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Original Articles

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Discussion on PDCA Working Mode of Clinical Pharmacists in ICU

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Abstract: Objective: exploration of the application effect of PDCA working mode in the daily work of clinical pharmacists in ICU. Methods: on the basis of PDCA cycle theory, a plan for the construction of ICU clinical pharmacists' work mode is made, so as to evaluated its application effect combined with work examples. Results: the work mode of clinical pharmacists in ICU based on PDCA cycle theory adheres to initiative, timeliness and pertinence, which can solve the problem of irrational clinical medication, and improve the rationality and safety of medication. Conclusion: the application of PDCA cycle theory in the work mode of clinical pharmacists in ICU is worthy of promotion.

Keywords: Clinical Pharmacist; Intensive Care Unit; Working Mode

1. Introduction

It is necessary for clinical pharmacists to carry out pharmaceutical care in ICU ward, which is a necessary way to change the function of hospital pharmacy discipline and a practical embodiment of the concept of patient-centered, so it is imperative [1]. Based on the characteristics of ICU patients, complex diseases and rapid changes of illness, if there is no effective and reasonable work mode to guide clinical pharmacists to carry out various work, it is likely to lead to various clinical governance problems, and also increase the pressure on clinical pharmacists, so that they cannot quickly and effectively integrate into the pharmaceutical care work in ICU. In order to ensure the safety of drug use in ICU, combined with my own work experience, this paper explores the effective working mode of pharmaceutical care in ICU, hoping to promote the better development of clinical pharmacy.

2. PDCA working mode and implementation of clinical pharmacists in ICU

PDCA includes four stages: plan, do, check and action. Continuous quality improvement of clinical pharmacists is made according to P_ D_ C_ A cycle , and loop Continuously[2]. The structure diagram is shown in Figure 1

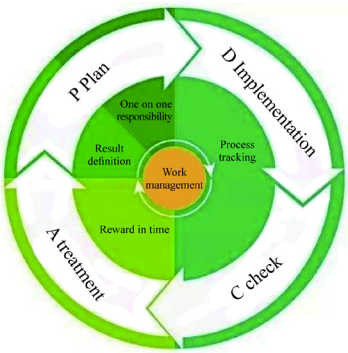

Figure 1 PDCA cycle diagram

Plan (P): developing the quality improvement plan for clinical pharmacists in ICU.

It investigates and finds the problems of clinical medication, analyzes the causes and makes plans, which are easily ignored by doctors in practice, such as drug selection, medication methods, usage and dosage, etc. After finding the problems, we should analyze the causes of medication problems, take targeted measures, and carry out systematic training for pharmacists, so as to improve their working ability, constantly improve, and set the expected goal to achieve it.

Implementation (D): developing training programs, strengthening pharmacist occupation skills training, and improving the professional level of pharmacists. The enthusiasm and participation of doctors are mobilized in the training process, and the results of pharmacist training are finally assessed combined with actual case analysis.

Check (C): checking the feasibility and scientific nature of the improvement plan. Check during the execution of the scheme is to evaluate whether the desired effect has been achieved.

Action (A): namely, summing up experience. The scheme needs to be improved again before entering the next cycle.

3. PDCA working mode and examples

Examples are shown in Table 1

Table 1 example analysis

Stage	Primary coverage	Specific events
P	Developing medication improvement plan	Based on the characteristics of carbapenem antibiotics PD, the different medication methods of meropenem were introduced
D	Implementation plan, clinician medication management	Doctors were trained twice on drug characteristics and medication methods of “meropenem”
C	Checking the degree of improvement / implementation	The patients with severe infection maintained medication for 2 weeks, and were supervised and intervened for many times
A	Summarizing experience, forming joint force and medication guidance	Soliciting clinical opinions, forming Reference of Meropenem Medication

After ward round, it was found that the actual dosage of meropenem was increased from 1g, q8h to 1.5g, q8h, and then to 2g, q8h. The patients with severe infection did not improve and still had fever. The problem is that pharmacists are not proficient in the clinical pharmacological characteristics of meropenem, and the use of meropenem is too single, resulting in the medication cannot achieve the desired effect. In view of the problems, the paper puts forward specific suggestions for the improvement of the work:

4. Suggestions on improving the working ability of clinical pharmacists in ICU

4.1 Focusing on key patients and medication, strengthening pharmaceutical care

Clinical pharmacists should reasonably choose the monitoring mode according to the characteristics of patients’ diseases and drugs. For ICU patients who use toxic drugs, drugs with severe properties, drugs that are prone to adverse reactions alone or in combination with large doses of drugs, or have special treatment methods such as enema, and liver and kidney dysfunction, they should strengthen the awareness of drug safety, drug varieties and their suitability monitoring of adverse reactions. According to the patient’s specific condition, individualized monitoring schedule plan is made, and the corresponding medication history is established. For example, to monitor whether there are gypsum, oyster, clam shell, cuttlebone and other high calcium components in drugs, so as to avoid increasing the cardiotoxicity

of patients with certain diseases.

4.2 Paying attention to the details of doctor's order review

Doctor's advice and its audit are the necessary work for clinical pharmacists to ensure the safety of drug use, and it is an important part of standardizing doctors' prescription behavior and carrying out intervention on irrational drug use. When clinical pharmacists review medical orders, they mainly include the review of electronic cases and medication information. In addition, in the process of ward round, they review newly issued pharmacies and medical orders. The review contents should include drug function indications, whether medication is consistent with treatment needs, whether drug usage and dosage are appropriate and based, whether there are repeated medication, whether there are drug contraindications, and whether there are incompatibility contraindications. We should pay more attention to the dosage and indications of injection drugs.

4.3 Paying attention to the management of drug storage and preparation

Drug storage and quality management are often loopholes in ICU medication service. There are many kinds of diseases in ICU, and most of them are high-risk diseases, involving many kinds of drugs. Insulin, sedative analgesics and high concentration electrolytes are very common, which increase the difficulty of drug management. Clinical pharmacists should often check the display, use and shift management of drugs, pay attention to whether there are inappropriate storage conditions and expired drugs, and strengthen the management of narcotic drugs and psychotropic drugs, so as to propose potential safety hazards and improvement measures to nurses and other direct managers if problems are found. In the process of drug preparation, the quality management should be strengthened, and the configuration environment and operation process should be standardized to avoid drug contamination. For example, in the configuration of enteral nutrition preparations rich in protein, sugar and other substances, it is necessary to add ingredients in the clean area according to the requirements of aseptic operation. Whether oral or intravenous drugs, strict quality management should be given.

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The Effect of Obesity on Insulin Resistance in Terms of Cytokines and Hormones

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Abstract: With the increasing incidence and mortality of obesity, obesity-related health problems have become a worldwide priority. Clinical observation shows that obesity related to adipocyte differentiation is an important pathogenic factor of insulin resistance, and weight loss can reduce insulin resistance, indicating that obesity is related to insulin resistance. As the understanding of mechanism between obesity, cytokines, hormones and insulin resistance becomes clear, it is possible that these cytokines or hormones could be used in the use of biomarkers and the design of targeted therapies for insulin resistance. This review provides an overview of how obesity effect adipokines，hepatokines and inflammatory cytokines whose changes result in or exacerbate insulin resistance.

Keywords: obesity, insulin resistance, cytokines, hormones

1. INTRODUCTION

Obese patients are often accompanied by insulin resistance (IR). Insulin resistance (IR) is the reduction or disappearance of the response of target organs and tissues of insulin action, such as liver, muscle and adipose tissue, to the biological effect of insulin, resulting in a series of pathophysiological changes and clinical manifestations.

Adipokines are a class of cytokines or hormones secreted by white fat cells. It has shown that the occurrence of obesity is mainly due to abnormal secretion of adipocytes, large increase of adipocytes and excessive deposition of lipids in cells. Hepatokines are liver-derived proteins. The first hepatokine that has been proven to have a major pathogenetic role in metabolic diseases is α2-HS-glycoprotein (fetuin-A).Inflammatory cytokines are various cytokines involved in the inflammatory response. Mainly has the tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), interleukin 6 (IL - 6), transforming growth factor β (TGF - β), etc.

There is clear evidence that adipokines, hepatokines, inflammatory cytokines play an important role in the development of abnormal glucose and lipid metabolism, especially about the cause of insulin resistance. In this article I discuss some of the cytokines or hormonal changes caused by obesity that cause or exacerbate insulin resistance.

2.ADIPOKINES

Adipokines are produced by white or brown fat tissue. As a result patients that are obese or overweight will change the body fat rate or the ratio of white to brown fat which will change the level of adipokines content in serum.

2.1 Leptin

Leptin and its receptors play an important role in the process of glucose metabolism. Leptin can enhance the sensitivity of surrounding tissues to insulin and the uptake of glucose. As a negative regulator of insulin, leptin may be partly involved in insulin resistance. The insulin reactivity and inhibition of glycogen synthesis were reduced in

hepatoma cells and isolated fat cells exposed to high concentrations of leptin. Lu Hongyun et al. found that the variation frequency of THE leptin receptor gene at exon 203057 G-A was significantly different between T2DM and normal glucose tolerance group. It is the abnormal expression of leptin that damages the feedback regulation system of the hypothalamic-pituitary-adrenal axis in OB/OB mice, thus causing insulin resistance. Studies have shown that serum leptin levels are associated with body mass index, and levels of the adipocytokine gene rise when body fat levels are high.

2.2 Resistin

Resistin is a kind of peptide hormone secreted by fat cells in the body. As it is related to insulin resistance, it was named resistin. Studies have found that resistin has a significant pro-inflammatory effect. Resistin is closely related to inflammatory responses, and many inflammatory responses are accompanied by the elevation of resistin. It was found that the expression level of inflammatory factors in monocytes of human peripheral blood was significantly increased by stimulating human peripheral blood monocytes with high concentration of resistin. Steppan found that resistin does not directly reduce phosphorylation of IRS-1 serine residues, but indirectly by reducing phosphorylation of IR tyrosine residues. Resistin induces insulin signaling abnormalities by stimulating inflammatory signaling pathways. Both theory and experiment suggest that obese people have higher levels of resistin.

2.3 Adiponectin

Adiponectin (ADI) was first discovered to be an endocrine active serum protein secreted by adipose tissue. ADI in human body is not only mainly produced by white fat, but also can be produced in small amounts in liver, myocardium, fetal disk and other tissues. [1] Adiponectin can stimulate the body to release anti-inflammatory cytokines, inhibit the production of pre-inflammatory factors, and play an anti-inflammatory role. But, when the body remains in the prolonged state of insulin resistance, inflammation would expand gradually, forming of chronic inflammation. [2] However, after obesity is reached, the ability of adipose tissue to secrete ADI decreases, and the body becomes less sensitive to insulin, resulting in IR。 [3] Kralisch et al. used the mouse model of adiponectin gene elimination, and found that mice showed severe insulin resistance. And they also indicates that adiponectin is involved in the occurrence and development of insulin resistance.

2.4 Zinc-α2-glycoproteins，ZAG

ZAG, a soluble protein with a molecular weight of about 43kDa, is a member of the major histocompatibility complex Type I family. Studies suggest that the increase of circulating ZAG level can increase insulin sensitivity and reduce the body’s insulin resistance through the glucose metabolism signaling pathway. The new study found that ZAG interacts with adipokines，such as adiponectin (ADI), in different tissues to regulate the body's insulin sensitivity. A study on metabolic syndrome suggested that serum ZAG level and ADI level of newly developed metabolic syndrome patients were lower than those of healthy control group, both of which were significantly negatively correlated with BMI. Studies on subcutaneous fat ZAG reported that the level of subcutaneous fat ZAG in people with normal body mass index was about 3.3 times higher than that in visceral fat tissue. However, the difference disappeared among the extremely obese.[1]

In summary, adipose tissue in obese people changes the amount of these adipokines they secrete. Then some adipokines would cause inflammation at last which contribute to the insulin resistance. And others can reduce insulin resistance by making cells more sensitive to insulin. After all their working mechanism are similar in general.

3 HEPATOKINES

Obesity has a huge impact on the liver, changing the amount of hepatokines.

3.1 Fibroblast Growth Factor,FGF-21

FGF21, a member of the FGF superfamily, is a secreted protein expressed mainly in the liver[4]，It is mainly regulated by the peroxisome proliferator-activated receptor and the insulin/protein kinase 1 pathway. It can be expressed in liver, fat, pancreas and muscle tissues, and plays an important role in improving insulin sensitivity and glucose and lipid metabolism. Xu Tongyu et al. speculate FGF21 improving insulin resistance in type 2 diabetic model mice may be by reducing inflammatory factors. The study of Zhang Nan et al. showed that the serum FGF21 level of obese or overweight patients was significantly increased, which was related to BMI, IR and other factors. The mechanism may be related to “FGF21 resistance” caused by compensatory increase of serum FGF21 level in pathological conditions such as obesity or overweight, hyperglycemia, etc.

3.2 Hepassocin

Hepassocin is a liver-specific growth factor that has been found to participate in the regulation of proliferation of hepatocytes and regeneration of the liver. The study of Wu Hung-Tsung et al. which based on HepG2 liver cancer cells showed that Hepassocin could block insulin signaling pathway and induce insulin resistance through an ERK1/2 dependent signaling pathway. The study of Ru-Lai Huang et al. provides evidence that subjects who are overweight or obese had significantly higher hepassocin concentrations than those of subjects who had a normal weight. Taken together, it suggest that hepassocin might be a link between obesity, and IR, and could be a potential candidate in developing comprehensive diagnostic/therapeutic approaches to manage these diseases.

3.3 Fetuin A

Fetuin-A is an endogenous natural insulin receptor tyrosine kinase inhibitor. It can directly inhibit the phosphorylation of insulin receptors, alter the downstream signaling molecules AMPK (AMP kinase) and AKT, and cause signal transduction disorder, causing IR.[5] Free fatty acids are known to stimulate the secretion of pro-inflammatory cytokines by adipocytes through toll-like receptor 4 (TLR4), leading to IR. Pal and Dasgupta et al. have shown Fetuin-A ACTS as an adaptor protein between free fatty acids and TLR4, and these findings suggest that Fetuin-a can enhance IR by this pathway.[6] To establish the link with obesity, the study showed that fetuin-A concentration in the T2DM group was higher than that in the control group.

3.4 Fetuin B

Fetuin B is the second member of the fetuin family, an endogenous inhibitor of the insulin receptor tyrosine kinase, and is produced primarily in liver tissue. In hepatocytes, fetuin B inhibits glucose metabolism pathways by inhibiting genes encoding 6 phosphoglucose and phosphoenolpyruvate carboxykinase, thereby reducing insulin sensitivity. [7] However, further studies are needed to elucidate the differences between in vitro and in vivo results and the specific molecular mechanisms by which fetuin B affects glucose metabolism. In humans, plasma fetuin B levels are increased in obese individuals with hepatic steatosis and T2D, and associated positively with intrahepatic triglyceride and insulin resistance.[8] Besides, Serum fetuin B levels were significantly higher in obese adults in relation to the metabolic syndrome than in the control group.

In conclusion, Liver factors can affect insulin resistance by affecting insulin-related pathways or changing other inflammatory cytokines, making the IR better or worse.

4 INFLAMMATORY CYTOKINES

Obesity is now widely recognized as a chronic inflammation which means that inflammatory cytokines and BMI have a strong relationship.

4.1 Secreted Frizzled Related Protein5,SFRP5

Secreted frizzled related protein 5 (SFRP5), which is one of the members of the SFRP protein family, can be

secreted by adipose tissue and is considered to be a bioactive substance closely related to autoinflammatory. Long-term chronic autoinflammation in the body is closely related to the occurrence of insulin resistance. Currently, it is believed that it can reduce the level of autoinflammation by antagonizing WNT/β -catenin pathway, and play a role in improving insulin resistance. Studies have found that the lung tissue expression of SFRP5 of the insulin resistance mice is less than that of mice without insulin resistance. Liu et al. believed that Sfrp5 may play an induction role in the proliferation, differentiation and maturation of adipogenic precursor cells, thereby reducing lipid deposition. And SFRP5 was negatively correlated with BMI.

4.2 TNF-α

TNF-α is the first inflammatory factor to link inflammation with insulin function. Studies have shown that increased production of fat-derived TNF-α has an important impact on insulin resistance in obese people. TNF-α can affect insulin function directly or indirectly through a variety of pathways. Direct pathways include induction of IRS-1 serine phosphorylation, down-regulation of IRS-1 expression, and reduction of GLUT-4. TNF-α can also indirectly induce insulin resistance in a number of ways. One of the most important is to increase FFA levels in the blood by stimulating MAPK mediated lipolysis of fat cells, which is activated by multiple pathways. Gasic et al. found that TNF-α induced G protein reduction is the most important mechanism causing lipolysis in rodents. In humans, increased levels of perilipin phosphorylation and decreased expression are the main factors causing the lipolysis effect of TNF-α. In addition, TNF-α can induce insulin resistance by inducing chronic inflammation in adipose tissue.[9] And Levels of TNF- were higher in both normal and T2DM patients than in non-obese patients.

4.3 IL-6

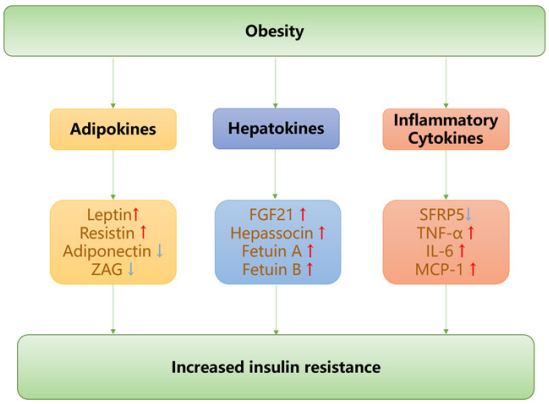
Adipose tissue is the main secreted tissue of IL-6, and the concentration of IL-6 in blood is positively correlated with obesity, impaired glucose tolerance and insulin resistance. IL-6 has a direct effect on insulin conduction in adipocytes and hepatocytes. In fat cells, IL-6 reduces protein expression of insulin receptor subunits and IRS-1, lowers insulin-mediated tyrosine kinase phosphorylation levels and insulin receptor subunit activity, and inhibits insulin-mediated glucose transport and fat formation by down-regulating glut-4 expression. In the adipose tissue of insulin resistant people, IL-6 mRNA expression increases, leading to a decrease in the insulin-mediated glucose treatment ratio. Studies have shown that IL-6 enhances glucose transport by enhancing the intrinsic activity of Glut-1 after treatment of 3T3-L1 fat cells. And BMI is an independent influence factor for il-6 elevation.

4.4 MCP-1

MCP-1 is a member of the monocyte chemotactic protein family. MCP-1 promotes the migration of inflammatory cells through chemotaxis in upregulated inflammatory molecules in adipose tissue of obese animals and humans. JIMENEZ - SAINZ et al. study found that activated by MCP - 1 extracellular signal regulating kinase (ERK) can cause a variety of downstream signal transduction events. MCP - 1 separately passivation of muscle cells and skeletal muscle insulin signaling and insulin stimulates glucose uptake, the two ways of alternating [10] may lead to insulin resistance. Tang et al. found that the McP-1 level of simple obesity patients was 25% higher than that of the normal control group, and the difference was statistically significant.

Inflammatory cytokines often act directly on insulin signaling pathways or glucose signaling pathways, causing or exacerbating insulin resistance. Many of these receptor channels have been used as therapeutic targets for insulin resistance.

5 CONCLUSION:



The conclusion for the content of hormones and cytokines in obese people which increased insulin resistance(↑stands for higher concentration levels in serum ,↓stands for lower concentration levels in serum than that in normal weight)

Obesity can change the secretion of cytokines, thus affecting metabolism and immune regulation pathways, leading to or promoting metabolic disorders. These cytokines are part of a complex network that mediates communication between fat, liver, muscle and immune system. Disorders in the content of certain hormones and cytokines can lead to metabolic disorders. At present, these hormones and cytokines have not been all used directly in the clinical treatment of insulin resistance. To my knowledge, leptin is used as a drug which is the treatment of congenital leptin deficiency obesity only, not used to treat IR.

However, given the disease-related changes in levels of relevant cytokines, the factors may serve as biomarkers for the early detection of insulin resistance, for instance, the rise of leptin, reisitin, adiponectin, FGF21. Moreover, based on preclinical studies, certain cytokines (FGF21, leptin, adiponectin, ZAG, MCP-1) can improve insulin sensitivity and may emerge as novel targets for broader and more efficient treatments as well as for prevention of insulin resistance. For example, thiazolidinediones is currently used to reduce insulin sensitivity, it works by increasing circulating adiponectin levels.Celastrol can increase insulin sensitivity by increasing leptin levels (which has not been used clinically)

Some cytokine especially the inflammatory cytokines and hepatokines or others like reisitin that cause insulin signaling abnormalities due to their elevated levels can be a target. The decomposing enzymes or inhibiting enzymes of them should also be considered as targets for treatment of endocrine disorders caused by obesity (not only insulin resistance, but also other diseases, such as atherosclerosis).

It is also worth investigating whether the use of external factors to force the increase of certain hormones and cytokines (such as ZAG, SFRP5) can reduce insulin resistance. After all, there is only evidence that BMI and IR affect the levels of some cytokines, and there is no evidence that increasing their levels reduces insulin resistance. Last but not least, methods of targetting specific insulin receptors is also a question worth thinking about in drug development.

The exact cause of insulin resistance has not yet been determined, but once it is, the mechanism by which these hormones and cytokines act will become clearer. And in the future drug research will also be more clearly targeted.

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S1PR2 and S1PR3 as Emerging Targets for Treatment of Chronic Pain

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Abstract: Chronic pain has posed a serious challenge for many people's daily life all over the world, with approximately 41% of Europeans in developing countries suffering it. Until recently, major treatments have relied on agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotics, which, however, have become less acceptable due to side-effects. Therefore, novel classes of pain-relievers are urgently needed to fill this void and improve the life quality of patients.

Sphingosine-1-phosphate (S1P) is one of the most notable lysophospholipids, whose role on pain generation has been increasingly recognized. Drugs targeting sphingosine-1-phosphate receptors (S1PRs) could be developed as novel analgesics, either as monotherapy or potential adjuncts. In this review, recent advances of the roles of S1PRs in peripheral sensory aspects are summarized, especially S1PR3 and S1PR2.

Keywords: S1P, S1PRs, Chronic pain, Rheumatoid arthritis

1. METABOLIC PATHWAY AND FUNCTION OF S1P

S1P is generated by phosphorylation of sphingosine in reactions catalyzed by sphingosine kinase 1&2 (SPHK 1&2)[1] in cells like immune cells, epithelial cells and neurons when stimulated by chemo-attractants such as tumour necrosis factor (TNFα) and nerve growth factor (NGF)[2, 3]. Both extracellular and intracellular level of S1P are tightly regulated to ensure a low constitutive level of S1P in most tissues[3], but high concentrations of free S1P would occur at inflammation sites with releasing of activated immune-competent cells[2].

S1P has received much attention owing to its potential role in diverse cellular processes in inflammation and immune responses like cell survival, proliferation, differentiation, migration, adhesion, lymphocyte trafficking, cytokine and chemokine production[3], etc.

Recent findings have also identified important roles of S1P for modulating sensory neuronal excitability[2, 4, 5], which has been implicated in pain and pain hypersensitivity[5, 6]. Additional studies demonstrated that S1P augmented both heat- and capsaicin-activated membrane currents in all size classes[7] of mouse sensory neurons. Furthermore, according to recent reports, S1P mediates both antinociception and pronociceptive effects in central nerve system (CNS) and peripheral nerve system (PNS), respectively[8]. Thermal antinociception was produced after the intracerebroventricular administration of S1P in mice[9], suggesting that the antinociceptive role of S1P in CNS. In contrast, increased nociceptive sensitivity arose after the administration of S1P in DRG[7], indicating the pronociceptive role of S1P in PNS. Although the role of S1P in CNS and PNS is different, not all studies have noticed this and still used DRG to study the block of pain from original but concluded without emphasis of this important distinction. Therefore, more attention should be paid about the distinction during the description of the conclusion in future.

Taken together, the concept that S1P not only regulates inflammation but simultaneously contributes to pain sensitivity is interest. If so, the development of agonists or antagonists targeting S1P-S1PR signals would be of great

clinical benefit for chronic pain in many diseases like RA.

2. S1PRs

S1P functions most through S1PR 1-5, a family of five G protein-coupled receptors originally named Edg receptors. Several reports supported the expression of S1PR 1-3 in DRG neurons[2, 10], whereas the expression of S1PR 4&5 was controversially discussed[2, 10] with only a few researches supporting the expression of S1PR4[4, 10] or S1PR5[11]. The research-based on S1PR1 has been done extensively, therefore the focus of this review will be on S1PR 2&3 as well as their modulators.

Table 1. Existing agonists and antagonists of S1PR2&3[8, 12]

	Agonists	Antagonists
S1PR2	CYM-5520, CYM5478, XAX-126	JTE-013
S1PR3	VPC23153, FTY720-P	CAY10444, VPC01091, VPC-23019

2.1. THE ROLE OF S1PR3

With the extensive research and application of S1PR1 in the sensory field, the role of S1PR3 in sensory neurons has been focused recently due to a series of notable phenomena. After exposing to S1P, a slowly activating and deactivating inward current was also observed in many neurons, followed by S1PR1-mediated pro-algesic action[5]. In addition, some sensory neurons treated with S1PR1-targeted siRNA were still capable of increasing excitability under treatment of S1P. These all far support the idea that there must be other S1PRs capable of mediating the S1P-induced enhancement of excitability, not only S1PR1[10]. The same scholar who discovered this problem later confirmed this idea and supplemented the conclusion as “the enhanced excitability produced by S1P is mediated by activation of S1PR1 and/or S1PR3”, which has since been confirmed by a growing number of scholars[5, 6] in different perspectives. For example, Hill RZ et al. exemplified in studies using blocking technique and antagonist treatment, showed that loss of S1PR3 decreases mechanical sensitivity and inflammatory pain, together with a selective S1PR3 antagonist can decrease action potential (AP) firing and inflammatory hypersensitivity[6].

2.2. APPLICATION OF S1PR3 MODLATORS

With the increased attention of S1PR3, more and more studies on its agonists and antagonist have been conducted (Table 1.). Although there was no clinical application case, it has been often used in experiments to study the function of receptors. CYM5541 is a well-applicated selective S1PR3 agonist, one of its researches showed that low concentration could not change both AP firing and resting membrane potential (RMP), medium concentration caused dramatical AP firing change but not RMP, high concentration changed RMP obviously, at the meantime two apparent APs in depolarization and recovery period were produced[13]. This was later proved by the same author that high-concentrated CYM5541 depolarized the neuronal membrane by not only S1PR3 but also S1PR1. These observations suggested that the drug concentration is a non-negligible factor during application. In the future, antagonists targeting S1PR3 showed in Table 1. may play as important a role in pain inhibition as S1PR1, and other selective antagonists still need to be developed.

2.3. THE ROLE OF S1PR2

There are a limited number of studies specifically focused on S1PR2. There are shreds of evidence captured from parts of studies about other S1PRs showed that S1PR2 itself cannot increase neuronal excitability[13] but S1PR2 antagonist JTE-013 itself can ameliorate neuronal excitability, which indicates S1PR2 may have inhibitory function

rather than excitatory function. Indeed, few pieces of research have been undertaken to explore the sensory effect of S1PR2 in some diseases. For example, a study about neuropathic pain showed S1PR2 deficiency can reduce mechanical threshold and hence increase pain sensitivity in the mouse model[14]. Another study about chronic constriction injury (CCI) rats demonstrated that S1PR2 overexpression can raise mechanical and thermal pain thresholds while knockdown of S1PR2 aggravated pain sensitivity[15]. Intriguingly, the effect of S1PR2 on pain sensitivity can be abolished by activation of S1PR1 using its specific agonist, CYM-5442, which suggests S1PR2 owning different mechanisms with S1PR1 in terms of hyperalgesia development[15]. Future applications of S1PR2 in other disease models like RA are considered promising.

2.4. APPICATION OF S1PR2 MODULATORS

Regarding S1PR2, all evidence suggests that S1PR2 may play inhibitory roles in peripheral sensation, if so, agonist-induced activation of S1PR2 constitutes a novel therapy for the treatment of pain. However, the detailed functions of S1PR2 are still rudimentarily understood, and hence the development of selective agonists and antagonists is much behind that of S1PR 1&3 (Table 1.). Early on, JTE-013 was developed as a selective S1PR2 antagonist and used in numerous studies to unravel possible functions of S1PR2, during which both of its time- and concentration-dependent effects on excitability together with its narrow activation range was reported. However, later it was proved that JTE-013 was capable of functioning in the condition of lacking S1PR2[16] and even working on other S1PRs. Its exhibited low selectivity, together with low potency and short half-life led to the development of many derivatives with better potency, such as AB1[17]. Interestingly, a series of S1PR2 agonists have also been described like CYM5520, CYM5478 and XAX-126, but so far their biological effects are poorly understood and hence there are no in vivo reports[12]. Taking one with another, it remains to be further studied whether S1PR2 related drugs, like selective S1PR2 agonists, can also be applied to the treatment of pain in certain diseases like RA.

3. LIMITATION AND FUTURE DIRECTION

In conclusion, with the deepening of research on the function of S1PRs in the sensory area, the function of S1PR3 to accelerate hyperalgesia has gradually come into our view. Therefore, the application of S1PR3 antagonists has been discussed too. S1PR2, however, is rarely valued in contrast. What is easily overlooked is that S1PR2 may have an inhibitory effect on neuronal excitation which is opposite to that of S1PR 1&3. Therefore, using selective S1PR2 agonists instead of antagonists may explore a new idea for related analgesic research. Few studies indicated that S1PR 4&5 are not sufficient to mediate the S1P-induced sensitization, but whether they have supplementary or other function remains unknown. Overall, the family of S1PRs appears worthy of continued study and may provide significant therapeutic opportunities in many areas especially pain area[18], and new generation S1PR drugs are also needed to be developed to target more specific S1PRs. Besides all advances of S1PRs in the sensory area and relevant drug, some limitations in past researches like techniques for inhibiting a receptor, the difference between human and mouse DRG, the difference between in vivo and in vitro and drug tolerance, etc. still need to be considered.

In addition, there is evidence showed that S1P not only can directly increase the excitability of rat nociceptor sensitivity and cause thermal hyperalgesia[19] in vitro[4] and in vivo[2] but also can exert its actions at least in part via the upregulation of peroxynitrite[19]. This demonstration about the other functional pathway of S1P besides through S1PRs is also an interesting topic. Besides, previous in vitro studies of S1P on sensory neurons mainly focused on small-diameter neurons, but evidence from a study suggests that larger diameter neurons may also play important roles in mediating pain behaviours in various rodent pain models[20]. The study of neurons with different diameters is another topic of concern.

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Analysis of Anti Infection Effect of Piperacillin Tazobactam and Cefoperazone Sulbactam in Elderly Patients with Coronary Heart Disease

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Abstract: Objective: to analyze the anti infection effect of piperacillin tazobactam and cefoperazone sulbactam in elderly patients with coronary heart disease. Methods: the experiment was carried out in groups from January 2019 to December 2020. The control group (cefoperazone sulbactam) and the study group (piperacillin tazobactam) were divided into two groups. The experimental patients were 98 elderly patients with coronary heart disease (49 cases in each group). Two groups of comparative indicators: pathogen clearance rate, incidence of adverse reactions. Results: the pathogen clearance rate of the study group was 94.63%, and that of the control group was 81.48%, which was higher than that of the control group ($P < 0.05$). The incidence of adverse reactions was 3.57% in the study group and 16.33% in the control group, which was lower in the study group than in the control group ($P < 0.05$). Conclusion: piperacillin tazobactam is better than cefoperazone sulbactam in the treatment of anti infection in elderly patients with coronary heart disease, which can better remove pathogenic bacteria, control various adverse reactions during drug treatment, and ensure the effectiveness and safety of drug use.

Keywords: Piperacillin Tazobactam; Cefoperazone Sulbactam; Elderly; Coronary Heart Disease; Infection

1. Introduction

Coronary heart disease (CHD) is a kind of human coronary artery atherosclerosis, which leads to vascular stenosis, occlusion and other phenomena, leading to myocardial ischemia, hypoxia or necrosis, and heart diseases. As an elderly multiple disease, the disease is often accompanied by infection, which leads to the aggravation of the disease, increases the difficulty of treatment, and increases the mortality. Therefore, in the process of disease treatment, we need to pay attention not only to the control of coronary heart disease, but also to the intervention of infection. Elderly patients have a variety of basic diseases, such as hypertension, diabetes, and so on. They have higher requirements for treatment drugs. They not only need to pay attention to the effectiveness of disease treatment, but also need to pay attention to the safety of drug treatment. Piperacillin tazobactam and cefoperazone sulbactam are effective in the treatment of senile coronary heart disease [1], but there are still some differences between the effect and safety, which need to be analyzed in detail to provide more effective disease treatment measures [2]. In this paper, we analyzed the effect of piperacillin tazobactam and cefoperazone sulbactam on anti infection in elderly patients with coronary heart disease:

2 Data and Methods

2.1 General information

The experiment was carried out in groups from January 2019 to December 2020. The control group (cefoperazone

sulbactam) and the study group (piperacillin tazobactam) were divided into two groups. The experimental patients were 98 elderly patients with coronary heart disease (49 cases in each group). Inclusive indicators: 1) diagnosis was made after dynamic ultrasound and coronary CT examination; 2) all examinations and clinical data were complete; 3) there was no problem of drug allergy in the past; 4) patients signed the experimental consent. Exclusion criteria: 1) coagulation dysfunction; 2) kidney injury; 3) congenital heart disease; 4) severe mental and consciousness disorders; 5) deficiency of autoimmune system. In the control group, there were 25 males and 24 females, with a median age of (73.57 ± 4.65) years old ranging from 60 to 87; in the study group, there were 26 males and 22 females, with a median age of (74.14 ± 4.38) years old ranging from 60 to 88. There was no significant difference between the two groups ($P > 0.05$).

2.2 Method

Control group: cefoperazone sulbactam (Suzhou Dongrui Pharmaceutical Co., Ltd., Guoyao Zhunzi h20013055) was given by intravenous drip. 2-4g of cefoperazone sulbactam was dissolved in 5% glucose injection or sodium chloride injection, and then diluted to 50-100ml with the same solvent for intravenous drip. The drip time was 30-60min for 7 days.

Research group: piperacillin tazobactam (Zhongshan branch of Zhuhai federal Pharmaceutical Co., Ltd., national medicine Zhunzi h20054307) was also given intravenous drip, with a dose of 3.375g (piperacillin 3g and tazobactam 0.375g) / time. After fully dissolved with 20ml diluent (0.9% sodium chloride injection or sterile water for injection), 250ml liquid (5% glucose injection or 0.9% sodium chloride injection) is immediately added, and the course of treatment are 7 days.

2.3 Observation indexes

First of all, the clearance rates of pathogens in the two groups were evaluated, and the laboratory staff carried out pathogen culture to compare the clearance rates.

Secondly, the incidence of adverse reactions in the two groups was evaluated, including loss of appetite, nausea and fatigue.

2.4 Statistical analysis

The statistical software used in this study was SPSS23.0, the expression of count data was ($x \pm s$), and the statistical t value test was performed; the expression of measurement data was (n,%), and the chi square （X^2）test was performed. The standard of significant difference was $P < 0.05$.

3 Results

3.1 Evaluating the clearance rate of pathogens in the two groups

The pathogen clearance rate of the study group was 94.63% (54 / 56), and that of the control group was 81.48% (44 / 54), which was higher in the study group than in the control group $P < 0.05$.

3.2 Evaluating the incidence of adverse reactions in the two groups

The incidence of adverse reactions in the study group was 3.57%, including 1 case of decreased appetite and 1 case of fatigue. The incidence of adverse reactions in the control group was 16.33%, including 3 cases of decreased appetite, 2 cases of nausea and 13 cases of fatigue. The incidence of adverse reactions in the study group was lower than that in the control group, $X2 = 4.009$, $P = 0.045 < 0.05$.

4. Discussion

Coronary heart disease (CHD) is a disease with high incidence in Department of Cardiology. The body's resistance is significantly reduced, and it is prone to infection, which increases the difficulty of disease treatment. Therefore, it is necessary to control the infection in time. For the elderly patients with coronary heart disease, anti infection treatment mainly focuses on drug control, and penicillin and cephalosporins are widely used. Therefore, it is necessary to analyze the effect and safety of the above two drugs, so as to provide guidance for clinical treatment [3].

The data showed that: the pathogen clearance rate of the study group was 94.63%, and that of the control group was 81.48%, the study group was higher than that of the control group, $P < 0.05$. The incidence of adverse reactions was 3.57% in the study group and 16.33% in the control group, which was lower in the study group than in the control group, $P < 0.05$. Analysis reason: both cefoperazone sulbactam and piperacillin tazobactam are compound drugs. The main components of cefoperazone sulbactam are cephalosporin and sulbactam. The cefoperazone component in the drug can inhibit the synthesis of cell wall of hand bacteria and has significant antibacterial effect, while sulbactam can have a positive effect on cefoperazone and improve the drug effect. [4] The hydrolysis of β - lactam in the body can inhibit the gram bacteria and other bacteria causing infection, but the drug treatment process will lead to some adverse reactions of patients, and the clearance effect of some special bacteria is also low [5]. Piperacillin tazobactam is a compound drug of piperacillin and tazobactam, and the ratio of the two components is 8:1. Its function mechanism is similar to cefoperazone sulbactam, but with better the stability and fat solubility, and more uniform ratio. Therefore, the drug has higher stability, faster antibacterial speed, better safety and more ideal [6-8].

To sum up, piperacillin tazobactam is better than cefoperazone sulbactam in the treatment of anti infection in elderly patients with coronary heart disease, which can better remove pathogenic bacteria, control various adverse reactions during drug treatment, and ensure the effectiveness and safety of drug use.

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To use wild resources properly: a lesson from two species of human coronaviruses

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Abstract: The global pandemic of COVID-19, a disease caused by a severe acute respiratory syndrome-related coronavirus (SARSr-CoV), is responsible for over a hundred million confirmed cases and more than two hundred deaths worldwide. Accumulating evidence indicates correlations between the abuse of wild resources and the outbreaks. To reduce the risks of getting infected with human coronaviruses (HCoVs), brief introductions to HCoVs were made, the hosts of them are listed, the probable transmission routes of the SARSr-CoVs and MERS-CoVs are analyzed, and the recommendation that we use wild resources properly was put forward.

Key words: severe acute respiratory syndrome-related coronaviruses; Middle East respiratory syndrome coronavirus; hosts; transmission routes

1.Introductions to human cornaviruses

Cornaviruses (CoVs), previously known as picornaviruses, are named for the crown-like spikes on their surfaces [1]. These viruses are enveloped positive-sense, single-stranded ribose nucleic acid viruses with their 5' ends capped and 3' ends polyadenylated [2].

Human CoVs (HCoVs) are actually close to us, however, the cognition of them is relatively limited. In fact, it wasn't until 1965 that Tyrrell et al. found a novel virus when cultivating the pathogens responsible for common colds, and the virus is now known as HCoV-229E[3]. Two years later, another HCoV, HCoV-OC43, was reported by Mcintosh K et al.[4]. HCoV-229E and HCoV-OC43 are really common etiological agents that are unlikely to be responsible for severe symptoms[5], consequently, the discoveries of the two HCoVs didn't raise much attention.

However, in 2002 and 2003, the world was struck by an outbreak of an unknown infectious disease, and in February 2003, severe acute respiratory syndrome (SARS) was put forward by Carlo Urbani, an expert on communicable diseases[6], and the pathogen, now known as the first SARS-related CoV (SARSr-CoV), SARS-CoV, was isolated in March 2003[7].

In 2004, Lia et al. identified HCoV-NL63[8], and in 2005, HCoV-HKU1 was characterized by Patrick et al.[9]. HCoV-NL63 and HCoV-HKU1 are very common etiological agents as well, and at the same time, not really harmful[5]. In 2012, another lethal HCoV was reported[10], and named as Middle East respiratory syndrome CoV (MERS-CoV) later.

At the end of 2019, Zhang et al. reported several cases with pneumonia. It didn't take much time to confirm that the etiological is a novel SARSr-CoV[11]. And the diseases caused by the virus, now named as COVID-19, threaten

global public health greatly, and is responsible for more than a hundred million confirmed cases and has caused two hundred deaths worldwide [12].

Until today, six species of HCoVs have been discovered, several strains of SARSr-CoVs and MERS-CoV are lethal, while the others are usually not life-threatening.

2.Bats, the natural reservoir hosts

Bats are ideal natural reservoir hosts of tens of lethal human viruses, as the viruses fail to kill the hosts, and at the same time, the incomplete immune systems of the hosts fail to erase the pathogens.

However, the natural reservoir hosts are almost certain. In 2017, Ben et al. discovered a rich gene pool of bats, and concluded that, horseshoe bats (Rhinolophus species) are likely to be responsible for the outbreak of SARS[13], and Zhou et al. announced that the natural reservoir hosts of SARS-CoV-2 might be horseshoe bats as well[11]. Besides, accumulating evidence indicates that, MERS-CoV originates from Nycteris species, Pipistrellus species, or Egyptian tomb bats (Taphozous perforatus).

However, bats do react to viral infections, at least viral infections would usually trigger humoral immune responses, and the immunoglobulins against CoVs, WNV, EBOVs and Nipah Virus had been isolated in the serum of bats.

3.Evidence for the association between the outbreaks and the exposures to wholesale markets

Wholesale markets are the places where direct contact with infected animals. Shortly after the outbreak of SARS-CoV infection, Guan et al. isolated a SARSr-CoV from the masked palm civets (Paguma larvata) and a raccoon dog in a live animal market in Guangdong, even though the sequences of these isolates differs from most of the human isolates[14].

Coincidentally, studied the early cases, and most of us have heard of Huanan seafood market, a wholesale market in Wuhan. This market mightn't be the origin of the outbreak of SARS-CoV-2 infection in Wuhan, most of the exposed to and the samples collected there were tested positive. Evpidemiology studies indicated the correlation between another outbreak of SARS-CoV-2 infection and the exposure Xinfadi wholesale market, and the samples collected there tested positive, too.

However, Li reviewed the clinical uses of bats, he listed a fetal case of severe acute diarrhea in the Tang Dynasty, then he mentioned the clinical observations, and concluded that, bats are toxic, and would usually lead to diarrhea[15]. Actually, diarrhea is one of the typical symptoms of coronaviral infections[5][16]. Even though a variety of etiological agents are responsible for diarrhea, and we couldn't conclude whether HCoVs contributed to that death, the fact that hunting or slaughtering bats greatly increase the risks of bat-to-person transmissions of lethal etiological agents is self evident.

4.Wild meat trades increase zoonotic infection risks

We've mentioned that the live animal market in Guangdong is really likely to be responsible for the outbreak of SARS-CoV infection, and the first case isn't alone. Shortly after the outbreak of SARS-CoV-2 infection, the clinicians found that, at the beginning of the outbreak, most patients were exposed to Huanan Seafood Market[17].

Even though there isn't enough evidence to conclude that, pangolins are responsible for the SARS-CoV-2 pandemic, the fact that pangolins could be infected with SARSr-CoVs that greatly resemble SARS-CoV-2 is evident[18].

It's well known that masked palm civets prefer eating fruits, however, growing evidence has shown that, the civets are capable for hunting, and enjoy eating meat as cats and dogs, their relatives, Zhou et al. found that, the food categories that masked palm civets consume could vary from seasons to seasons, while fruits, mammals and birds are

favorable[19], indicating that the civets might hunt bats for food, and might somehow bite we human beings. The civets might bite we human beings, while some people hunt the civets for food, both would be risky. In other words, the bat-to-civet transmission is possible to be accomplished via the grazing food chain, and the exposure is usually increased greatly when slaughtering.

As for pangolins, their skins are typically covered by scales, which would reduce the exposure and prevent them from being bitten by other animals. More importantly, they're toothless.

As mentioned, bats are used in tradition Chinese medical practices. Actually, pangolins are even much more popular. The patients mightn't get infected when consuming, but hunting, slaughtering and preparing the drugs are really risky.

Even though Liu et al. suspected that reptiles could be the sources of SARS-CoV-2 infection[20], up to now, any non-mammalian animal-to-person transmissions of SARSr-CoVs or MERS-CoV haven't been reported, hunting other wild animals isn't always safe. Wild birds would be responsible for the transmission of H5N1 avian influenza virus[21], and wild non-mammalian animals would make great contributions to the transmission of bacteria and parasites as well[22].

In summary, reducing consuming wild animals, particularly wild mammals, would usually limit the unnecessary exposure, and protect us from getting infected.

5.Conclusion

This paper analyzed the probable transmission routes of the SARSr-CoVs and MERS-CoVs, and the conclusion that wild resources properly should be used properly was drawn. First of all, the HCoVs were introduced. Secondly, the natural reservoir hosts and candidate sources of infections of emerging infectious diseases, particularly SARSr-CoVs were analyzed. Thirdly, based on the analyses, we drew a conclusion that making uses of wild resources properly would help limit the risks and provide us with more solutions to the diseases.

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Efficacy Assessment of Emergency Percutaneous Coronary Intervention (PCI) for Acute Myocardial Infarction (AMI)

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Abstract: Objective: to assess the clinic effect of percutaneous coronary intervention in the treatment of acute myocardial infarction. Methods: 90 patients with acute myocardial infarction in our hospital were chosen to be research objects and they were divided into two groups: control group and research group. Patients in control group were only treated by thrombolytic therapy while those in research group were further treated by percutaneous coronary intervention on the basis of this treatment. Result: the efficacy of research group was higher than that in control group. The incidence of adverse events was 4.44%, which is lower than that in control group. Conclusion: we should effectively apply percutaneous coronary intervention in treating acute myocardial infarction so as to improve the cardiac function of the patients. In addition, this treatment is safer and will lower the incidence of heart and renal failure.

Key words: acute myocardial infarction; thrombolytic therapy; percutaneous coronary intervention

1 Introduction

Acute myocardial infarction is a very common severe case in clinic treatment. It frequently occurred in the mid-aged and the elderly group. When patients were attacked by such disease, there is always a significant higher level of myocardial enzyme series in their bodies, which will badly affect their daily life. With reference to the clinic treatment of myocardial infarction and a further exploration on this issue, we find that the efficacy is significantly raised when applying percutaneous coronary intervention in the treatment, which will highly improve the patients' health conditions by raising their cardiac function and will also lower the case fatality.

2 Data and methods

2.1 Data

From March 2017 to March2019, 90 patients with acute myocardial infarction in our hospital were chosen to be research objects and they were divided into two groups: control group and research group. [1]Among the 45 patients in control group,there are 28 male patients and 17 female patients with an average age of 58.76±7.04. And among the 45 patients in research group, 26 are male and 19 are female, with an average age of 57.47±6.34. Since there was no significant difference in data between the two groups, the data are comparable.

2.2 Methods

Patients in control group were treated by thrombolytic therapy, that is to say, they were treated by intravenous

infusion by giving 500,000 units of urokinase when diluted to 1 million units and mixed with 100mL of normal saline.[2] However, patients in research group will be further treated by treated by percutaneous coronary intervention on the basis of this treatment. Detail treatments are as follows: firstly, transferring patients and then treating them by percutaneous coronary intervention: patients who are not suitable for thrombolytic therapy should be transferred to hospitals with percutaneous coronary intervention.[3] Secondly, directly treating patients by percutaneous coronary intervention: to further dredge infraction artery 12 hours before the outbreak and the treatment time shall be controlled within 90 minutes.

2.3 Observation index and assessment standard

2.3.1 Observation index

To figure out and compare the incidence of adverse events and the changes of patients' cardiac function level before and after the treatment.

2.3.2 Efficacy assessment standard

Excellent Efficacy: the patients' conditions of coronary artery stenoses significantly improved after treatment; Average efficacy: the patients don't occur angina and have no adverse reaction after treatment; Naught efficacy: there are no improvement in acute myocardial infarction or the patients died after treatment.[4]

2.4 Statistical methods

Statistic software SPSS22.0 is used to analyze the data. The measurement data are expressed as "x±s" and will be testified by t. The adoption rate of enumeration data is expressed by % and is testified by $\chi 2$. $P < 0.05$ represents the difference. When the probability of the difference is below 0.05, the data bears statistical significance.

3 Results

3.1 Comparison of incidence of adverse events between two groups

The incidence of adverse events in research group is 4.44%, lower than 17.78% in control group. And this difference bears great statistical significance（$P < 0.05$）.See in Table 1.

Table 1 The incidence of adverse events in tow groups［n(%)］

Groups	Cases	Hemmorrhage	Renal Failure	Angina	Incidence
Research Group	45	0	1（2.22）	1（2.22）	2（4.44）
Control Group	45	3（6.67）	3（6.67）	3（6.67）	9（20.00）
X^2					4.050
p					0.044

3.2 Comparison of Clinic efficacy between two groups

The total efficacy in research group is higher than that in control group and the difference bears great statistical significance($P < 0.05$). See in Table 2.

Table 2 Comparison of Clinic efficacy between two groups

Groups	Cases	Excellent Efficacy	Average Efficacy	Naught Efficacy	Total Efficacy
Research Group	45	20（44.44）	24（53.33）	1（2.22）	44（97.78）
Control Group	45	18（40.00）	20（44.44）	7（15.56）	38（84.44）
X^2					4.939
p					0.026

4 Discussion

Acute myocardial infarction is characterized by severity and urgency in outbreak. It is usually caused by an emergency block in coronary artery in patients' body.[5] If the patients don't get immediate treatment, the size of myocardial infarction will gradually expand, thus leading to arrhythmia, renal failure as well as shock. What's worse, the patients may probably get a sudden death when their conditions get worse, which exerts a great threat to their physical safety. The experimental results show that the total efficacy of research group is 97.78% and is much higher than that of 84.44% in control group. In general, the incidence of adverse events happened in patients with acute myocardial infarction is gradually declining after percutaneous coronary intervention and is far lower than that of patients treated only by thrombolytic therapy. At the same time, when treated by percutaneous coronary intervention, the patients will be better treated and all their index of cardiac function will be improved, which is helpful to further control their treatment efficacy and improve their block in coronary artery.[6] As a doctor, it is necessary to choose appropriate treatment for the patients when treating. Only when we scientifically carry out our treatment, shall we better cure our patients who are suffering myocardial infarction.

Percutaneous coronary intervention is a form of operative treatment, which needs to perform coronary artery bypass operation for the patients when operating. It will use intracoronary stenting to further improve patients' conditions of myocardial infarction so as to achieve an effective adjustment to their conditions of myocardial infarction.[7] Meanwhile, it shall effectively improve their conditions of coronary artery stenoses by percutaneous coronary intervention so as to ensure the preservation and recovery of their cardiopulmonary function. In addition, by using percutaneous coronary intervention, it shall further improve their conditions of coronary arteriosclerosis and dredge their clogged artery so as to raise the dredge capability of the coronary artery and help improve patient's conditions. It can be find from clinic experiment that percutaneous coronary intervention had sound efficacy in treating patients with acute myocardial infarction.[8] It can quickly change the conditions of coronary artery stenoses and improve their cardiopulmonary function and cardiovascular supply, so as to get enough time for treatment. And after treatment, it shall effectively control the incidence of adverse events and improve patients' conditions of myocardial infarction.

In conclusion, we should actively apply percutaneous coronary intervention in the treatment of acute myocardial infarction so as to improve patients' cardiopulmonary function. Since its low incidence of heart and renal failure, safety and significant treatment efficacy in treatment, percutaneous coronary intervention bears great significance in clinic treatment.

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Analysis of Acupoint Selection Rules for Electroacupuncture Treatment of Osteonecrosis of the Femoral Head Based on Data Mining Technology

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Abstract: Objective: Analysis was focused on the data mining technology of electroacupuncture (EA) of osteonecrosis of the femoral head (ONFH) of the rules and characteristics of point selection in the clinical treatment, to provide a basis for clinical electroacupuncture treatment of ONFH. Methods: The Chinese and English literatures obtained from the CNKI and PubMed database on the treatment of ONFH by electroacupuncture, the Endnote database for the treatment of osteonecrosis of the femoral head by electroacupuncture was established, and the rule of point selection was analyzed by data mining and statistical software Excel ,SPSS,SPSS Modeler. Results: A total of 17 articles were included, and 44 acupoints were selected with a total frequency of 169 times. The most frequently used acupoints in turn are Juliao(GB29),Shenshu (BL23), Biguan (ST31);The selected acupoints mainly belonged to bladder meridian; The acupoints are mainly distributed in the lower limbs, the five shu points are used mostly in the special points, among them, the he-sea points is the most widely used; the dense-sparse waves is mostly used in the electroacupuncture waveform. Cluster analysis can be divided into three categories. The result of correlation analysis showed that "Shenshu(BL23)→Ashi Point" had the highest support degree. Conclusion: electroacupuncture treatment of acupoint selection of Osteonecrosis of the femoral head is centered on Juliao (GB29), Shenshu (BL23), Biguan (ST31), Huantiao (GB30) and Ashi acupoints, with emphasis on selection of acupoints along local points and dialectical matching.

Keywords:Acupuncture; Osteonecrosis of the Femoral Head； Acupoint Selection Rule； Data Mining

Introduction

ONFH is a refractory orthopedic disease characterized by hip pained joint dysfunction [1、2]. The patients' number of ONFH in China is 5 million to 7.5 million [3]. The main causes of ONFH were inappropriate hormone use and alcohol consumption [4]. The main pathological process includes the collapse of the femoral head caused by various factors which destroy the microstructure of the femoral head. Clinically, electro-acupuncture treatment of femoral head necrosis is also a more common clinical means. In order to improve the effectiveness of clinical treatment, the rules of selecting Meridians and acupoints in clinical study of using electro-acupuncture to treat ONFH was discussed and analyzed by using data mining technology.

1.Data and methods

1.1 scope of Literature Retrieval

China National Knowledge Infrastructure Database (CNKI), PubMed. Search Time: from build up to 2021. Type selection of search words: subject words plus free words. The key words are “osteonecrosis of the FEMORAL head” and “acupuncture” and “electroacupuncture”, “ELEC troacupunture” and “osteonecrosis of the female head” and “acupunture”. Retrieval method: Set the above words as subject words, key words, using the general retrieval strategy of the database.

1.2 literature inclusion criteria

(1) clinical related studies on ONFH; (2) intervention using electro-acupuncture therapy or electro-acupuncture combined with other treatment methods; (3) specific selection of points in electro-acupuncture prescription; (4) literature with significant clinical therapeutic effect.

1.3 criteria for exclusion of the literature

(1) non-clinical trials;(2) intervention did not involve electroacupuncture therapy;(3) complications;(4) full-text Literature was not available; (6) republished literature.

1.4 data extraction and data analysis

The documents retrieved by the computer are stored in the Endnote X9 database and the duplicate documents are excluded. The literatures were sorted according to the inclusion and exclusion criteria, and the relevant data were sieved and extracted. The frequency and regularity of acupoints and meridian are analyzed by establishing a Excel table of the extracted data. SPSS 23.0 is used to cluster the acupoints, and the APRIORI ALGORITHM IN SPSS Modeler subscription 1.0 is used to analyze the association rules of acupoints.

2. Results

2.1 literature search results

The first search included 95 articles, 87 articles are in Chinese and 8 articles are in English, among which 2 duplicate articles were found.17 Chinese literatures and 0 English literatures were selected. The prescriptions of electro-acupuncture points included in the literature are clear.

2.2 Rules of acupoint selection

2.2.1 Results of acupoints selection

The number of acupoints used in 17 articles is 44, the total frequency of acupoints used is 169, the frequency of acupoints used in 5 times or more is 16, accounting for 73.96% of the total number of acupoints, see Table 1.

Table 1 Statistics on acupoints frequency ≥ 5

sequence number	acupoint	frequency	relative frequency	sequence number	acupoint	frequency	relative frequency
1	GB29	14	8.28%	10	ST36	6	3.55%
2	BL23	14	8.28%	11	BL40	6	3.55%
3	ST31	13	7.69%	12	GV3	6	3.55%
4	GB30	10	5.92%	13	BL36	5	2.96%
5	ashi point	8	4.73%	14	LR12	5	2.96%
6	K13	8	4.73%	15	BL60	5	2.96%
7	GB39	7	4.14%	16	GV4	5	2.96%
8	GB34	7	4.14%	17	other acupoints	44	26.03%
9	BL54	6	3.55%				

2.2.2 selected acupoints according to Meridian Analysis and Statistics

10 Meridians were applied in electroacupuncture treatment of ONFH (see table 2).

2.2.3 Analysis of the acupoints selection distribution sites

Distribution analysis of acupoints selected for electro-acupuncture treatment of osteonecrosis of the femoral head were statistically analyzed (see table 3).

table 2 Statistics on the meridian which the acupoints belongs to

Sequence number	Meridians	Frequency statistics		Acupoints		Acupoint include
		frequency	relative frequency(%)	number	relative frequency(%))	
1	bladder meridian	45	26.63	11	25.00	BL23(14)，B L40(6)， BL54(6)，BL36 (6)，BL60(5)，BL18(2)，BL 20(2)，BL32(1),BL17(1)，BL13(1)，BL21(1)
2	gall bladder meridian	41	24.26	5	11.36	GB29 (14)，GB30(10)，GB39(7)，GB34(7)，GB31(3)
3	Stomach Meridian	22	13.02	5	11.36	ST31(13)，ST36(6)，ST3(1)，ST41(1)，ST34(1)
4	governor meridian	13	7.69	4	9.09	GV3(6)，GV4(5)，GV20(1)，GV 14 (1)
5	liver meridian	11	6.50	3	6.82	IR12(5)，LR11(3)，LR 10(3)
6	Spleen Meridian	10	5.92	4	9.09	SP10(4)，SP6(4)，SP9(1),SP 12(1)
7	kidney meridian	8	4.73	1	2.27	K13 (8)
8	ren meridian	5	2.96	3	6.82	CV4(2)，CV6(2)，CV12(1)
9	large intestinal meridian	3	1.78	3	6.82	LI11(1)，LI4(1)，LI5(1)
10	pericardium channel	1	0.59	1	2.27	PC6 (1)

2.2.4 analysis of specific acupoints selected for electroacupuncture treatment of ONFH (see table 4).

Table 3 Statistics on the distribution sites which the acupoints belongs to

Sequence number	distribution sites	Frequency statistics		Acupoints		Acupoint include
		frequency	relative frequency(%)	number	relative frequency(%))	
1	lower limb	80	47.34	16	35.56	ST31(13)，K13(8)，ashipoint(8)，GB39)(7)，GB34(7)，ST36(6)，BL40 (6)，BL60(5)，SP6(4)，SP10(4)，LR10 (3)，LR11(3)，GB31 (3)，SP9(1)，ST34(1)，ST41(1)
2	buttock	39	23.08	7	15.91	GB29 (14)，GB30(10)，BL54(6)，BL36(6)，juliaoxiadian(1)，waichengfu(1)，BL32(1)
3	Lower back	26	15.38	4	9.09	BL23(14)， GV3(6)，GV4(5)，tunshuang(1)
4	Chest back	7	4.14	5	11.36	BL18(2)，BL20(2)，BL13(1)，BL21(1)，BL17(1)
5	abdomen	6	3.55	4	9.09	CV4(2)， CV6(2)，CV12(1)，SP12 (1)
6	groin	5	2.96	1	2.27	LR12(5)
7	Upper limb	4	2.37	4	9.09	PC6(1),LI11(1)，LI4(1)，LI5(1)
8	head and neck	3	1.76	3	6.82	GV14(1)，GV20(1)，GB29(1)

Table 4 Frequency statistics of Specific Acupoints for electroacupuncture treatment of ONFH

Sequence number	Specific Acupoints	Frequency statistics		Acupoints		Acupoint include
		frequency	relative frequency (%)	number	relative frequency(%)	
1	five-shu point	36	32.72	9	20.45	K13(8)，GB34(7)，BL40(6)，ST36(6)，BL60(5)，SP9(1)，ST41(1)，LI 11(1)，LI5(1)
2	Back-shu point	21	19.09	6	13.64	BL23(14)，BL18(2)，BL20(2)，BL13(1)，BL17(1)，BL21(1)
3	lower He point	19	17.27	3	6.82	GB34(7)，ST36(6)，BL40 (6)
4	eight influential points	15	13.64	3	6.82	GB39 (7)，GB34(7)，ST36(6)
5	yuan-primary point	9	8.18	2	4.55	K13(8)，LI4(1)
6	crossing point	4	3.64	1	2.27	SP6(4)
7	front-mu point	3	2.73	2	4.55	CV4(2)，CV12(1)
8	eight convergent points	1	0.90	1	2.27	PC6(1)
9	luo-connecting point	1	0.90	1	2.27	PC6（1)
10	Xi-Cleft acupoint	1	0.90	1	2.27	ST34(1)

2.3 cluster analysis

Cluster analysis was carried out on the first 16 acupoints. The results of Dendrogram showed that the acupoints could be divided into 3 types: Cluster 1 was GB34-GB39-BL54-BL36-BL23-GB29-GB30-ST36-ST31-BL40-SP9-SP10, cluster 2 was Ashi point, cluster 3 was K13-CV4. (see figure 1)

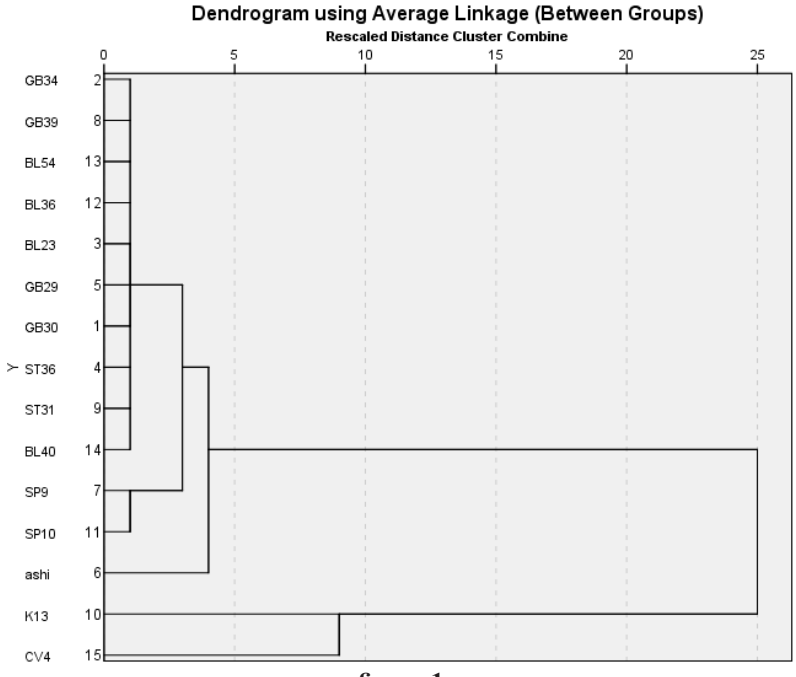

figure 1

2.4 Association Rule Analysis

Association rule analysis to select the 16 acupoints with the highest frequency, and the adjustment parameter is "support degree ≥30% , confidence degree ≥90% ".The Network Graph of association rules can display the correlation of each prescription acupoint in the form of network under the support degree of setting for reference. The results showed that the most common compatibility of acupoints was "Shenyu→Ashi" and "Shenyu→Taixi", the support rate was 47.059% and the confidence rate was 100.0%. (see Table 5, figure 2)

Table 5 Statistical of association analysis of acupoint selection rules for electroacupuncture treatment of ONFH

consequent	Antecedent	Support(%)	confidence(%)	Lift
Shenshu(BL23)	ashi point	47.059	100.0	1.308
Shenshu(BL23)	Taixi (K13)	47.059	100.0	1.308
huantiao(GB30)(10)	Weizhong (BL40)(6)	35.294	100.0	1.7
huantiao(GB30)(10)	yanglingquan（GB34）	35.294	100.0	1.7
ashi point	Yaoyangkuan(GV3)	35.294	100.0	2.125
Biguan(ST31)(13)	Yaoyangkuan(GV3)	35.294	100.0	1.308
ShenshuBLI23)	Yaoyangkuan(GV3)	35.294	100.0	1.308

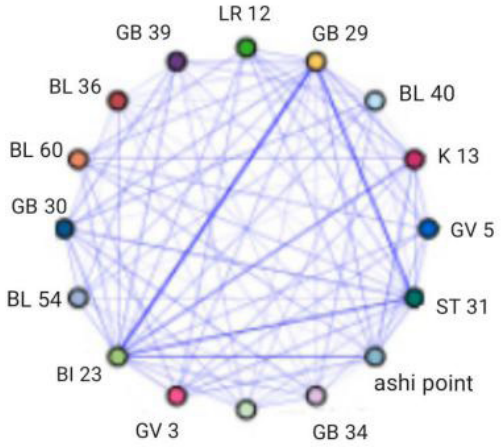

Figure 2. Mesh Graph of association rule analysis

3.Discussing

The concept of “bone erosion”, “bone arthralgia” are the understanding of the ONFH in the theory of traditional Chinese medicine, the etiology and pathogenesis are concluded as stagnation of Qi and blood caused by external factors such as blood stasis, cold, etc. [5]. Therefore, the rules of treatment should be based on strengthening the liver and kidney, warming Yang, dispersing cold, supplementing Qi, removing dampness and promoting blood circulation, eliminating phlegm and removing blood stasis.

The results of this study showed that the clinical electroacupuncture treatment of ONFH mainly used Bladder Meridian, Gall baldder Meridian, Stomach Meridian, and the function of the Meridians were matched with the treatment rules of ONFH.

The Bladder Meridian acupoints are selected for the treatment of ONFH by the function of promoting yang and promoting Qi circulation, relaxing the tendons and communicating the meridian, dispersing cold and dampness [6]. It is the main meridian for the treatment of ONFH. Gall bladder meridian can diffuse cold and dampness, communicating Qi and blood. Stomach Meridian can benefit Qi and blood to comfort joints.

In clinical application, the specific acupoints have their unique function. The most commonly used specific acupoints in electro-acupuncture treatment of ONFH are the five-Shu acupoints, of which the he-sea points are the most widely used, it is considered that the combined acupoints have the function of treating cold pathogen Qi entering the interior.

In this study, we found the highest frequency of use of five acupoints for Ju Liao, Shen Yu, Bi Guan, Huan Tiao, Ashi acupoints, which have a general function of comforting joints.

In this study, we analyzed the waveform selection of electro-acupuncture treatment of ONFH. We found that the clinical selection was mainly the dense-sparse waves. According to Xiao Liang [7], dense-sparse waves have better analgesic effect. The main objective of electroacupuncture waveform selection in clinical treatment of ONFH is to relieve pain and promote circulation and metabolism.

The cluster analysis method was used to analyze the results with the theory of TCM. The results can be divided into 3 categories. Cluster 1 is GB34-GB39-BL54-BL36-BL23-GB 29-GB30-ST36-ST31-BL40-SP9-SP10. Cluster 2 was Ashi point, is a point of analgesic effect, cluster 3 was K13-CV4, tonifying the kidney and strengthening the bone.

The results of association rule analysis showed that the combination of acupoints in the order of the top 2 in support degree was “Shenshu → Ashi acupoint” and “Shenshu → Taixi” .Taixi, Shenshu and Ashi acupoints are used together for the purpose of tonifying the kidney and strengthening the bone, dispersing pathogenic factors and relieving pain.

4.Conclusion to sum up,

Electroacupuncture treatment of ONFH takes Ju Liao, Shen Yu, Bi Guan, Huan Tiao and Ashi acupoints as the core acupoints selection; bladder meridian is more used. The selected acupoints are mainly distributed in the lower limbs. The wave form of electroacupuncture usually uess dense-sparse waves, focusing on reducing pain and promote circulation and metabolism. In the treatment, it is important to select the acupoints according to syndrome differentiation by combining the pathogenesis, and to select the acupoints locally around the Meridians and the painful sites.

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