addition, music analgesia delivery method can improve maternal respiratory skills, guide correct breathing, breath holding and use of strength, and reduce the incidence of neonatal asphyxia by shortening the labor process. Music analgesia delivery is worthy of further promotion.

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Research Progress on the Role of Atorvastatin in the Treatment of Coronary Heart Disease

Shupeng Jiang
Gannan Medical University, Ganzhou 341000, China.

Abstract: The basic pathological change of coronary heart disease is atherosclerosis, and the main risk factor is abnormal lipid metabolism. Atorvastatin is the most commonly used lipid-lowering drug. This paper mainly describes the research progress of atorvastatin in terms of pharmacological effects, dosing and deficiencies.

Keywords: Atorvastatin; Coronary Heart Disease; Treatment

1. Coronary heart disease overview

Coronary atherosclerotic heart disease (CHD) is a disease in which atherosclerosis of the coronary arteries causes luminal narrowing or occlusion leading to myocardial ischemia and hypoxia, followed by myocardial necrosis, resulting in chest pain, angina and other discomfort, and is one of the more common and urgent types of cardiovascular diseases. If not treated in time, it can have serious consequences, such as heart failure, various arrhythmias, and even death. Studies have shown that this disease is caused by multiple factors, such as smoking,hypertension,hyperglycemia, hyperlipidemia, age, and gender. Among them, abnormal lipid metabolism is its basic pathological factor and the most important risk factor. It is now generally accepted that cholesterol,triglycerides(TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and Lp (α) are involved in the progression of atherosclerosis. The basic pathological changes are lipid deposition under the intima to form lipid pattern, and then fibrous tissue proliferation to cover the lipid surface to form a fibrous cap, and smooth muscle proliferation in the intima to cause lumen thickening and narrowing, forming a stable angina. If the plaque ruptures, a thrombus will be formed, which can cause acute coronary events and serious harm. Therefore, lipid lowering is the core treatment. Clinically used lipid-lowering drugs can be divided into those that mainly lower TC and LDL, those that mainly lower TG and VLDL, and those that lower LP(α), etc. Atorvastatin is the former. Current research on atorvastatin focuses on the pharmacological effects of the drug, the efficacy of patients' blood lipids, cardiac function and other factors, and the comparison of the lipid-lowering effect at different doses, as well as its side effects and shortcomings.

2. Pharmacological effects of atorvastatin

Statins are also known as hydroxymethylglutarate monoacyl coenzyme A (HMG-CoA) reductase inhibitors. Among the statins, atorvastatin is the most commonly used. Its main effect is to lower blood lipids, followed by non-lipid-regulating effects. It is widely used in clinical practice because of its significant effect and low side effects.

2.1 Hypolipidemic effect of atorvastatin

Atorvastatin is the most commonly used lipid-lowering drug in clinical practice and has significant lipid-regulating effects. Jinlong Zhang proposed in 2022 that it can reduce blood viscosity, improve hemodynamics and thus prevent thrombosis, and is an important component of secondary prevention after PCI. At therapeutic doses, it primarily lowers

cholesterol and low-density lipoprotein (LDL), and to a lesser extent triglycerides (TG), with a slight increase in high-density lipoprotein (HDL). The effect of the drug starts in about two weeks and reaches a peak in 4-6 weeks, requiring long-term use. Cholesterol is mainly synthesized in the liver, and the key enzyme for synthesis is HMG-CoA reductase. HMG-CoA reductase is the target of atorvastatin, because the drug or its metabolites are similar in spatial structure to the substrate HMG-CoA and have a much greater affinity for the reductase than HMG-CoA, so they can compete with the substrate for inhibition, thus impeding cholesterol synthesis. Cholesterol in the blood is mainly transported by low-density lipoprotein (LDL) as a carrier (LDL-C), mediated into the cell with the help of LDL receptors on the liver cell membrane. When plasma cholesterol is lowered, the LDL receptor on the surface of hepatocytes is increased or its activity is enhanced through a negative feedback mechanism to lower LDL. LDL is mainly converted from VLDL and therefore causes a secondary acceleration of VLDL metabolism.VLDL and LDL have similar physiological functions, i.e. transport of endogenous cholesterol and triacylglycerol (TG), which also leads to a further decrease in TG. HDL is synthesized primarily by the liver and small intestine and, unlike LDL and VLDL, is responsible for transporting cholesterol from extrahepatic tissue cells. The first step is binding to the cell surface, and some studies suggest that this process may be mediated by HDL receptors, but does not enter the cell, but rather by some sort of signaling that moves intracellular cholesterol to the cell surface and then into HDL. The increase in HDL may be an indirect result of the decrease in VLDL, as the cholesterol in the body is continuously transferred from celiac (CM) and VLDL to HDL through a series of conversions after the release of neonatal HDL into the blood. In addition, small and dense low-density lipoprotein cholesterol (sdLDL-C) is also involved in the development process of AS. There are few reports related to the effect of atorvastatin on the expression level of sdLDL-C. Wanjiang Tan studied the expression level of this substance in patients with coronary artery disease and the effect of the drug after administration in 2019. His study showed that sdLDL-C was an independent predictor of the development of cardiovascular disease and that atorvastatin may alter sdLDL-C levels and thus have a positive effect on disease regression. Numerous clinical trials have shown that postoperative use of atorvastatin in patients with coronary artery disease or acute infarction significantly decreased serum TC, TG and LDL-C and slightly increased HDL, while patients' LVEF increased ($P<0.05$), significantly reducing patient mortality. Therefore, atorvastatin can play a role in endothelial protection, delaying atherosclerosis, protecting target organs and improving prognosis. This drug can be used to prevent and treat a variety of atherosclerotic cardiovascular diseases, such as acute coronary syndrome (ACS), stable angina pectoris, and post-PCI.

2.2 Non-lipid-modulating effects of atorvastatin

A large body of clinical evidence suggests that CHD occurs not only due to lipid accumulation, but also due to myocardial damage and vascular endothelial cell damage from inflammatory responses and cellular damage from oxidative substances. For example, Zhang ZG et al. mentioned in 2017 that PCI is often accompanied by some myocardial injury, and that vascular endothelial system injury and inflammatory response play an important role in adverse cardiovascular events after PCI. Other studies such as macrophages engulf LDL-C and oxidize it during endothelial injury, forming peroxides and superoxide ions, while atorvastatin exerts antioxidant effects by scavenging oxygen free radicals. Moreover, macrophages can secrete many inflammatory mediators, such as PDGF, FGF, TNF-α, IL-1, etc. Liu Suge et al. mentioned in 2019 that TNF-α inhibits myocardial contraction and mediates ventricular remodeling; excessive hs-CRP leads to coagulation system activation and vascular endothelial injury; Hcy damages endothelial cells and promotes smooth muscle proliferation. The above inflammatory substances decreased significantly after treatment with atorvastatin. Atorvastatin also attenuates the inflammatory response by inhibiting the adhesion and secretion function of monocytes-macrophages. Wang Shan mentioned in 2019 that serum C-reactive protein may be an independent predictor of coronary heart disease occurrence, and IL-6 may also be involved. The clinical trials observed that these two indicators were significantly lower with atorvastatin than before

the use of the drug. Cao A. et al. proposed in 2017 that hs-CRP is an important indicator of the level of inflammation in the response organism and the level is positively correlated with the degree of lesions. The level of this indicator decreased significantly after one month of oral atorvastatin. In conclusion, a number of studies have shown that atorvastatin is effective in suppressing the inflammatory response, improving cardiac function and preventing vascular and ventricular remodeling in patients.

3. Comparison of the efficacy of atorvastatin at different doses

There are more clinical comparative studies on the therapeutic effects of conventional and higher doses of atorvastatin. Most of them are based on 20 mg/d as the conventional dose and 40 mg/d as the higher or moderate dose. Zhao Pei et al. noted in 2017 that Europeans and Americans are more tolerant of atorvastatin than Asians, and given that China is a large country with liver disease, patients are not easily given intensive treatment with atorvastatin, usually not at a dose of 80 mg/d. Its clinical study showed that atorvastatin lowered TC, TG, LDL-C and hs-CRP in both the experimental group (40 mg/d) and the control group (20 mg/d), but the modulatory and anti-inflammatory effects were more pronounced in the experimental group than in the control group ($P<0.05$), with fewer side effects and no significant differences. Liu, Bin and Su, Hailong in 2022 suggested that there is still a significant proportion of patients with suboptimal doses of statin lipid modulation using conventional doses. Their study used the same approach and came to similar conclusions: serum CDF-15 and PTX3 levels were reduced in both groups and were more significant ($P<0.05$) in the observation group (40 mg/d) than in the control group (20 mg/d), with fewer side effects and no significant differences. They also compared the patients' left heart function, LVEF was significantly higher, LVESD, LVEDD and plasma NT-proBNP levels were significantly lower after treatment, and the observation group was significantly better than the control group. Regarding left heart function, Liu Suge et al. performed a similar clinical trial and showed that the magnitude of changes in LVESD, LVEDD and NT-proBNP in the high-dose (40mg/d) treatment group was significantly greater than that in the low-dose (20 mg/d) group, and LVEF was greater than that in the low-dose group. The same experiment was done by Zhang Lianfang, Mu Mian, Liu Lihua and others, and the conclusions obtained were consistent. All of the above results indicate that treatment with 40 mg/d atorvastatin after PCI in patients with coronary artery disease is safe and effective, with significant lipid-lowering and anti-inflammatory effects compared to 20 mg. However, this option is not yet widespread, and its specific efficacy and risk level need to be further studied. In addition, Huali Wang studied the therapeutic effect of small doses (10 mg/d) in 2022. The results showed that the patients in the small dose group (10 mg/d) had lower cardiac function indexes and higher NT-proBNP levels, with better clinical outcomes than the high dose group (40 mg/d). It was concluded that low-dose atorvastatin therapy is of high value in elderly patients with chronic heart failure in coronary artery disease.

4. Side effects, shortcomings and outlook of atorvastatin

4.1 Side effects

In the above clinical observation experiments, some patients experienced temporary reactions such as gastrointestinal reactions, skin flushing, headache and insomnia. A small number of people have asymptomatic transaminase elevation, indicating that the drug has a certain degree of hepatotoxicity, regular liver function tests are required during the use of the drug, and people with a history of liver disease should use with caution. This class of drugs can also cause muscle adverse reactions, manifested as myalgia, myositis and rhabdomyolysis, and those with muscle discomfort or weakness need to test for creatine kinase (CK) and reduce or discontinue the drug if necessary. However, overall, atorvastatin has few and mild adverse effects, a wide range of safety, and can reduce overall mortality, making it a first-line agent for lipid lowering.

4.2 Drawbacks

Atorvastatin has some hepatotoxicity, but the overall side effects are small and the clinical application is less restricted. Wei Gaohui et al. concluded that adverse effects of statin therapy are more likely to occur in elderly patients (over 80 years of age). Choruo Zhang and Feilong Dai proposed in 2022 that atorvastatin is orally administered via gastric mucosal clearance and hepatic first-pass elimination effect with low systemic utilization, and its use alone may prolong the therapeutic cycle and limit the clinical application, so it was proposed to be combined with trimetazidine. Trimetazidine has myocardial protective effects and reduces oxidative damage. Combined with atorvastatin, it can play a synergistic role to improve myocardial cell metabolism, restore normal blood supply to the myocardium and improve cardiac function. Zhang Churuo and Dai Feilong divided the patients into the combined trimetazidine group and the atorvastatin alone group to observe the efficacy of the two groups in the experiment. The study showed that LVEF, LVSD, and ET-1 were higher in the combination group than in the atorvastatin group, and LVEDD, NO, TC, and LDL-C were lower than in the atorvastatin group ($P<0.05$), suggesting that the combination was more effective than atorvastatin alone. And in terms of safety, the combination of drugs will not increase the adverse drug reactions, high safety. The same study was done by Yang Jun et al. in 2019, which noted that trimetazidine has a relatively long onset of action after dosing, and that the combination with atorvastatin can effectively take advantage of both to achieve a fast and long-lasting onset of action. In addition, Bin Liu and Hailong Su in 2022 mentioned a variety of novel biomarkers, such as PCSK9 and Sortilin. PCSK9 is a preprotein convertase that degrades the LDL-C receptor on the surface of hepatocytes, decreases the metabolism of LDL by the liver, and causes elevation of peripheral LDL. Sortilin is a lysosomal sorting receptor that induces VLDL synthesis and release, promotes LDL-C elevation, and accelerates LDLR degradation by interacting with PCSK9. They detected an increase in PCSK9 levels after treatment with atorvastatin in the trial, which is one of the reasons for its limiting lipid-regulating effect. Therefore, some investigators have proposed that the use of conventional doses of atorvastatin in combination with PCSK9 inhibitors. There have also been many recent studies on the effects of statins on glucose metabolism. Liu Sining and Tian Xuefeng et al. showed that fasting blood glucose and Hb1Ac levels increased and fasting insulin levels decreased in the atorvastatin group 12 weeks after treatment compared with those before treatment ($P<0.05$), indicating that long-term statin use may have an effect on glucose metabolism. Their study also showed that regular doses of atorvastatin did not increase the risk of new-onset glucose metabolism abnormalities in patients with ACS, but that moderate doses increased. If you need to take atorvastatin for a long time, you need to test the patient's glucose metabolism first, and use the drug to lower blood sugar at the same time. In contrast, pitavastatin has little effect on non-diabetic CHD glucose metabolism and does not increase the risk of new-onset diabetes in patients with CHD. In addition, atorvastatin has limited HDL-elevating effects and is weaker than pitavastatin. Pitavastatin is also less hepatotoxic than atorvastatin and has a better clinical application.

4.3 Conclusion and Outlook

CHD has become a hot disease of global concern. Atorvastatin is the first choice of clinical lipid-lowering drug, with significant lipid-lowering effect, small side effects and high safety. There are certain shortcomings and better treatment options are being investigated clinically. Such as coadministration of trimetazidine, PCSK9 inhibitors, and switching to other statins. In 2017, a new domestic self-developed lipid-lowering drug, PCSK9 inhibitor, has been qualified for clinical trials and will surely play an important role.

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