

Original Research Article

Effect of butylphthalide combined with edaravone d-borneol on efficacy in elderly patients with acute cerebral infarction

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Abstract

Purpose: To investigate the efficacy of butylphthalide combined with edaravone d-borneol in elderly patients with acute cerebral infarction.

Methods: From October 2020 - October 2021, 166 elderly patients suffering from acute cerebral infarction in Affiliated Hospital of Youjiang Medical College for Nationalities, Baise City, China were selected as the study subjects, and randomly divided into study and control groups, respectively, with 83 patients each. Control group was treated with edaravone d-borneol injection (15 mL of edaravone d-borneol in 100 mL of saline), while the study group was treated with butylphthalide and sodium chloride injection, combined with edaravone d-borneol injection (15 mL of edaravone d-borneol and 30 mL of butylphthalide and sodium chloride in 100 mL of saline). Clinical efficacy, as well as the levels of cytokines, viz, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and IL-8, vascular endothelial function indicators, namely, nitric oxide (NO) and vascular endothelial growth factor (VEGF) as well as oxidative stress indicators, viz, malondialdehyde (MDA), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) of the two groups were evaluated.

Results: Total efficacy/effectiveness in the study group was 93.98 %, which was significantly higher than 73.49 % in the control group ($p < 0.05$). Post-treatment, the levels of cytokines, vascular endothelial function and oxidative stress in the two groups were significantly improved compared with the values before treatment ($p < 0.05$). Furthermore, patients in the study group showed better treatment outcomes when compared with control group ($p < 0.05$).

Conclusion: The combination of butylphthalide and sodium chloride injection with edaravone d-borneol injection (15 mL of edaravone d-borneol and 30 mL of butylphthalide and sodium chloride in 100 mL of saline) is more effective than edaravone d-borneol injection (15 mL of edaravone d-borneol in 100 mL of saline) alone in the treatment of elderly patients with acute cerebral infarction, as it regulates microcirculation and improves cellular inflammatory state and oxidative stress reaction. However, further clinical trials should be conducted prior to application in clinical practice.

Keywords: Butylphthalide, Edaravone d-borneol, Elderly cerebral infarction, Clinical efficacy

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INTRODUCTION

Clinical studies have shown that the pathogenesis of acute cerebral infarction is based on abnormal cerebral blood circulation caused by cerebral artery vascular dysfunction or local lesions, and on this basis, it further leads to a series of clinical symptoms in the patient's local brain tissue due to ischemia and hypoxia [1]. Acute cerebral infarction is one of the clinically common types of cerebrovascular disease [2]. Recently, with the aging of the population, the incidence of acute cerebral infarction in the elderly has been increasing [3]. The rates of disability and mortality of patients are relatively high because of the dangerous progression of this disease [4]. Therefore, studies on the effective treatment methods for acute cerebral infarction have always been one of the focus areas as well as a hot issue.

Currently, Western medicine is the main therapy in the clinical treatment of elderly patients with cerebral infarction in the acute stage, the main treatment purpose being an improvement in the clinical symptoms of patients through anticoagulation, thrombolysis and microcirculation improvement [5]. Based on clinical experience, the clinical efficacy monotherapy in the treatment of acute cerebral infarction needs to be further researched [6]. As a new drug approved for marketing in the past two years, edaravone d-borneol has a better comprehensive efficacy in the treatment of acute cerebral infarction in combination with butyphthalide, and shows a better prognosis for patients [7,8].

Consequently, this study aims to explore the effect of butyphthalide combined with edaravone d-borneol on the clinical efficacy of elderly patients with cerebral infarction in the acute stage.

METHODS

Patient information

A total of 166 elderly patients with acute cerebral infarction who were admitted by the Affiliated Hospital of Youjiang Medical College for Nationalities from October 2020 to October 2021 were selected for this study. They were randomly divided into study and control groups, respectively. In the study group, there were 44 males and 39 females who were aged 65 - 80 years, with mean age of 71.47 ± 3.64 years, BMI index of 21.45 ± 1.02 kg/m² and duration from disease onset to admission of 19.45 ± 1.16 h. As for educational background, there were 28 with

bachelor degree or above, 35 with a high school education, and 20 below high school education. With regard to place of residence, there were 80 locals (i.e., resident in the city where the hospital is located) while 3 were non-local residents (i.e., reside outside the city). With regard to marital status, 65 were married, 15 divorced and 3 widowed.

In the control group, there were 45 males and 38 females who were aged 65 - 82 years, with mean age of 71.39 ± 3.96 years, a BMI index of 21.55 ± 1.11 kg/m² and duration from disease onset to admission of (19.50 ± 1.09 h). With regard to educational background, there were 29 with a bachelor's degree or above, 35 with a high school qualification, and 19 with lower than high school education. As for registered residence, there were 79 locals and 4 non-local residents. As regards marital status, 66 were married, 14 divorced and 3 widowed. Clinical data of the two groups were not significantly different.

Ethical matters

All procedures performed in the studies involving human participants were in accordance with the standards provided by the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities who approved the study {approval no. YYFY-LL-2022-53(48)}. The human study also complied with the guidelines of 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [9].

Inclusion and exclusion criteria

Inclusion criteria

- (1) Patients who met the diagnostic criteria of the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2014 [10];
- (2) Patients with duration from onset to admission of < 48 h;
- (3) Patients older than 65 years old;
- (4) patients or their family members gave informed consent.

Exclusion criteria

- (1) Patients with liver and kidney dysfunction;
- (2) those with intracranial hemorrhage;
- (3) cancer patients;
- (4) those allergic to related drugs;
- (5) those with mental or consciousness disorders.

Treatments

After admission, all patients received conventional treatment, including oxygen inhalation, control of cerebral edema, reduction

of intracranial pressure, reduction of blood pressure, reduction of blood lipid and sugar, improvement of microcirculation, maintaining of water-electrolyte balance, and protection of cranial nerves.

Control group

Besides conventional treatment, patients in the control group were given edaravone d-borneol via intravenous drip (Simcere Pharmaceutical Co. Ltd; approval no. H20200007; specification, 5 mL:10 mg) mixed with 0.9 % sodium chloride injection (Harbin Sanlian Pharmaceutical Co. Ltd; approval no. H20033125; specifications: 10 mL: 15 mg) with 15 mL and 100 mL, respectively, 2 times/day.

Study group

Besides conventional treatment, patients in the study group were given intravenous drip of a mixture of edaravone d-borneol injection and butylphthalate sodium chloride injection (Manufacturer, CSPC Group Enbip Pharmaceutical Co. Ltd; approval no. H20100041; specifications, 100 mL, butylphthalate 25 mg, sodium chloride 0.9 g) with 100 mL and 15 mL, respectively, 2 times/day.

Efficacy the treatments was assessed after 2 weeks of continuous treatment in both groups.

Evaluation of parameters/indices

Clinical efficacy, levels of cytokines (TNF- α , IL-6 and IL-8), vascular endothelial function indices (NO and VEGF) and oxidative stress indices (MDA, GSH-Px and SOD) of the two groups were determined.

Clinical efficacy

The National Institutes of Health Stroke Scale (NIHSS) with a score range of 0 - 42 points was used to assess the patients for efficacy/effectiveness of treatment. The lower the score, the better the neurological function recovery.

1. *Patients who were cured.* The NIHSS score was reduced by > 90 % after treatment and clinical symptoms disappeared

2. *Patients who showed significant therapeutic improvement.* The NIHSS score was reduced by > 45 % and \leq 90 % after treatment, and the clinical symptoms did not completely disappear, but improved significantly;

3. *Patients who showed moderate improvement.* The NIHSS score was reduced by >20 % and \leq 45 %, and clinical symptoms improved;

4. *Patients who did not show any significant improvement.* Symptomd remained largely unchanged in the patients.

Cytokine indicators

Enzyme-linked immunosorbent assays (ELISA) were performed to determine the serum concentrations of TNF α , IL-6 and IL-8, using the kits provided by Wuhan Addison Biotechnology Co. Ltd; the respective procedures were in accordance with the manufacturer's protocols.

Vascular endothelial function indicators

The concentrations of VEGF and NO in the serum were determined by ELISA and nitric acid reduction method, respectively, in accordance with the kit manufacturer's protocols.

Statistical analysis

SPSS 22.0 software was used for data analysis. Quantitative and enumeration data were presented as mean \pm standard deviation (SD) and proportion (%), respectively, using *t*-test for the quantitative data and Chi-square test for the enumeration data. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical efficacy

The total efficacy rate in the study group was 93.98 %, which was significantly higher than 73.49 % in the control group, and the difference was statistically significant ($p < 0.05$; Table 1).

Cytokine levels

Before treatment, there was insignificant difference ($p < 0.05$) in cytokine levels between the two groups ($p > 0.05$); after treatment, the levels of cytokines in both groups were significantly decreased to varying degrees compared with those before treatment ($p < 0.05$). There were greater decreases as regards to these factors in the study group compared with the control group ($p < 0.05$), as shown in Table 2.

Table 1: Comparison of clinical efficacy between the two groups (%)

Group	N	Cured	Significant effect	Valid	Invalid	Total efficacy
Study group	83	18 (21.69)	35 (42.17)	25 (30.12)	5 (6.02)	78 (93.98)
Control group	83	7 (8.43)	26 (31.33)	28 (33.73)	22 (26.51)	61 (73.49)
t value	—	—	—	—	—	12.7828
P-value	—	—	—	—	—	0.0004

Table 2: Comparisons of cytokine indicators in the two groups (mean ± SD, N = 83)

Group	TNF-α (pg/mL)		t-value	P-value	IL-6 (pg/mL)		t-value	P-value	IL-8 (pg/mL)		t-value	P-value
	Before treatment	After treatment			Before treatment	After treatment			Before treatment	After treatment		
Study group	136.54 ± 12.35	76.35 ± 7.09	38.507	0.0	79.98 ± 8.19	47.98 ± 4.16	31.7369	0.0	50.98 ± 5.46	27.98 ± 2.16	35.6862	0.0
Control group	137.06 ± 11.76	99.06 ± 9.07	23.311	0.0	80.16 ± 8.27	62.34 ± 7.06	14.9304	0.0	51.09 ± 4.98	39.04 ± 3.06	18.782	0.0
t-value	0.2778	17.9719	—	—	0.1409	15.9652	—	—	0.1356	26.9016	—	—
P-value	0.7815	0.0000	—	—	0.8881	0.0000	—	—	0.8923	0.0000	—	—

Table 3: Comparison of vascular endothelial function indices for the two groups (mean ± SD, N = 83)

Group	NO (μmol/L)		t-value	P-value	VEGF (pg/L)		t-value	P-value
	Before treatment	After treatment			Before treatment	After treatment		
Study group	51.04 ± 5.16	79.06 ± 8.06	26.6738	0.0	419.68 ± 39.25	231.29 ± 21.16	38.4906	0.0
Control group	50.98 ± 4.99	64.01 ± 6.16	14.9743	0.0	420.16 ± 38.16	349.35 ± 33.26	12.7441	0.0
t-value	0.0762	13.516	—	—	0.0799	27.2848	—	—
P-value	0.9394	0.0000	—	—	0.9364	0.0000	—	—

Table 4: Comparison of oxidative stress indicators for the two groups (mean ± SD, N = 83)

Group	MDA (nmol/mL)		t-value	P-value	GSH-Px (U/L)		t-value	P-value	SOD (U/mL)		t-value	P-value
	Before treatment	After treatment			Before treatment	After treatment			Before treatment	After treatment		
Study group	13.86 ± 1.32	5.64 ± 0.54	52.5092	0.0	47.36 ± 4.53	109.35 ± 9.35	54.3579	0.0000	179.35 ± 17.35	324.56 ± 30.25	37.9362	0.0
Control group	13.79 ± 1.26	8.91 ± 0.99	27.7451	0.0	48.09 ± 487	78.35 ± 7.69	30.2868	0.0000	179.98 ± 18.09	245.36 ± 25.06	19.2719	0.0
t-value	0.3495	26.4177	—	—	0.9999	23.3289	—	—	0.229	18.3684	—	—
P-value	0.7272	0.0000	—	—	0.3188	0.0000	—	—	0.8192	0.0000	—	—

Vascular endothelial function indices

Before treatment, there was no difference in vascular endothelial function indicators between the two groups ($p > 0.05$). After treatment, vascular endothelial function indicators in the two groups were significantly improved to varying degrees compared with the values before treatment ($p < 0.05$). To a greater extent, the level of NO increased while the level of VEGF decreased in the study group compared with the control group ($p < 0.05$), as Table 3 shows.

Oxidative stress indicators

Prior to treatment, there was little difference in oxidative stress indicators between the two groups ($p > 0.05$). However, after treatment, there was improvement in the levels these indicators were in both groups ($p < 0.05$). The changes in the levels of MDA, GSH-Px and SOD were more pronounced in the study group than in the control group ($p < 0.05$), as shown in Table 4.

DISCUSSION

Elderly patients in the acute stage of cerebral infarction often have a very sudden clinical onset, and the disease progresses rapidly and dangerously after that. If treated inappropriately and untimely, it will not only lead to a poor prognosis, but also directly threaten the patient's life. Besides that, the rate of disability and mortality is quite high [11].

Clinical studies have shown that scientific improvement in cerebral microcirculation disorders was largely emphasized in the treatment for elderly patients in the acute stage of cerebral infarction [12,13]. However, the targeted treatment of ischemic semi-dark zone should also be considered in clinical practice in order to prevent the occurrence of reperfusion injury caused by ischemia, thus effectively promoting the recovery of patients' nerve function and improving the survival rate of related cells in brain tissue [14]. For this reason, pharmacological therapy is currently the main method used in the treatment of elderly patients in the acute phase of cerebral infarction [15].

Edaravone d-borneol injection (concentrated solution) is a new drug approved for marketing in 2020. Its main components are edaravone and d-borneol, with the former accounting for 80 % and the latter 20 %, and this drug is one of the oxygen radical scavengers for clinical use [16]. It has a significant protective effect on the patient's nerve tissue, and its rapid action quickly removes the patient's reactive oxygen species. It also has

a significant inhibitory effect on the generation of oxygen-free radicals, which in turn prevents brain damage caused by oxygen-free radicals [17,18].

D-borneol in concentrated solution of edaravone d-borneol injection also has a good antioxidant radical effect, and it resists local inflammatory response. As a result, it can effectively protect brain tissue through the dual inhibition of oxygen radicals and inflammatory response [19]. Butylphthalide sodium chloride injection exerts a strong improvement effect on the local microcirculation and stimulates the release of glutamic acid in the local tissues of the patient's brain, thus inhibiting the production of oxygen-free radicals. Therefore, it effectively controls or reduces the area of the ischemic semi-dark zone of the brain [20].

Clinical studies have confirmed that butylphthalide has an obvious comparative advantage in protecting patients from impaired neurological function and neurons [21]. This shows that the combination of the above two drugs exerts a synergistic effect, and improves the comprehensive clinical efficacy in the treatment of elderly patients with cerebral infarction in the acute stage.

In this study, the total effectiveness in the study group was 93.98 %, which was significantly higher than 73.49 % in the control group. Post-treatment, the indices of cytokines, vascular endothelial function and oxidative stress in the two groups improved to vary extents when compared with pre-treatment values; the improvements were more pronounced in the study group than in the control group. These results further confirmed the clinical comparative advantage of butylphthalide combined with edaravone d-borneol in the treatment of elderly patients with acute cerebral infarction, and are consistent with similar reports in China and elsewhere [22].

Furthermore, it has been observed that the synergistic effect of the combination of butylphthalide and edaravone d-borneol is mainly under the premise that oxygen-free radicals are effectively removed, the brain is in a microcirculation state, and oxidative stress state and inflammatory response state have been more significantly controlled, and that the mitochondria of patients have been effectively protected. On the basis of these effects, the vascular endothelial tissues are further activated, causing it to release prostaglandins, in order to promote the increase of nitric oxide levels, and then to prevent platelet aggregation to avoid thrombosis [23].

CONCLUSION

The combination of butylphthalide and sodium chloride injection with edaravone d-borneol for injection has a significantly greater therapeutic effect in elderly patients with acute cerebral infarction, as it regulates microcirculation, improves cellular inflammatory state and oxidative stress reaction, making it one of the reliable treatment schemes for elderly patients with acute cerebral infarction. However, further clinical trials are recommended prior to the application of this combination in clinical practice.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Li Su designed the studies and carried them out; Li Su, Shengshan Yuan, Xinhan Yang and Yongming Jiang supervised the data collection, analyzed the data, interpreted the data, prepare the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript.

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