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A combination of tetramethylpyrazine hydrochloride and butylphthalide on serum S100B, CRP, Hcy levels and NIHSS score in patients with acute cerebral infarction: A retrospective study

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Abstract: To investigate the effect of tetramethylpyrazine hydrochloride combined with butylphthalide on serum S100B, CRP, Hcy and NIHSS score in patients with acute cerebral infarction. 80 patients with acute cerebral infarction treated in our hospital from February 2019 to February 2021 were selected for retrospective analysis, and according to different treatment methods, the patients were equally divided into control group (conventional treatment) and experimental group (tetramethylpyrazine hydrochloride and butylphthalide). After treatment, the total effective rate of patients in the experimental group was significantly higher than that in the control group (P<0.05); the levels of serum S100B, CRP and Hcy, and NHISS scores in the two groups decreased, and the experimental group was significantly lower than the control group (P<0.05); the ADL scores of the two groups increased and the experimental group witnessed higher score (P<0.05); the number of patients in the experimental group with scores of 0-2 and 5 were significantly larger than that in the control group (P<0.05). The combination of tetramethylpyrazine hydrochloride and butylphthalide emanates a promising result in the treatment of patients with ACI. It reduces serum S100B, CRP and Hcy levels, protects nerve tissue, and improves nerve function, and thus merits clinical application.

Keywords: Acute cerebral infarction, butylphthalide, inflammatory factor, neurological function, tetramethylpyrazine hydrochloride.

INTRODUCTION

Acute cerebral infarction (ACI) is a cerebrovascular disease with a higher incidence and complex pathogenesis. The stenosis and blockage of cerebral arteries caused by abnormal blood vessels, blood and hemodynamics are all influencing factors and large artery atherosclerosis, cardiac embolism and arteriolar occlusion are the main causes (Xie *et al*., 2020; Zhang *et al*., 2018). At present, the clinical treatment of ACI remains a challenging issue, and its disability rate and fatality rate are rather high. Serum S100B, highly expressed in ACI, can reflect the neurological status and rehabilitation of ACI patients, which is beneficial to monitor their condition (Li and Xin, 2020). As a sensitive marker of inflammation, CRP induces the secretion of inflammatory factors and increases the instability of the atherosclerotic plate, and further leads to thrombosis and embolism, which is closely related to the prognosis of ACI patients (Liu *et al*., 2021). Hcy is an independent risk factor for cardiovascular diseases such as atherosclerosis. Studies have shown that Hcy can damage the endothelial cells of the heart and brain vessels and affect lipid metabolism, accelerate the proliferation of smooth muscle cells in the vascular wall and aggravate atherosclerosis to cause cerebral infarction. Therefore, Hcy participates in the pathogenesis of ACI patients and its level mirrors the condition of ACI (Chen *et al*., 2020; Sun *et al*., 2020). Tetravomezine hydrochloride, with the property of anti-platelet aggregation and dilation of small arteries, is widely used in cerebrovascular diseases. It can promote blood flow, improve nerve function and reduce thrombosis, which provide a pharmacological basis for the treatment of ACI (Cheng *et al*., 2021; Li *et al*., 2021). Butylphthalide, a new type of neuroprotective drug, is believed to improve the infarct size, protect nerve function, reduce the level of inflammatory factors, and protect the structure of blood vessels (Kim *et al*., 2021). Relevant studies have shown (Wang H *et al*., 2021) that tetrahydrochloride combined with butylphthalide produces a promising effectiveness profile in the treatment of ACI, but the specific mechanism of action is still unclear. Currently, it is urgent to shift the focus to serum S100B, CRP, Hcy and other related factors and neurological functions.

MATERIALS AND METHODS

Case grouping

Altogether 80 patients with ACI admitted to our hospital from February 2019 to February 2021 were recruited for retrospective analysis. According to the different treatment methods, the patients were divided into a control group and an experimental group, with 40 cases in each group.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) Patients who met the diagnostic criteria for ACI (Wang W. *et al*., 2021), and were diagnosed by CT and MRI; (2) Onset and admission time

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<72h; (3) No anticoagulation, thrombolysis and anti-fibrosis therapy were received 4 weeks before admission; (4) The study was approved by the hospital ethics committee, and the patients and their families knew the purpose of the study and signed an informed consent form.

Patients who were suffering from (1) severe liver and kidney dysfunction (3) had severe coagulation dysfunction (4) allergic to the drug in the study (5) had immune system disease were excluded from the study.

Ethical approval

This study was conducted in accordance with the protocol of the ethic committee of our hospital, with the approval No.2018-29-02.

Method

The control group received conventional treatment methods, such as anti-platelet aggregation, promoting blood circulation and removing blood stasis, neurotrophic treatment, lipid-lowering. Symptomatic intervention was given to patients with hypertension and diabetes to control blood pressure and blood sugar, and maintain patients' water and electrolytes balance; the treatment continued for 14 days.

On the basis of conventional treatment, the experimental group was additionally given tetramethylpyrazine hydrochloride (manufacturer: Sinopharm Rongsheng Pharmaceutical Co., Ltd.; National Medicine Standard: H20057041; specification: 2ml: 40mg) combined with butylphthalide (manufacturer: CSPC Enbipu Pharmaceutical Co., Ltd.; National Medicine Standard: H20100041; Specification: 100ml: 25mg); the usage and dosage of tetramethylpyrazine hydrochloride were as follows: 80mg limoxine hydrochloride was added to 250ml normal saline and then intravenously administered after being fully diluted, 1 time/d; the usage and dosage of butylphthalide was as follows: 100ml were intravenously administered, 1 time/d, and the treatment continued for 14 days.

Observation indicators and evaluation criteria

(1) Clinical efficacy. Markedly effective: the patient's NHISS score is reduced by 85%-100%; effective: the patient's NHISS score is reduced by 40%-80%; ineffective: the patient's NHISS score is reduced by ≤39%; total effective rate = markedly effective rate + effective rate. (2) 5ml of fasting venous blood in the morning before and after treatment was collected, centrifuged at 3000r/min and stored at low temperature. Enzyme-linked immunosorbent assay was used to detect the serum S100B concentration of patients. The kit was purchased from Shanghai Hengyuan Biotechnology Co., Ltd.; the concentration of Hcy and CRP was determined by the AU480 automatic biochemical analyzer, and the kit was purchased from Beckman Coulter Co., Ltd., USA. All operation steps are carried out in strict accordance with the instructions. (3) The National Institutes of Health Stroke Scale (NHISS) (Runck *et al*., 2021) was used to evaluate the patient's neurological function. The lower the score, the better the neurological function recovery. (4) The Activity of Daily Living Scale (ADL) (Im *et al*., 2021) was used to evaluate the daily activity ability of the two groups. The full score is 100 points and the score is directly proportional to the daily activity ability. (5) The patients were followed up for 3 months to observe the patient's recovery and the patient's Modified Rankin Scale (MRS) score was evaluated after 3 months(Huang *et al*., 2021). A score of 0 means no symptoms at all; a score of 1 means that despite symptoms, there is no obvious dysfunction and can complete all daily duties and activities; a score of 2 points indicates mild disability, unable to complete all activities, but do not need help, can take care of themselves; a score of 3 points indicates moderate disability, and require some help, but do not need help walking; a score of 4 points indicates severe disability, unable to walk independently and unable to meet their own needs without the help of others; a score of 5 points indicates severe disability, bedridden, incontinence and requiring continuous care and attention; higher scores indicate the more serious condition of the patient. (6) The incidence of adverse reactions in the two groups were recorded.

STATISTICAL ANALYSIS

All data analysis was done by SPSS20.0, and graphics rendering were by GraphPad Prism 7 (GraphPad Software, San Diego, USA); the count data were tested by x^2, and expressed as [n(%)]; the measurement data were tested by t test and expressed as (x±s). Statistical significance was claimed at a p-value of 0.05 or lower.

RESULTS

Comparison of the clinical data

There was no statistical difference between the two groups in clinical data such as gender, average age, average course of disease, underlying diseases, TOAST classification, smoking and drinking, education level and place of residence (P>0.05) (table 1).

Comparison of the clinical efficacy

After treatment, the total effective rate of patients in the experimental group was significantly higher than that in the control group (P<0.05), as shown in table 2.

Comparison of serum S100B, CRP and Hcy levels before and after treatment between the two groups

After treatment, the levels of serum S100B, CRP and Hcy in the two groups decreased and the experimental group was significantly lower than the control group (P<0.05) (table 3).

Table 1: Comparison of the clinical data of the two groups of patients[n(%)]

	Control group (n=40)	Experimental group (n=40)	X^2/t	P
Gender				
Male	23 (57.50)	22(55.00)	0.051	0.822
Female	17(42.50)	18(45.00)		
Average age (year)	58.34±4.59	59.23±4.61	0.865	0.390
Mean course of disease (h)	11.58±3.27	12.33±3.15	1.045	0.299
Underlying disease				
coronary heart disease	11(27.50)	9(22.50)	0.267	0.606
Diabetes	17(42.50)	18(45.00)	0.051	0.822
hypertension	12(30.00)	13(32.50)	0.058	0.809
Smoking history	16(40.00)	18(45.00)	0.205	0.651
TOAST type				
arge-artery atherosclerosis	24(60.00)	23(57.50)	0.052	0.820
Arteriole occlusion	9(22.50)	8(20.00)	0.075	0.785
Cardiogenic obstruction	7(17.50)	9(22.50)	0.313	0.576
Drinking history	19(47.50)	21(52.50)	0.200	0.655
Educational background				
College	13(32.50)	15(37.50)	0.220	0.639
Middle school	18(45.00)	14(35.00)	0.833	0.361
Primary school	9(22.50)	11(27.50)	0.267	0.606
Places of residence				
Township	22(55.00)	21(52.50)	0.050	0.823
Rural areas	18(45.00)	19(47.50)		

Table 2: Comparison of clinical efficacy between the two groups[n(%)]

	Control group (n=40)	Experimental group (n=40)	X^2	P
Markedly effective	12(30.00)	27(67.50)		
Effective	18(45.00)	11(27.50)		
Ineffective	10(25.00)	2(5.00)		
Total effectiveness	30(75.00)	38(95.00)	6.275	0.023

Table 3: Comparison of serum S100B, CRP and Hcy levels between the two groups before and after treatment

		Control group (n=40)	Experimental group (n=40)	t	P
S100B(ug/L)	Before treatment	2.59±1.38	2.61±1.41		
	After treatment	0.82±0.34	0.54±0.12	4.912	0.043
CRP(mg/L)	Before treatment	25.17±9.45	26.28±9.67		
	After treatment	12.39±4.12	7.25±1.83	7.211	0.030
Hcy(umol/L)	Before treatment	29.58±6.93	30.24±7.05		
	After treatment	11.47±2.21	7.44±1.36	9.822	0.021

Table 4: Comparison of the incidence of adverse reactions between the two groups [n(%)]

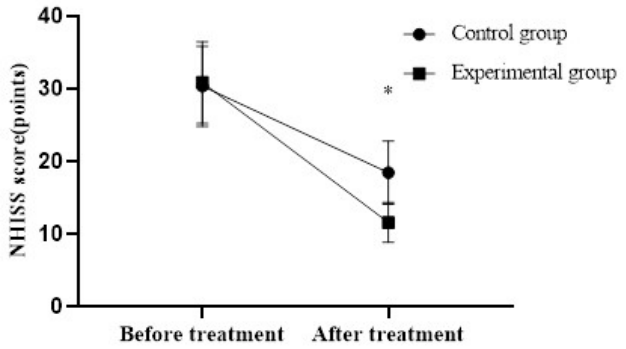
	Control group (n=40)	Experimental group (n=40)	X^2	P
Nausea and vomiting	3(7.50)	2(5.00)		
diarrhea	2(5.00)	1(2.50)		
Neurological symptoms	1(2.50)	1(2.50)		
Symptomatic intracerebral hemorrhage	2(5.00)	0(0.00)		
Total incidence	8(20.00)	4(10.00)	1.569	0.075

Comparison of the NHISS scores of the two groups before and after treatment

After treatment, the NHISS scores of the two groups were reduced, with lower results observed in the experimental group (P<0.05), as shown in fig. 1.

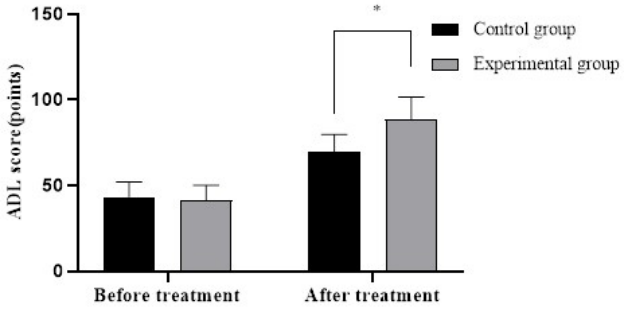
Comparison of the ADL scores of the two groups before and after treatment

After treatment, the ADL scores of the two groups increased, and the experimental group witnessed higher score (P<0.05), as shown in fig. 2.



Note: abscissa indicates before and after treatment; The ordinate represents the NIHSS score, point;
The NIHSS scores of the control group and the experimental group before treatment were (30.37±5.51) and (30.89±5.64), respectively;
The NIHSS scores of the control group and the experimental group were (18.49±4.34) and (11.63±2.75) respectively;
* indicates that there is a significant difference in NIHSS score between the two groups after treatment (t = 8.444, P<0.001).

Fig. 1: Comparison of NHISS scores between the two groups before and after treatment (X ± S)



Note: abscissa indicates before and after treatment; The ordinate represents ADL score, point;
The ADL scores of the control group and the experimental group before treatment were (43.29±8.75) and (41.36±8.84), respectively;
The ADL scores of the control group and the experimental group were (69.37 ± 10.46) and (88.39 ± 13.25) respectively;
*indicates that there is significant difference in ADL score between the two groups after treatment (t = 7.126, P<0.001).

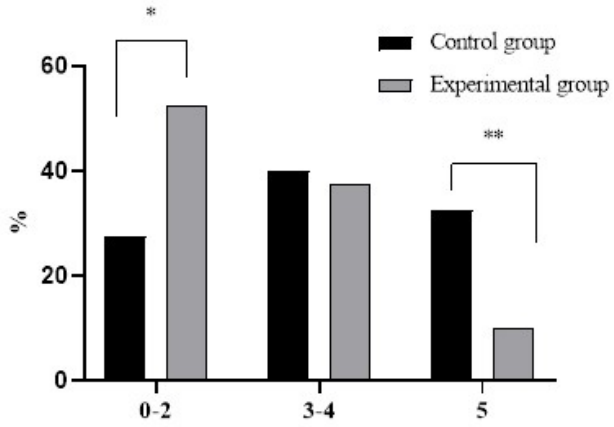
Fig. 2: Comparison of ADL scores between the two groups before and after treatment (X±S)

Comparison of the MRS scores of the two groups of patients after treatment

The number of patients in the experimental group with scores of 0-2 and 5 were significantly larger than that in the control group (P<0.05) and there was no significant difference in patients with scores of 3-4 (P>0.05) (fig. 3).

Comparison of the incidence of adverse reactions between the two groups of patients

The incidence of adverse reactions did not differ between the two groups of patients (P>0.05, table 4).



Note: the abscissa represents the evaluation dimension; ordinate represents percentage, %;
There were 11 cases in the control group with a score of 0-2; 16 cases with 3-4 points; 13 cases with 5 points;
There were 21 cases in the experimental group with a score of 0-2; 15 cases with 3-4 points; 5 points, 4 cases;
*indicates that there is a significant difference in the incidence of 0-2 points between the two groups (x2 = 5.208, P < 0.05)
**indicates that there is a significant difference in the incidence of 5 points between the two groups (x2 = 6.050, P < 0.05)

Fig. 3: Comparison of MRS scores between the two groups after treatment

DISCUSSION

ACI is the necrosis of brain tissue caused by the sudden interruption of blood supply to the brain, and its onset is sudden and usually occurs during quiet rest or sleep. Clinically, the presentations are headache, dizziness, hemiplegia, difficulty swallowing, slurred speech, and nausea. If patients fail to detect these symptoms and be treated in time, they will have a serious impact on the patient's neurological function and threaten the life of the patient (Xiao *et al*., 2021; Zhu *et al*., 2021). Traditionally, treatment of ACI patients uses thrombolytic therapy to reduce the patient's intracranial pressure and cerebral edema, prevent respiratory and urinary system infections, inhibit pulmonary embolism and the formation of deep vein thrombosis of the lower extremities, control blood pressure and blood sugar, etc.. Still, some patients miss the optimal time for thrombolysis at the time of admission. It is consequently urgent to find new effective treatment methods to reduce the mortality of ACI patients and improve the efficacy.

Tetravomezine hydrochloride, an organic compound, is widely used in the treatment of occlusive cerebrovascular disease. Modern pharmacological studies have confirmed that it can pass through the blood-brain barrier, exist stably in the brain tissue for a long time and accelerate blood flow, prevent thrombosis, resist platelet aggregation, improve red blood cell deformation, restore nerve function, reduce neuronal death and boost nerve

function (Huang *et al*., 2021; Im *et al*., 2021). With the similar structure as natural L-Apigenin, butylphthalide is a synthetic racemic n-butylphthalide and can block multiple pathological links of ischemic brain injury and allow nerve cells in the condition of hypoxia and low glucose to be not damaged, improve the energy metabolism after cerebral ischemia and the effect of microcirculation and blood flow in the ischemic brain area, consequently the infarct area after focal cerebral ischemia is reduced, and the neurological damage is minimized (Lee *et al*., 2021; Sechi *et al*., 2021). In this study, patients with ACI were treated with tetramethylpyrazine hydrochloride combined with butylphthalide and the total effective rate of treatment in the experimental group was 95% significantly higher than that of the control group, indicating that the combined treatment is superior to the conventional treatment alone.

Serum S100B is an acidic calcium-binding protein with a molecular weight of 21kD. It mainly acts as an intracellular calcium receptor protein in the organism. Low-concentration S100B exerts a neurotrophic effect, and glial cells can paracrine and autocrine S100B to promote nerve growth and repair; high concentrations of S100B are neurotoxic and induce neuronal death in vitro through NO-dependent pathways. Therefore, the changes in serum levels of S100B are closely related to blood-brain barrier, brain damage and other nerve damage and pathological changes (Runck *et al*., 2021; Zhou *et al*., 2021). Serum CRP is a more sensitive indicator that responds to various infections and pulmonary infectious inflammations in the body. It is a non-specific marker of systemic inflammation. When inflammation occurs in the body, CRP levels are highly expressed; the larger the cerebral infarction area, the higher the degree of neurological damage (Broocks *et al*., 2021; Rava *et al*., 2021; Yang *et al*., 2021). Hcy is a metabolized product of methionine amino acid after demethylation. Its metabolism will produce superoxide and peroxide, promote platelet adhesion and aggregation, accelerate the oxidation of low-density lipoprotein, increase foam cell formation, and promote the production of inflammatory factors, induce atherosclerosis, and its increase can lead to cerebrovascular disease (Sugiyama *et al*., 2021). In this study, after the treatment the levels of serum S100B, CRP, and Hcy in the two groups decreased, with lower results in experimental group, suggesting that the combination of the two inhibits cerebral ischemia-reperfusion injury, suppresses neuronal cell apoptosis, protects the patient's nervous system, and lower inflammatory reactions. In addition, the NHISS scores of the two groups were reduced and the experimental group was significantly lower than the control group, which was consistent with the research results of Bilgin Cem (Bilgin *et al*., 2021) who suggested that the combination of the two drugs can improve the neurological deficit in patients with ACI, control the development of the disease and promote the physical recovery of patients. Moreover, the patients with MRS scores of 0-2 and 5 in the experimental group were significantly higher than those in the control group, and the ADL scores in the experimental group were significantly higher than those in the control group, indicating thattetramethylpyrazine hydrochloride combined with butyl benzene Phthalo yields a desirable outcome in treating ACI patients. Reassuringly, the recovery and quality of life were better than conventional treatment alone and no difference was found in the adverse reactions between the two groups, suggesting a good safety profile. Inevitably, this study has following limitations: the sample size is small, which may lead to a certain bias in the results; the effect of serum changes caused by the treatment of ACI patients with tetramethylpyrazine hydrochloride combined with butylphthalide on the development of ACI patients remains unclear. Thus, further research and exploration are needed.

Taken together, the combination of tetramethylpyrazine hydrochloride and butylphthalide emanates a promising result in the treatment of patients with ACI. It reduces serum S100B, CRP, and Hcy levels, protects nerve tissue, and improves nerve function, and thus merits clinical application.

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