Clinical Study of Urinary Kallidinogenase in the Treatment of Progressive Cerebral Infarction

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ABSTRACT **Objective:** To evaluate the efficacy and safety of Urinary kallidinogenase in the treatment of progressive cerebral infarction. **Method:** 104 cases of patients with acute cerebral infarction were randomly divided into treatment group and control group; where control group (52 cases) patients on with only basic medicine, while treatment group (52 cases), besides the basic medicine, patients will on urinary kallidinogenase 0.15 PNAU + 0.9% normal saline 100 mL intravenous injection, 1 times per day, and continuous for 14 days. The degree of neurological impairment (NIHSS) was assessed before and after treatment, and the changes of blood pressure were monitored. The liver, renal function, fibrinogen, platelet, and the adverse reactions were recorded and followed up in three month. **Results:** After treatment, NIHSS scores of the both groups were decreased ($p < 0.05$), however, total effective rate for treatment group were better than control group ($p < 0.05$). **Conclusion:** Urinary kallidinogenase is safe and effective in the treatment of progressive cerebral infarction.

1. Introduction

Progressive cerebral infarction refers to after the onset of the symptoms of slightly neurological impairment, but showed increase in a progressive way. The progression can extended up to 48 h, until the emergence of serious defect of nervous function of acute ischemic stroke, which accounted 26−43% from total cerebral infarction [1]. The mortality rate and disability rate is higher, and the conventional treatment effect was not ideal. In this paper, discussion was done on the application of urinary kallidinogenase in acute progressive cerebral infarction treatment. The domestic class I new drug, urinary kallidinogenase, namely the urinary kinin original enzyme, which able to induce selective dilation in cerebral arterioles, and promote formation of neovascularization of ischemic area. 52 patients with progressive cerebral infarction patients from department of Neurology in our hospital which hospitalized since February 2010 to February 2013 achieved certain curative effect in the treatment application

of urinary kallidinogenase.

2. Materials and methods
2.1. General information

104 patients with progressive cerebral infarction were randomly divided into control group and treatment group with 52 cases in each group. The control group consist of male 34 cases and female 18 cases, aged 23−73, and time interval between drug administration and disease onset time was less than or equal to 48 hours. There were 32 cases of hypertension, 16 cases of hyperlipidemia, 15 cases of diabetes, 3 cases of atrial fibrillation, 2 cases of transient ischemic attack (TIA), 27 cases of smoking or/and wine addiction. In 52 cases of treatment group, 35 cases were male and 17 were female, aged from 31−80, and time interval between drug administration and disease onset time was less than or equal to 48 hours. There were 35 cases of hypertension, 17 cases of hyperlipidemia, 16 cases of diabetes, 4 cases of atrial fibrillation, 5 cases of TIA history, 25 cases of smoking or/and wine addiction. There was no significant difference in gender, age, past history, treatment of neurological function defect score (NIHSS) in the two groups ($p > 0.05$). There was no significant difference between the two groups ($p > 0.05$).

2.2. Inclusion criteria

The onset within 48 hours, and in accordance with

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through 1995 the 4th National Conference on cerebrovascular disease diagnostic criteria [2]; (1) The age is more than or equal to 18 years of age, (2) NIHSS score of 4 to 20; (3) Confirmed by cranial CT and/or MRI 2–3, and exclusion of hemorrhagic infarction; (4) Without hemorrhage or bleeding tendency within the last 1 month; (5) Does not on vascular angiotensin converting enzyme inhibitor class of drugs within 24 hours; (6) Signed a written informed consent. Exclusion criteria: (1) Cerebral hemorrhage and other bleeding tendency, brain tumor, brain contusion and laceration of brain organic disease; (2) Combined cardiac insufficiency; (3) Chronic liver disease which cause ALT increased (1.5 times greater than normal); (4) Serum creatinine increased (1.5 times greater than normal); (5) Age > 85 years old; (6) Allergic constitution; (7) Dementia and psychosis.

2.3. Control group

The basic drugs were: Bayaspirin 300 mg/d for 7 d, then reduce to 100 mg/d, Atorvastation 20 mg, Ginkgo biloba extract 20 mL + 0.9% normal saline, 250 mL intravenous infusion once per day. Treatment group: Basic Medicine and give 0.15 PNA urinary kallidinogenase with 0.9% normal saline 100 mL intravenous drip for 1 h, 1 times/day, treatment for 14 days. Patients with primary disease in both groups was treated with respective symptomatic therapy, such as adjusting blood sugar, control blood pressure and other conventional treatment such as rehabilitation therapy. During the treatment period ACEI drugs administration was restricted.

2.4. Efficacy evaluation

NIHSS score of patients were recorded before and after 14 d of drugs administration, and determine according increase or decrease of the score. Healing: functional defect score decreased from 91% to 100%; Significant progress: functional defect score decreased from 46% to 90%; Progress: functional defect score decreased from 18% to 45%; Invalid: functional defect score was reduced by 17%. Total effective rate = (basic recovery + significant progress + progress) case number/total number of cases × 100%. Telephone follow-up at 3 months, to estimate BI score. Blood routine, liver, renal function, glucose and blood lipid were detected before and after treatment, careful observation and detailed record of adverse reactions.

2.5. Statistical methods

Using SPSS 13.0 statistical software, measurement data ($\bar{x}$ ± s); between the two groups compared with t test; count data with x^2 test.

3. Results
3.1. Comparison of neural function defect score

The score of neurological function in the treatment group before treatment was (7.91 ± 0.89), and the neurological function score after treatment was (3.82 ± 0.81). The score of neurological function in the control group before treatment was (7.78 ± 1.02), and the neurological function score after treatment was (5.76 ± 0.43). Two groups of patients before treatment, t test value for neurological function score was 1.236541, and p value was 0.985612, the difference was not statistically significant ($p > 0.05$); after treatment, t test value for both neurological function score was 12.956587, and p value was 0.000125, two groups were significantly different ($p < 0.05$). Specific results are shown in Table 1.

Table 1. NIHSS score of two groups of patients after treatment.

Group	n	Before treatment	After treatment
Treatment group	52	7.91 ± 0.89	3.82 ± 0.81
Control group	52	7.78 ±1.02	5.76 ± 0.43
t	-	1.236541	12.956587
p	-	0.985612	0.000125

3.2. Comparison of the two groups of patients

Comparison of two groups of patients in the treatment: treatment group 5 cases of healing, 18 cases of significant progress, 20 cases of progress, unchanged in 7 cases, and 2 cases of death. While, for the control group, there were 2 cases of healing, 10 cases of significant progress, progress in 17 cases, unchanged in 3 cases and 20 cases of death. The effective rate of treatment group was significantly higher than that of control group ($p < 0.01$). There were significant differences in total effective rate between the two groups ($p < 0.05$) (Table 2).

3.3. Laboratory index

Liver and kidney function, blood routine, urine routine, PT, TT, APTT before and after treatment and between the two groups had no obvious changes.

Table 2. Comparison of clinical efficacy between the two groups (%).

Group	n	Basic healing	Significant progress	Progress	No change	Death deterioration	Explicit efficiency	Total efficiency
Treatment group	52	5	18	20	7	2	44.2%	82.6%
Control group	52	2	10	20	17	3	23.1%	61.5%
x^2	-	1.37849	3.12782	0.00	5.41667	0.21010	5.21077	5.78575
p	-	0.240357	0.07697	0.00	0.01994	0.64669	0.02245	0.01616

3.4. Follow up results

Three month after discharged from hospital, followed up was done by telephone, which control group and treatment group were followed up 40 and 43 cases, respectively. The result was analyzed with B1 and MRS to measure the daily life ability of patients. If B1 > 95 points, basic life can be independent; whereas if B1 < 95 points, basic life cannot be independent. There was no significant difference in NHISS score between the two groups, and the follow-up results showed that the x^2 test showed that the two groups had significant difference after three month ($p < 0.05$).

Table 3. B1 values of 3 months after follow-up.

Group	n	B1 index	
		B1 > 95	B1 < 95
Treatment group	43	31	12
Control group	40	19	21

4. Discussion

At present, the pathogenesis of progressive stroke was cause by the formation of primary thrombus, subsequently resulted disappearance of collateral circulation, and the changes of blood coagulation factors which is caused by the blockage of collateral vessels. Therefore, the establishment of collateral circulation can be improved as soon as possible after the onset of the disease, and it can inhibit the formation of thrombus, and save the function of the cells in the area of the ischemic and the half dark zone is the key to the treatment [3]. Urinary kallidinogenase is a new drug developed in recent years, which is extracted from the urine of healthy men. The pharmacodynamic experiment shows that in a certain dose of urinary kallidinogenase cause selective dilation of the ischemic area small arteries, increase cerebral ischemia tissue blood flow, improve the cerebral microcirculation, increase the red cell deformation and the oxygen dissociation ability, promote the organization's use of glucose, inhibit platelet aggregation and blood coagulation [4,5]. In addition, in clinical practice, effect of urinary kallidinogenase on blood pressure was being concern. Research shows that urinary kallidinogenase and ACEI class of antihypertensive drugs have synergistic effect, co-administration shown significant effect to blood pressure. The mechanism as follows: angiotensin converting enzyme induced peptidase II, rapidly hydrolyzes bradykinin and angiotensin converting enzyme inhibitor (ACEI) can increase blood concentrations of bradykinin and enhanced bradykinin antihypertensive effect [6], so in clinical practice should avoid the combination of the two.

The authors observed, acute cerebral infarction progress period the use of urinary kallidinogenase, NIHSS score was significantly decreased after treatment, and compared with the control group, it reduce significantly ($p < 0.05$). From the clinical efficacy, the treatment group achieved 44.2%, which higher than the control group, there was significant difference ($p < 0.05$), indicating that the drug having rapid onset of action. Besides, side effect of urinary kallidinogenase was low and mild, generally disappear of symptoms after slowing down the administration rate, and so far no adverse reaction was observed. Strict monitoring of blood pressure did not fall. There was no significant difference between the treatment group and the control group. So for no thrombolysis syndrome cases, because the current lacking of effective method in the treatment, timely use of urinary kallidinogenase in treatment of acute progressive cerebral infarction is a safe and effective treatment. The long-term effects of the follow-up were observed, and the clinical effect was further evaluated.

Conflicts of interest

These authors have no conflicts of interest to declare.

Authors' contributions

These authors contributed equally to this work.

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