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Original Article

Effect of butylphthalide on serum CRP, PARK7, NT-3 and neurological function in patients with acute cerebral infarction

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Abstract: Objective: The effects of butylphthalide on serum C-reactive protein (CRP), Parkinson disease protein 7 (PARK7), and neurotrophin-3 (NT-3) levels, and neurological function in patients with acute cerebral infarction (ACI) were explored in order to provide a reference for clinical treatment of the disease. Methods: One hundred and twenty patients with ACI treated in our hospital from September 2016 to June 2018 were selected and randomized into the control group and the study group, with 60 cases in each group. Patients in the control group were treated with conventional therapy, while those in the study group were treated with butylphthalide. Clinical efficacy, serum levels of CRP, PARK7, and NT-3, as well as the scores of National Institutes of Health Stroke Scale (NIHSS), Fugl-Meyer Assessment (FMA), and Barthel Index (BI) before and 2 months after treatment were analyzed and compared between the two groups. Results: The study group had a significantly higher effective rate (93.33%) than the control group (73.33%; $P<0.05$). Before treatment, differences in serum CRP, PARK7, NT-3, IL-6, IL-8, and IL-10 levels between the study group and the control group were barely notable ($P>0.05$). After treatment, the study group observed lower serum levels of CRP, PARK7, IL-6, IL-8, and a higher levels of IL-10, NT-3 in comparison with those of the control group ($P<0.05$). Before treatment, NIHSS, FMA, and BI scores between the two groups did not show significant differences ($P>0.05$). After treatment, the study group yielded a remarkably lower NIHSS score and higher FMA and BI scores than the control group ($P<0.05$). Conclusion: Butylphthalide is effective in the treatment of ACI. It can effectively facilitate the recovery of neurological and motor functions of patients, enhance their quality of life and improve serum CRP, PARK7, and NT-3 levels, which is worthy of clinical promotion.

Keywords: Acute cerebral infarction, butylphthalide, c-reactive protein, neurotrophin, parkinson disease protein, neurological function

Introduction

Acute cerebral infarction (ACI) refers to the necrosis of brain tissues caused by sudden interruption of cerebral blood supply. Generally, it is induced by thrombosis and atherosclerosis in the arteries supplying blood to the brain, which results in luminal stenosis or occlusion, thus leading to cerebral blood supply insufficiency (acute focal). It may also be due to abnormal substances such as gas, liquids, and solids following the blood into the cervical artery (supplying blood circulation to the brain) or cerebral artery, causing a sudden decrease in blood flow or blood flow occlusion, resulting in brain tissue necrosis and softening in the corresponding dominated area [1]. ACI is characterized by rapid change, severe conditions, and sudden onset. The key to mitigation and treatment of the disease is timely thrombolytic therapy. However, most patients have already missed the optimal time when diagnosed due to the narrow time window for thrombolytic therapy [2]. Neuronal necrosis will occur within a short period of time after the onset of the disease. Therefore, when ACI is found, collateral circulation should be constructed as soon as possible to ensure adequate oxygen and blood supply to the brain tissue for rapid recovery of neurological function [3]. Butylphthalide, a drug that can treat and prevent ACI, has the advantages of anti-oxidation, ischemic penumbra preservation, anti-apoptosis, microcirculation reconstruction, and promoting ener-

gy metabolism [4]. In this study, a total of 120 patients with ACI treated in our hospital from September 2016 to June 2018 were selected as the research subjects to explore the effects of butylphthalide on serum CRP, PARK7, NT-3 levels, and neurological function of patients with ACI.

Materials and methods

General information

This study enrolled 120 patients with ACI who were treated in our hospital from September 2016 to June 2018. The experiment was ethically approved by the Ethics Committee of Pingyi County People's Hospital (Linyi city, Shandong Province, China; license no. KY 2015-93-502). According to the random method, the patients were randomized into the control group (n=60) for conventional treatment and the study group (n=60) for butylphthalide therapy.

Methods

Inclusion and exclusion criteria: Inclusion criteria: (1) Pateints aged between 40-80 years; (2) Pateints met the diagnostic criteria for acute cerebral infarction [5]; (3) Pateints with onset time less than 7 days; (4) NIHSS score ≥6 points; (5) The family members or the patient signed the written informed consent to participate in this trial. Exclusion criteria: (1) Pateints with onset time exceeding 7 days; (2) Patients with cerebral infarction caused by brain tumors and vascular malformations confirmed by examination; (3) Patients who died within 24 hours of admission; (4) Accompanied by severe heart disease, cardiac insufficiency, liver dysfunction, renal insufficiency, respiratory failure, malignant tumor, gastrointestinal bleeding, etc.; (5) Mentally ill patients.

Treatment: Patients in the control group were treated with conventional therapy, specifically as follows: (1) Compound antihypertensive tablets (China Resources Double-Crane Pharmaceutical Co., Ltd., SDFA approved No. H1102-2335) were used for antihypertensive treatment, 1-2 tablets orally, twice a day; (2) Atorvastatin calcium (Beijing jialin pharmaceutical co., LTD., SDFA approved No. H20093819) and enalapril (Shanghai Modern Pharmaceutical Co., Ltd., SDFA approved No. H31021938) were used for lipid-lowering and glucose-reducing, once a day, 100 mg each time; (3) Aspirin (Bayer Health Care Co., Ltd., SDFA approved No. J20171021) was used for antiplatelet aggregation therapy, once a day, 100 mg each time; (4) Compound cerebroprotein hydrolysate tablet (Xiuzheng Pharmaceutical Group Stock Co., Ltd., SDFA approved No. H22024371) was used to provide nutrients for nerves, 1-2 tablets orally, three times a day; (5) Oxygen therapy; (6) Patients were also assisted with rehabilitation. They were instructed to eat low fat and low-salt diet with more fresh fruits and vegetables, and stop smoking and drinking. In addition, patients were guided to develop an appropriate exercise plan and maintain a happy and stable mood.

Patients in the study group received butylphthalide treatment on the basis of the control group, specifically as follows: patients were treated with 100 mL butylphthalide injection (CSPC NBP Pharmaceutical Co., Ltd., NMPA Approval No. H20100041, specification: 100 mL, 25 mg, 0.9 g injection) twice a day by intravenous infusion, for 15 consecutive days.

Fasting venous blood was drawn from patients before and after treatment, and the supernatant was collected after high-speed centrifugation at a centrifugal radius of 12 cm and a centrifugal rate of 2800 rpm for 2 minutes. Enzyme-linked immunosorbent assay (ELISA) kits provided by eBioscience were adopted to detect the serum levels of CPR (Catalog # KHA0031), PARK7 (Catalog # EH359RBX5), NT-3 (Catalog # EHNTF3), IL-6 (Catalog # BMS213-2), IL-8 (Catalog # BMS204-3) and IL-10 (Catalog # BMS215-2).

Outcome measures

Clinical efficacy, serum CRP, PARK7, and NT-3 levels, as well as scores of the National Institutes of Health Stroke Scale (NIHSS), the Fugl-Meyer Assessment (FMA), and Barthel Index (BI) before and after treatment in the two groups, were analyzed and compared.

Patients' neurological function was assessed with the NIHSS [6], with 0 point indicating no neurological impairment and 10 points indicating severe neurological impairment on the 10-point scale. The FMA was used to assess the motor performance of patients, with a total score of 100 points. Higher scores represent better motor ability. The BI was used to measure performance in activities of daily living,

Table 1. Comparison of gender and age between the two groups

Group	Number of cases	Gender (male/female)	Age (years old)
Control group	60	25/35	75.23±12.15
Study group	60	22/38	76.94±8.29
t/χ^2		0.315	0.900
P		0.575	0.370

with a total score of 100. Higher scores indicate better ability for daily living.

Evaluation criteria for clinical efficacy [7]: The NIHSS was used to score the neurological function of patients before and 15 days after treatment. Basically cured was translated in the disappearance of clinical symptoms and signs, and a decrease in the NIHSS score by more than 90%. Markedly effective corresponds to significant improvement in clinical symptoms and signs with a reduction of the NIHSS score between 45% and 90%. Improved indicates modest improvement of clinical symptoms and a reduction of the NIHSS score ranging from 18% to 45%. Ineffective means that clinical symptoms and signs remained unchanged and the NIHSS score was reduced by less than 18%. Total effective rate = (basically cured + markedly effective + improved) cases/total cases ×100%.

Statistical analysis

SPSS18.0 was adopted for data porcessing. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd) and the differences were compared by t-test. The count data was represented as [n (%)] and the differences were measured by χ^2. The rank data was analyzed by rank-sum test. When P<0.05, the difference was statistically significant.

Results

Comparison of the general data between the two groups

In the control group, there were 25 male and 35 female patients with a mean age of 75.23±12.15 years; In the study group, there were 22 male and 38 female patients with the age of 76.94±8.29 years. The general data of the two groups were comparable with no significant difference (all P>0.05). As shown in **Table 1**.

Comparison of clinical effects between the two groups

In the control group, 17 cases were basically cured, 13 cases were markedly effective, 14 cases were improved, and 16 cases were ineffective, with the total effective rate of 73.33% (44/60). In the study group, 26 cases were basically cured, 21 cases were markedly effective, 9 cases were improved, and 4 cases were ineffective, with the total effective rate of 93.33% (56/60). The study group had a remarkably higher total effective rate than the control group (P<0.05). As shown in **Table 2**.

Comparison of serum CRP, PARK7, and NT-3 levels between the two groups

Before treatment, the two groups had similar serum CRP, PARK7, and NT-3 levels (P>0.05). However, after treatment, serum CRP and PARK7 levels were lower and NT-3 level was higher in the study group as compared to the control group, with statistically significant differences (P<0.05). As shown in **Figure 1**.

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

Before treatment, the NIHSS scores were 9.75±1.24 in the control group and 9.68±1.81 in the study group; 2 months after treatment, the NIHSS scores were 3.26±1.19 the control group and 1.26±1.03 in the study group. The two groups showed no significant difference in the NIHSS score before treatment (P>0.05). After treatment, the study group had a significantly lower NIHSS score than the control group (P<0.05). As shown in **Table 3**.

Comparison of FMA scores between the two groups before and after treatment

Before treatment, there was no remarkable difference in the FMA score between the study group and the control group (P>0.05). However, the NIHSS score was notably higher in the study group than in the control group after treatment (P<0.05). As shown in **Table 4**.

Comparison of BI scores between the two groups before and after treatment

Before treatment, the difference in the FMA score between the study group and the control group was barely shown (P>0.05). After treatment, the BI score was significantly higher in

Table 2. Comparison of clinical effects between the two groups [n (%)]

Group	Number of cases	Basically cured	Markedly effective	Improved	Ineffective	Total effective rate
Control group	60	17 (28.33%)	13 (21.67%)	14 (23.33%)	16 (26.67%)	44 (73.33%)
Study group	60	26 (43.33%)	21 (35%)	9 (15%)	4 (6.67%)	56 (93.33%)
χ^2						5.641
P						<0.001

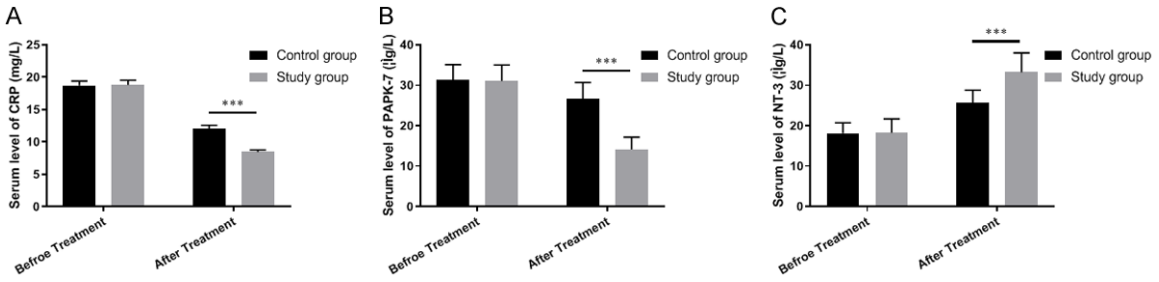

Figure 1. Comparison of serum CRP, PAPK7, and NT-3 levels between the two groups. A. The serum CRP level; B. The serum PAPK7 level; C. The serum NT-3 level. ***P<0.001.

Table 3. Comparison of NIHSS scores between the two groups before and after treatment ($\bar{x}$ ± sd)

Group	Number of cases	Pre-treatment	2 months after treatment
Control group	60	9.75±1.24	3.26±1.19
Study group	60	9.68±1.81	1.26±1.03
t		0.584	6.491
P		0.869	<0.001

Table 4. Comparison of FMA scores between the two groups before and after treatment ($\bar{x}$ ± sd)

Group	Number of cases	Pre-treatment	2 months after treatment
Control group	60	44.14±8.24	60.22±11.57
Study group	60	46.26±9.19	69.18±12.35
t		1.330	4.101
P		0.186	<0.001

Table 5. Comparison of BI scores between the two groups before and after treatment ($\bar{x}$ ± sd)

Group	Number of cases	Pre-treatment	2 months after treatment
Control group	60	55.36±11.35	67.13±13.22
Study group	60	57.42±12.35	77.16±14.57
t		0.951	3.949
P		0.343	<0.001

the study group than that in the control group (P<0.05). As shown in **Table 5**.

Comparison of serum levels of inflammatory factors between the two groups before and after treatment

Serum IL-6, IL-8, and IL-10 levels were not significantly different between the two groups before treatment (P>0.05). After treatment, IL-6 and IL-8 in the study group were significantly lower while IL-10 was higher than those in the control group (P<0.05). As shown in **Figure 2**.

Adverse drug reactions

The control group had 1 case of dizziness, 2 cases of rash, and 1 case of nausea, and the incidence of adverse reactions was 6.67% (4/60). The study group had 1 case each of dizziness and nausea, and the incidence of adverse reactions was 3.33% (2/60). There was no statistical significance in the incidence of adverse reactions between the two groups (P= 0.402). As shown in **Table 6**.

Discussion

ACI, with high disability, morbidity and mortality, is closely related to collateral circulation, vascular endothelial injury, free radical injury, cerebral artery stenosis, abnormal blood composition, microemboli shedding, and hemodynamic changes [8]. The key to the treatment of patients with

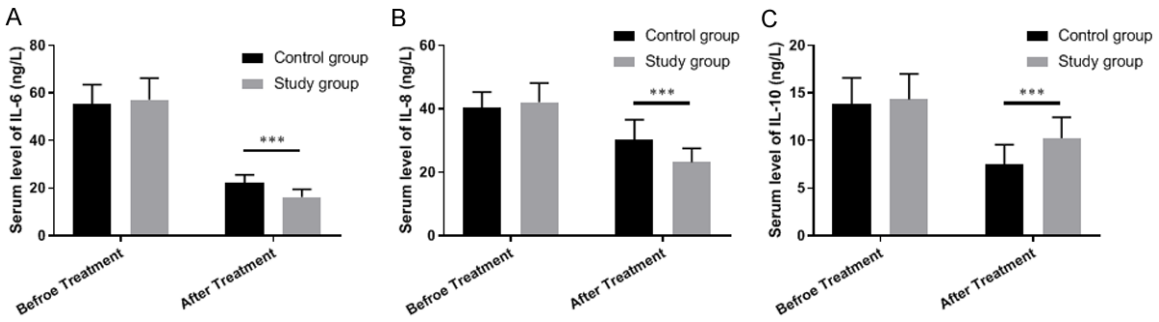

Figure 2. Comparison of serum levels of inflammatory factors between the two groups before and after treatment. A. The serum IL-6 level; B. The serum IL-8 level; C. The serum IL-10 level. ***P<0.001.

Table 6. Comparison of adverse drug reactions between the two groups

Group	Number of cases	Dizziness	Rash	Nausea	Total adverse reaction rate
Control group	60	1	2	1	6.67%
Study group	60	1	0	1	3.33%
χ^2					0.702
P					0.402

ACI lies in the early rescue of the ischemic penumbra, restoration of blood flow, and patency of blood vessels. Although evidence-based medicine has demonstrated that intravascular thrombolysis can be an effective measure for the treatment of ACI, it has the disadvantages of high cost and limited time window; hence, most patients can not receive effective thrombolytic therapy [9, 10]. According to the survey conducted by the China National Stroke Registry, only 1.6% of patients with cerebral infarction received thrombolytic therapy in time. Currently, the clinical treatment for patients with ACI is composed of the protection of cranial nerves and the promotion of cerebral perfusion by drugs [11]. As reperfusion and cerebral ischemia have complex injury mechanisms, drugs that can block the ischemic injury mechanism through multiple links are crucial for the treatment [12].

Butylphthalide is a new drug for the treatment of ACI, which protects the integrity of blood vessels, increases the number of microvessels and blood flow velocity, improves blood perfusion in the ischemic area, and alleviates brain hypoxia and ischemia in patients as soon as possible [13]. At the same time, it can bolster the activity of mitochondrial ATP-synthase, ensure the stability of mitochondrial membrane, protect the mitochondrial structure, and reduce cell mortality, thereby enhancing the energy metabolism of patients [14]. Moreover, butylphthalide can effectively inhibit inflammation and reduce the release of calcium storage and arachidonic acid in cells, so as to reduce cell mortality, inhibit the release of glutamic acid and enhance the activity of antioxidant enzymes. In addition, the drug can recover the neurological function of patients and effectively reduce the infarct size [15, 16].

Atherosclerosis is the main manifestation of ACI, which is a process of lipid accumulation on the one hand, and chronic inflammatory response on the other hand [17]. As an important inflammatory factor, CRP plays a vital role in the occurrence and progression of ACI through the complement system, the coagulation and fibrinolysis system, and the inflammatory system. Butylphthalide, as a drug for the treatment of ACI, can effectively reduce CRP levels and relieve inflammation [18, 19]. The causes of ACI include cerebral atherosclerosis, increased blood viscosity, and platelet aggregation. Part of the cerebral artery is suddenly blocked, resulting in severe cerebral vascular insufficiency, thus inducing acute hypoxia-ischemia necrosis of the brain tissue and damaging the patients' neurological function [20].

In this study, butylphthalide was used to treat patients with ACI. The results showed that treatment with butylphthalide led to a remarkably higher effective rate than the conventional method, without increasing adverse reactions, indicating that butylphthalide is condu-

cive to treating ACI with a high safety profile. A number of studies have confirmed the clinical efficacy of butylphthalide in ACI [21-23]. Butylphthalide has a neuroprotective effect, and it can increase the levels of NO and PGI 200 in cerebral vascular endothelium, reduce intracellular calcium concentration, inhibit the release of glutamate, drive down the content of arachidonic acid, suppress oxygen free radicals, up-regulate the activity of antioxidant enzymes, and achieve the purpose of preventing thrombosis, thus improving cerebral microcirculation and cerebral blood flow [24]. After treatment, the serum levels of CRP and PARK7 of patients treated with butylphthalide were significantly lower than those of patients with conventional treatment, and the NT-3 level was significantly higher, which demonstrates that treatment with butylphthalide can regulate factors related to pathological changes, thereby protecting the nervous system and optimizing the neurological function of patients. Elevated CRP is an independent risk factor for ischemic cerebrovascular disease and is closely related to the severity of the disease. CRP interacts with smooth muscle cells and endothelial cells, and after binding to lipoproteins, it activates the complement system to produce a large number of terminal attack complexes, resulting in vascular intimal damage [25]. Clinical studies have shown that butylphthalide can predominantly reduce the serum hs-CRP content of patients and inhibit the inflammatory response mediated by serum hs-CRP [26]. IL-6 and IL-8 are common inflammatory factors involved in AMI, while IL-10 is a common anti-inflammatory factor. Interleukins are immune-activating factors produced by monocytes, namely lymphocytes and monocytes-macrophages. Studies have demonstrated that IL expression increases significantly during cerebral ischemia, acting on white blood cells, vascular endothelial cells, and nerve cells to play a dual role of neurotoxicity and neuroprotection [27]. In the present study, these inflammatory factors were lower in the control group than those in the study group, indicating that butylphthalide can mitigate inflammatory response. This may be the main mechanism of the effect of eugenol, but more studies are required for further verification. Moreover, patients treated with butylphthalide had a lower NIHSS score and higher FMA and BI scores than those who were intervened by conventional treatment, further demonstrating that butylphthalide treatment can promote the recovery of neurological and motor functions of patients and improve their quality of life. This study explored the clinical efficacy of butylphthalide in the treatment of ACI and discussed its mechanism in combination with changes in the levels of CRP, PARK7, and NT-3, which provides the evidence-based referential basis for the clinical application of butylphthalide and has achieved remarkable results. However, this study still has the following limitations: (1) This study did not further explore the specific mechanism of butylphthalide on inflammation; (2) The study did not carry out statistical analysis of related complications and long-term mortality due to time reasons, and the follow-up time was short. In the following study, follow-up will be continued to collect relevant data and evaluate the long-term efficacy; (3) The number of cases in this study was small, and classification and subgroup analysis were not performed.

Conclusion

In summary, butylphthalide is markedly effective in the treatment of ACI. It can effectively facilitate the recovery of neurological and motor functions of patients, enhance their life quality, and remarkably improve serum CRP, PARK7, and NT-3 levels, which is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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