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Effects of butylphthalide on the levels of serum C-reactive protein, Parkinson disease protein 7, and neurotrophin-3 and neurological function in patients with acute cerebral infarction

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Abstract: To explore the effects of butylphthalide on the levels of serum CRP, PAPK7, NT-3 and neurological function in patients with acute cerebral infarction (ACI). 120 patients with ACI who were treated at Peking University First Hospital from September 2014 to June 2016 were selected as the research objects. The patients were randomly divided into a control group and an observation group, with 60 cases in each group. Conventional methods were adopted in the control group, and the observation group used butylphthalide for treatment. Two months later, the clinical efficacy, serum C-reactive protein (CRP), Parkinson's disease protein 7 (PAPK7), neurotrophic factor-3 (NT-3) levels, and the National Institutes of Health Stroke Scale (NIHSS) score before and after treatment were put into comparison and analysis. Before treatment, the NIHSS score showed no significant difference between the two groups (p>0.05); An observably higher NIHSS score of the observation group compared with the control group was seen after treatment (p=0.000). Butylphthalide has a significant therapeutic effect on patients with ACI. It can effectively restore the patients' neurological function, and remarkably improve the serum CRP, PAPK7 and NT-3 levels, which is worthy of clinical promotion.

Keywords: ACI, butylphthalide, CRP, NT-3, PAPK7, neurological function.

INTRODUCTION

ACI refers to the phenomenon of brain tissue necrosis caused by the sudden interruption of cerebral blood supply. It is usually because of thrombosis and atherosclerosis in the arteries that supply blood to the brain, resulting in occlusion or stenosis of the lumen, thereby causing insufficient blood supply to the brain (focal acute). There are also abnormalities such as gas, liquid, and solids that follow the blood circulation and enter the carotid artery (supplying the blood circulation to the brain) or the cerebral artery, causing a sudden decrease in blood flow or blood flow blockage, resulting in necrosis and softening of the brain tissue in the corresponding dominated area (Ochiai *et al*., 2021).

The characteristics of the onset of ACI can be concluded as rapid changes, suddenness and severe illness. The key to slowing down and treating this disease is to provide patients with thrombolytic therapy timely. However, the time limit for thrombolytic therapy is very strict. But most patients have already missed the optimal thrombolytic treatment time at the time of diagnosis (Niu *et al*., 2016). Neuron necrosis will occur in a comparatively short time. Therefore, when ACI is discovered, it is necessary to construct collateral circulation as soon as possible to ensure sufficient oxygen and blood supply to the brain tissue to achieve faster recovery of nerve function (Tang *et al*., 2017). Butylphthalide is a drug that can treat and prevent ACI with advantages including anti-oxidation, saving penumbra, anti-apoptosis, reconstructing microcirculation, and promoting energy metabolism (Hao *et al*., 2015). However, majority of research concentrated on its effectiveness on the serum level, while neglecting the neurological outcome, the present trial thus was undertaken accordingly. A total of 120 patients with ACI admitted to Peking University First Hospital from September 2014 to June 2016 were selected as the research objects to explore the effects of butylphthalide on serum CRP, PAPK7, NT-3 levels and neurological function in patients with ACI. The report is as follows.

MATERIALS AND METHODS

General Data

120 patients with ACI who were treated at our hospital from September 2014 to June 2016 were selected as research objects. All patients were in accordance with the diagnostic criteria for ACI issued by the Fourth National Cerebrovascular Disease Conference in 1995

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(neuroscience, 1996), and were diagnosed by MRI or CT. Acute myocardial infarction, autoimmune diseases, heart, liver and kidney diseases, malignant tumors, cerebral hemorrhage and acute infectious diseases have been excluded. According to the random number table method, the patients were randomly divided into control group and observation group. There are 60 patients in the control group, 38 male patients and 22 female patients, aged between 68-83 years old, with an average of (75.23±2.15) years old. The control group was treated in a conventional way. There are 60 patients in the observation group, including 35 male patients and 25 female patients, aged 70-85 years old, with an average of (76.94±2.40) years old. The Observation group was treated with butylphthalide. Two groups' general data were not statistically significant (P>0.05).

Methods

The control group used conventional treatment methods, and the specific steps were as follows: (1) The patient used amlodipine besylate tablets for antihypertensive treatment, once a day, 1 tablet each time, orally; (2) Use atorvastatin calcium, metformin sustained-release tablets for lipid-lowering and hypoglycemic treatment; (3) Use aspirin for anti-platelet aggregation treatment, 100 mg once a day; (4) Choose compound brain protein hydrolysate tablets for trophic nerve treatment; (5) The patient needs oxygen therapy; (6) Help patients to take rehabilitation measures, and instruct them to have a low-fat and low-salt diet, eat more fresh fruits and vegetables, prohibit alcohol and smoke, and help patients develop appropriate exercise plans to maintain a happy and stable mood.

The observation group adopted butylphthalide for treatment on the basis of the control group. The specific steps were as follows: Use intravenous drip to give patients 100 ml of butylphthalide twice a day (Produced by CSPC ENP Pharmaceutical Co., Ltd., NMPA Approval Number H20100041, specification: 100ml:25mg:0.9g injection), continuously for 15 days.

CRP, PAPK7, NT-3 level inspection: Draws fasting venous blood from patients before and after treatment. Perform high-speed centrifugation for 2 minutes with a centrifugation speed of 2800r per minute and a centrifugation radius of 12 cm, and then take the supernatant. Employ immunoturbidimetric method to detect the patient's CPR, and enzyme-linked immunosorbent method to detect the patient's PAPK7 and NT-3.

Indexes Observation

The clinical efficacy, serum CRP, PAPK7, NT-3 levels and NIHSS scores before and after treatment were compared and analyzed between the two groups.

The NIHSS score was used to evaluate the neurological function of the patients. The total NIHSS score was 10 points. No neurological damage was represented by 0 points, and patients with severe neurological damage were represented by 10.

Clinical efficacy evaluation standard (Jisheng and Lingping, 2014): Before treatment and 15 days after treatment, patients will be scored with NIHSS. Almost recovered means that the clinical symptoms and signs disappear, and the NIHSS score has been reduced by more than 90%; Significant mproved means that the basic clinical symptoms and signs have been significantly improved, and the NIHSS score is reduced by 45%-90%; improved means that the basic clinical symptoms have been improved, and the NIHSS score has been reduced by 18%-45%; Ineffective means that the basic clinical symptoms and signs have not changed, and the NIHSS score reduction is less than 18%; the total effective rate = (Almost recovered+ Significant improved +improved) / number of cases × 100%.

STATISTICAL ANALYSIS

SPSS23.0 software was used for data processing. Measurement data were presented as mean ± standard deviation, and t-test was used for the comparison between groups. Enumeration data were presented as (%), and $\chi 2$ test was used for the comparison between groups. P<0.05 indicated a statistically significant difference.

RESULTS

Comparison of the clinical efficacy of the patients:

An observably higher total effective rate (93.33%) of the observation group than the control group (73.33%) was obtained (p<0.05). See table 2 for details.

Comparative analysis of serum CRP, PAPK7 and NT-3 levels in the two groups

No significant difference in serum CRP, PAPK7 and NT-3 levels between the two groups has been shown before treatment (P>0.05); After treatment, a greatly lower serum CRP and PAPK7 levels of the observation group were witnessed in the comparison with the control group (p<0.05); An evidently higher NT-3 level of the observation group was also obtained(p<0.05). See table 3 and fig. 1 for details.

Table 1: Comparison of baseline data between the two groups

	Age (years)	Male / female (n)	Hyper-tension	Coronary heart disease	Hyper-lipidemia	Diabetes	Mellitus, lesion location (left / right)	Single lesion / multiple lesion
Observation group (n=60)	76.94±2.40	35/25	11	14	10	9	29/31	27/13
Control group (n=60)	75.23±2.15	38/22	9	12	9	11	27/23	31/29
t/χ^2	0.391	0.012	0.459				0.191	0.233
P	0.695	0.914	0.928				0.662	0.629

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

Groups	Cases	Almost recovered	Significant improved	Improved	Ineffective	Total effective rate
Control group	60	17(28.33%)	13(21.67%)	14(3.33%)	16(26.67%)	44(73.33%)
Observation group	60	26(43.33%)	21(35%)	9(15%)	4(6.67%)	56(93.33%)
χ^2						5.641
P						0.000

Table 3: Comparison of serum CRP, papk7 and NT-3 levels between the two groups ($\overline{x} \pm s$)

Groups	CRP(mg/L)		PAPK7(μg/L)		NT-3(μg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	18.74±0.67	12.05±0.53*	31.25±3.86	26.71±4.01*	18.14±2.57	25.64±3.15*
Observation group	18.81±0.72	8.46±0.30*	31.08±3.94	14.11±3.08*	18.21±3.43	33.18±4.81*
t	0.348	3.492	0.315	4.569	0.362	3.864
P	0.834	0.004	0.875	0.001	0.856	0.002

Note: * indicates that there is a statistical difference as compared with the values before treatment

Table 4: Comparison of NIHSS scores between the two groups before and after treatment ($\overline{x} \pm s$)

Groups	N	Before treatment	2 months after treatment	t	P
Control group	60	9.75±1.24	3.26±1.19	5.942	0.001
Observation group	60	9.68±1.81	1.26±1.03	7.094	0.000
t		0.584	6.491		
P		0.869	0.000		

Comparison of NIHSS scores before and after treatment in the two groups

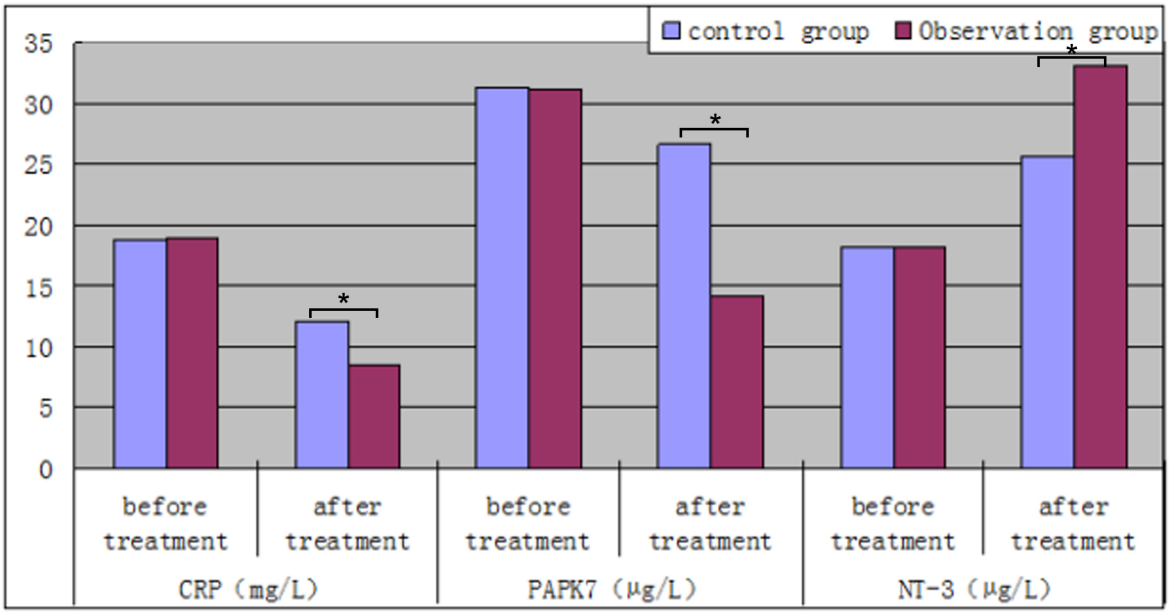
No significant difference in the NIHSS score between the two groups has been shown before treatment ($p>0.05$); after treatment, the NIHSS score of the observation group was markedly lower ($p<0.05$) by contrast with the control group. See table 4, fig.2 for details.

Adverse reaction record

Butylphthalide was used in the treatment for patients in the observation group, and there were no adverse reactions during the diagnosis and treatment.

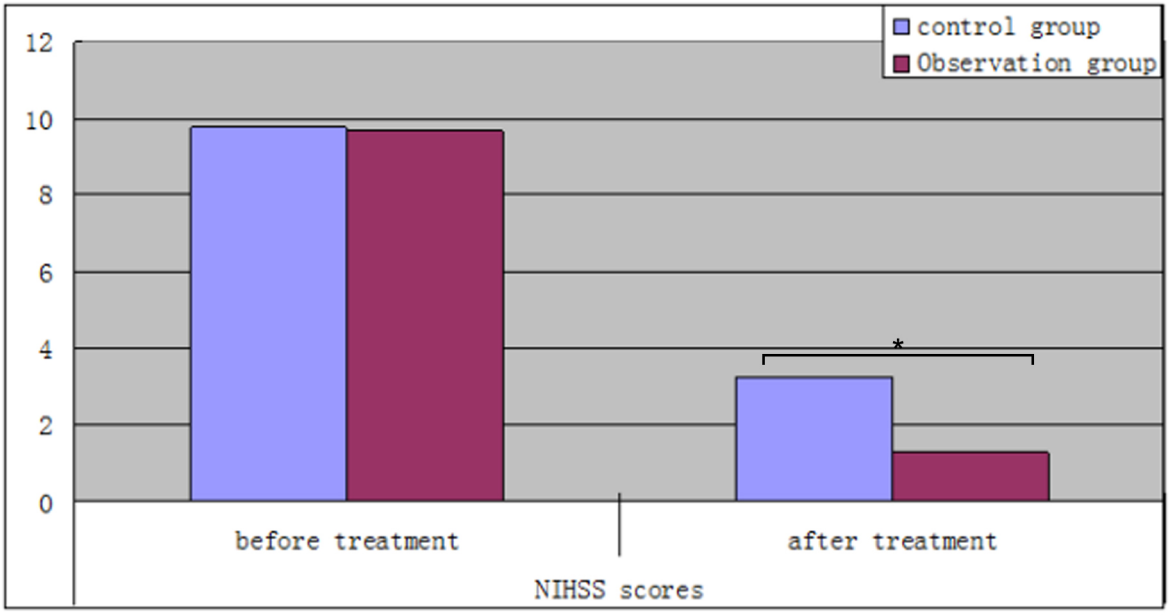
DISCUSSION

ACI has a high disability rate, prevalence rate, fatality rate, incidence rate, and its onset is closely related to collateral circulation, vascular endothelial damage, free radical damage, cerebral artery stenosis, abnormal blood composition, microemboli shedding and hemodynamics



(* indicates that the comparison between the observation group and the control group is significant P < 0.05)

Fig. 1: Comparison of serum CRP, papk7 and NT-3 levels between the two groups



(* indicates that the comparison between the observation group and the control group is significant P < 0.05)

Fig. 2: Comparison of NIHSS scores of two groups before and after treatment

changes (Zhou *et al*., 2020; Lingping *et al*., 2014).

The key to the treatment of ACI is to rescue the ischemic penumbra, restore blood flow, and dredge blood vessels as soon as possible. Although evidence-based medicine shows that intravascular thrombolysis can be an effective treatment for ACI, this method has disadvantages such as high cost and strict time window, so most patients cannot be effectively treated with thrombolysis (Lili *et al*., 2015; Linglie*t al*., 2015). In accordance with a survey conducted by the National Ischemic Stroke Registry, only 1.6% of patients with cerebral infarction can receive thrombolytic therapy timely. The current clinical treatments for patients with ACI are mainly to protect the brain nerves and use drugs to promote cerebral perfusion (Li *et al*., 2021). Because reperfusion and cerebral ischemia have complex injury mechanisms, drugs that can block the mechanism of ischemic injury through multiple links are critical to the treatment of this disease (Pilato *et al*., 2020).

Butylphthalide is a new type of drug for the treatment of ACI. After using the drug, it can completely protect blood vessels, increase the number of capillaries and blood flow speed, improve blood perfusion in ischemic areas, the brain tissue hypoxia and ischemia of patients as soon as possible. At the same time, it can increase the mitochondrial ATPase activity, ensure the stability of the mitochondria(Wang *et al*., 2016)

l membrane, protect the mitochondrial structure, reduce cell mortality, and enhance the energy metabolism of patients (Qin *et al*., 2019; Yitao *et al*., 2015). Butylphthalide can effectively inhibit the inflammatory response and the release of calcium store and arachidonic acid in the cells, so as to curb cell death, suppress the release of glutamate and elevate the activity of antioxidant enzymes. This drug can also restore the patient's nerve function, and can significantly reduce the area of infarction (Pi *et al*., 2021; Mamtilahun *et al*., 2021).

Atherosclerosis is the main manifestation of ACI. It is a process of lipid accumulation on the one hand, and a process of chronic inflammatory reaction on the other hand (Qian *et al*., 2019). As an important inflammatory cytokine, CRP is vital in the development and occurrence of ACI through the complement system, coagulation fibrinolysis system and inflammatory system. Butylphthalide, as a drug for the treatment of ACI, can obviously bring down the level of CRP and the inflammation in the patient (Lee *et al*., 2020; Li *et al*., 2021). The causes of ACI include cerebral atherosclerosis, increased blood viscosity, and platelet aggregation. The blood supply of the cerebral blood vessels is seriously insufficient as part of the cerebral arteries is blocked by sudden blood flow, which causes acute hypoxic-ischemic necrosis of the brain tissue and damages the patient's nerve function (Ziru *et al*., 2015).

In this study, butylphthalide was used to treat patients with ACI. The results showed that the total effective rate of patients who received butylphthalide for treatment is markedly higher than that of conventional treatment and there is no adverse reaction during the treatment period, which indicates that butylphthalide has a significant effect and a higher safety; After treatment, the serum CRP and PAPK7 levels of patients treated with butylphthalide were apparently lower compared with the conventional treatment, and the level of NT-3 was obviously higher than the conventional treatment. This shows that the use of butylphthalide to treat patients can adjust the related factors of lesion, thereby protecting the nervous system and improving the patient's nerve function; After treatment, a notably lower NIHSS score of patients treated with butylphthalide than the conventional treatment was obtained, which further indicates that the treatment of ACI with butylphthalide is able to enhance the recovery of patients' neurological function.

CONCLUSION

In conclusion, butylphthalide has a notable therapeutic effect on patients with ACI, can effectively restore the patients' neurological function, and can improve serum CRP, PAPK7, and NT-3 levels, which is worthy of clinical promotion.

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