ORIGINAL RESEARCH

Influences of Butylphthalide Injection in Combination with Edaravone on Clinical Efficacy and Cytokines in Elderly Acute Cerebral Infarction Patients

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ABSTRACT

Background • Acute cerebral infarction threatens human health and life safety. The edaravone is a new antioxidant and hydroxyl radical scavenger, which is used in the treatment of cardiovascular diseases. However, long-term use of edaravone is prone to drug resistance, resulting in limited therapeutic effect. Butylphthalein can improve collateral circulation, protect the integrity of vascular endothelial cells, improve vasospasm, increase blood perfusion in the ischemic area of brain tissue, and promote the recovery of cerebral nerve function.

Objective • To measure the influences of butylphthalide injection in combination with edaravone on clinical efficacy and cytokines in elderly acute cerebral infarction patients, aiming to provide reference for the treatment of acute cerebral infarction.

Design• This was a retrospective study.

Setting • This study was performed in Yantaishan Hospital.

Participants • A total of 168 elderly acute cerebral infarction patients who accepted therapy in our hospital from February 2022 to February 2023 were chosen and allocated into a combination group and a control group.

Interventions • The control group accepted the edaravone injection treatment. The combination group was treated with edaravone injection combined with butylphthalide injection.

Primary Outcome Measures • (1) Therapeutic effect (2) Cytokines (3) Vascular endothelial function (4) Oxidative stress (5) Degree of neurological impairment (6) Living ability.

Results • The total effective rate in the combination group presented elevation when in contrast to the control group ($P < .05$). After therapy, the levels of cytokines in the combination group presented reduction relative to the control group ($P < .05$), nitric oxide level in the combination group presented elevation when in contrast to the control group ($P < .05$), vascular endothelial growth factor level in the combination group presented lessened relative to the control group ($P < .05$), glutathione peroxidase along with superoxide dismutase levels in the combination group presented higher relative to the control group ($P < .05$) and malondialdehyde level in the combination group presented lower relative to the control group ($P < .05$). After therapy, the National Institute of Stroke Scale score in the combination group presented reduced when compared with the control group ($P < .05$). In contrast, the activity of daily living score in the combination group presented higher relative to the control group ($P < .05$).

Conclusion • Butylphthalide injection in combination with edaravone can effectively inhibit the inflammatory response and oxidative stress, promote vascular endothelial function, improve daily behavior ability as well as promote the neurological function of elderly acute cerebral infarction patients. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Cerebrovascular disease (CVD) is a general term for a class of diseases which cerebrovascular lesions cause brain dysfunction.[1] Among them, acute cerebral infarction (ACI) belongs to a more common cerebrovascular lesion, refers to the death of brain tissue after the sudden interruption of the blood supply to the brain. It is usually mainly due to atherosclerosis and thrombosis of the arteries supplying blood to the brain, so that the lumen is narrow or even blocked, resulting in focal acute cerebral insufficiency.[2] The clinical manifestations are headache, vertigo, tinnitus, and hemiplegia.[3] People with hypertension, coronary heart disease, diabetes, hyperlipidemia, smoking, drinking, and obesity are prone to ACI.[4] The main clinical characteristics of ACI are sudden onset and rapid onset of localized or diffuse brain functional impairment, which has a very serious influence on the quality of life of patients, as well as also bringing heavy burden and pain to the families of patients.[5] With the aging population structure in our country, the harm caused by cerebrovascular diseases is becoming more and more significant. ACI has become the second most high-risk disease after ischemic heart disease due to its high incidence, mortality, and disability.[4] Currently, patients can be treated clinically with mechanical thrombectomy and thrombolytic agents within the time window of onset.[6] In cerebral infarction patients, the function of brain cells may cause irreversible damage more than 6 hours after the onset of the disease. Even if thrombolysis is performed, the function of brain cells cannot be restored after thrombolysis, which may cause reperfusion injury and increase the risk of cerebral hemorrhage. Therefore, thrombolysis or mechanical thrombolysis can only produce significant effects on a small number of patients. The vast majority of ACI patients have no indications of thrombolysis and intravascular therapy when

admitted, and conventional treatment is the main treatment.[7] Therefore, the discovery and research of the most suitable therapeutic drugs for patients, especially brain protection drugs, has become an urgent problem in the field of cerebrovascular diseases.

Butylphthalide, commonly known as apigenin, is a new drug developed and synthesized after artemisinin and bicyclic alcohol in China.[8] Many studies have confirmed that butylphthalide is an effective treatment for patients with ACI.[9] On the one hand, butylphthalide has the effect of improving cerebral blood flow; on the other hand, it plays a protective role in nerve tissue cells, so it has become a new star drug in the clinical treatment of ACI.[10] Some scholars have found that butylphthalide injection can effectively inhibit the process of ischemic damage in brain tissue, especially in the treatment of ACI.[11]

As a first-line treatment drug for cerebral infarction, edaravone has certain promoting significance for reasonable control of prognostic complications and improvement of brain tissue function.[12] Edaravone injection is a new type of brain-protective agent, which can inhibit the damage of brain tissue and the death of neurons in the infarction area by inhibiting free radicals.[13] At the same time, it has a strong protective effect on the brain nerves and can effectively improve the neurological symptoms and dysfunction caused by ACI, which is often used in the treatment of cerebral ischemia.[14]

In this study, we explored the influences of butylphthalide injection in combination with edaravone on clinical efficacy, cytokines, vascular endothelial function, oxidative stress, degree of neurological impairment and living ability in elderly ACI patients.Our study might provide clinical reference for ACI treatment.

DATA AND METHODS

General data

A total of 168 elderly ACI patients accepted therapy in our hospital from February 2022 to February 2023 were chosen and divided into combination groups and control groups (CG) using the random number table method, with 84 cases in each group. Combination group: 44 men and 40 women; the average age was (69.74±6.68) years, ranging from 62 to 76 years; the onset time of disease was 6-38 h, with an average of (17.29±5.62) h. CG: 43 males and 41 females; the average age was (70.02±7.84) years, ranging from 61 to 78 years; the onset time of disease was 6-37 h, with an average of (17.32±5.65) h. No difference was discovered in general data between 2 groups ($P > .05$). Inclusion criteria: (1) Met the diagnosis of ACI; (2) 24 to 72 hours after onset; (3) Computed tomography (CT) and magnetic resonance imaging (MRI) diagnosis was clear; (4) Clear consciousness, no serious complications, can cooperate with treatment; (5) Patient and family members informed and consented to treatment. Exclusion criteria: (1) Symptoms of cerebral hemorrhage detected by head CT; (2) Severe heart, liver, and kidney dysfunction; (3) Women with malignant tumors or pregnancy. Our study was approved by the Ethics Committee of our hospital.

Methods

After admission, the two groups underwent complete examination and examination, and were treated with thrombolysis, cranial pressure reduction, nerve nutrition, etc., and began to protect nerves and reduce inflammation after the condition stabilized.

The CG was treated with edaravone injection (Huinan Changlong Biochemical Pharmaceutical Co., LTD.), 30 mg edaravone +0.9% sodium chloride injection 100 ml intravenously, 2 times a day, 2 weeks for 1 course of treatment. The combination group was combined with butylphthalide injection (Shi Yao Group Enbipu Pharmaceutical Co., LTD.) on the basis of CG treatment, 25 mg/100 ml intravenous infusion, twice a day, 2 weeks for 1 course of treatment.

Observation indicators

Criterion of therapeutic effect: Basically cured: the National Institute of Stroke Scale (NIHSS)[15] score of the patient was reduced by >90% after 14 days of treatment, and the patient's symptoms disappeared after 2 weeks of treatment, and the patient could take care of himself in daily life; Obvious effect: the NIHSS score of the patient was less than 45% and ≤90% after 2 weeks of therapy, and the symptoms were obviously improved, and the patient could basically take care of himself in daily life; Effective: After 2 weeks of treatment, NIHSS score was reduced by >20% and ≤45%, symptoms were improved, and the patient could take care of part of daily life; Ineffective: The NIHSS score of the patient was reduced by less than 20% after 14 days of treatment, and the patient's symptoms did not improve and the patient could not take care of himself in daily life. Total effective rate = (basically cured + obvious effect + effective)/total number of people ×100%.

Cytokines: 5 ml venous blood was gathered from patients, centrifuged, and then the serum of the supernatant was obtained. The concentrations of tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, IL-18, IL-1β along with IL-10 were examined by enzyme-linked immunosorbent assay (Shanghai Enzyme Linked Biotechnology Co., LTD, Shanghai, China).

Vascular endothelial function: Nitric oxide (NO) concentration was determined by nitric acid reduction method, and vascular endothelial growth factor (VEGF) concentration was determined by enzyme-linked immunosorbent assay (Shanghai Enzyme Linked Biotechnology Co., LTD, Shanghai, China).

Oxidative stress: The concentrations of malondialdehyde (MDA), glutathione peroxidase (GSH-Px), along with superoxide dismutase (SOD) were determined by colorimetry.

(5) **NIHSS Score**. The NIHSS score was adopted to measure the degree of neurological impairment. The total score of NIHSS was 42, and the higher the score, the more serious the neurological impairment.

(6) **ADL Scale**. The activity of daily living (ADL) scale[16] was implemented to measure the independent living ability of patients. The total score of the ADL scale was 100, and the higher the score, the better quality of life.

Statistical analysis

SPSS 20.0 software (IBM, Armonk, New York, USA) was implemented for statistical processing of all the data in this study. The measurement data were represented by ($x \pm s$), and t test was used for comparison, and the counting data were represented by the number of [cases (%)], and χ^2 test was performed. $P < .05$ was considered statistically significant.

RESULTS

Therapeutical effect in both groups

Table 1 showed that the total effective rate of the combination group was 95.24%, presented elevation when relative to that of 80.95% of the CG ($P < .05$).

Changes of cytokines in both groups

Figure 1 displayed that no difference was discovered in TNF-α, IL-6, IL-8, IL-18, IL-1β, and IL-10 levels between both groups before therapy ($P > .05$). Followed by therapy, the levels of the above cytokines were declined in both groups, and those in the combination group were (76.37±7.65) pg/mL, (48.76±4.87) pg/mL, (28.98±2.90) pg/mL, (106.96±10.72) pg/mL, (14.74±1.50) pg/L, and (21.36±2.14) pg/L, presented lower in contrast to those of (98.43±9.85) pg/mL, (62.24±6.24) pg/mL, (38.07±3.84) pg/mL, (172.13±17.25) pg/mL, (21.46±2.17) pg/L and (30.12±3.05) pg/L in the CG ($P < .05$). All these results suggested that butylphthalide injection combined with edaravone treatment could improve the inflammatory response in elderly ACI patients.

Vascular endothelial function in both groups

Figure 2 displayed that no difference was discovered in NO together with VEGF levels between both groups before therapy ($P > .05$). Followed by therapy, NO was elevated in both groups and that in the combination group was (78.34±7.85) μmol/L, presenting increased relative to that of (64.23±6.43) μmol/L in the CG ($P < .05$). Meanwhile, VEGF was declined in both groups after therapy, and that in the combination group was (237.89±23.87) pg/L, presented lower when comparing with that of (348.76±35.09) pg/L in the CG ($P < .05$). All these results suggested that butylphthalide injection combined with edaravone treatment could improve the vascular endothelial function in elderly ACI patients.

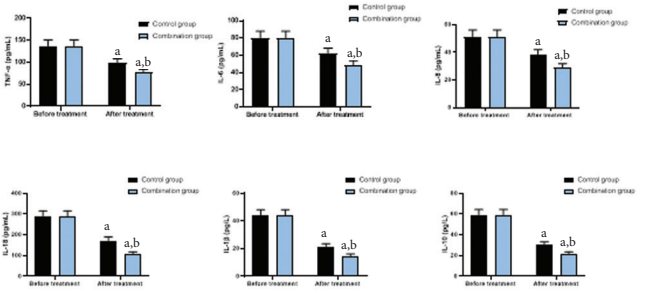
Oxidative stress in both groups

Figure 3 displayed that no difference was discovered in MDA, and GSH-Px along, with SOD levels between both groups before therapy ($P > .05$). After therapy, GSH-Px and SOD were elevated in both groups, and those in the combination group were (108.79±10.83) U/L and (323.45±32.36) U/ml, presented higher relative to those of (78.18±7.83) U/L and (243.27±24.35) U/ml in the CG ($P < .05$). Meanwhile, MDA declined in both groups after therapy, and that in the combination group was (5.74±0.58) nmol/ml, presented lower in contrast to that of (8.95±0.92) nmol/ml in the CG ($P < .05$). All these results suggested that butylphthalide injection combined with edaravone treatment could improve the oxidative stress response in elderly ACI patients.

Table 1 Therapeutical effect in both groups [cases (%)]

Groups	Cases	Basically cured	Obvious effect	Effective	Ineffective	Total effective rate (%)
Control group	84	9 (10.71)	20 (23.81)	39 (46.43)	16 (19.05)	68 (80.95)
Combination group	84	19 (22.62)	25 (29.76)	36 (42.86)	4 (4.76)	80 (95.24)
χ^2						8.17
P value						<.05

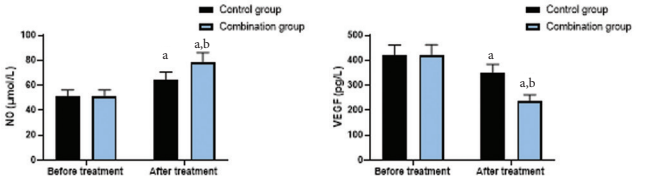
Figure 1. Changes of cytokines in both groups.



[a]$P < .05$, compared with before treatment
[b]$P < .05$, compared with CG

Abbreviations: TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; IL-8, interleukin-8; IL-18, interleukin-18; IL-1β, interleukin-1β; IL-10, interleukin-10.

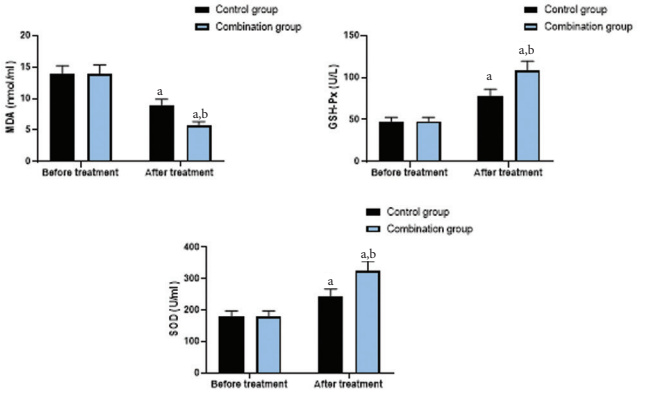
Figure 2. Vascular endothelial function in both groups.



[a]$P < .05$, compared with prior to treatment
[b]$P < .05$, compared with CG.

Abbreviations: NO, nitric oxide; VEGF, vascular endothelial growth factor.

Figure 3. Oxidative stress in both groups.



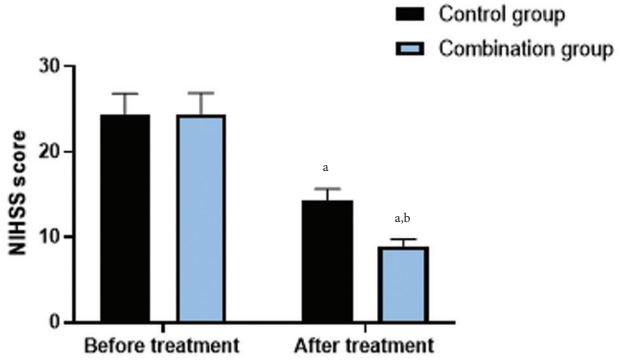
[#]$P<0.05$, compared with prior to treatment
[*]$P<0.05$, compared with CG.

Abbreviaitons: MDA, malondialdehyde; GSH-Px, glutathione peroxidase; SOD, superoxide dismutase.

NIHSS score in both groups

Figure 4 displayed that no difference was discovered in the NIHSS score between both groups before therapy ($P > .05$). After therapy, the NIHSS score declined in both groups, and that in the combination group was (8.86±0.89) points,

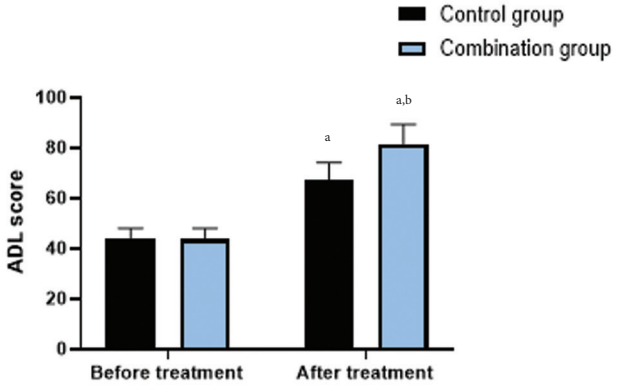
Figure 4. NIHSS score in both groups.



[a]$P < .05$, compared with prior to treatment
[b]$P < .05$, compared with CG.

Abbreviation: NIHSS, National Institute of Stroke Scale.

Figure 5. ADL score in both groups.



[a]$P < .05$, compared with prior to treatment
[b]$P < .05$, compared with CG.

Abbreviation: ADL: activity of daily living.

presented lower when compared with that of (14.20±1.43) points in the CG ($P < .05$). All these results suggested that butylphthalide injection combined with edaravone treatment could relieve the degree of neurological impairment in elderly ACI patients.

ADL score in both groups

Figure 5 displayed that no difference could be discovered in ADL scores between both groups before therapy ($P > .05$). Followed by therapy, the ADL score was elevated in both groups and that in the combination group was (81.19±8.16) points, presented elevated relative to that of (67.36±6.75) points in the CG ($P < .05$). All these results suggested that butylphthalide injection combined with edaravone treatment could improve the living ability in elderly ACI patients.

DISCUSSION

The pathogenesis of ACI is extremely complex, and its cause may be cerebral artery stenosis or obstruction caused by abnormal blood vessels and hemodynamics. The interruption of cerebral blood supply leads to local softening and necrosis of brain tissue.[17] At present, the treatment methods for ACI mainly include thrombolysis, reduction of intracranial pressure, anticoagulation, and nerve nutrition.[18] However, there are many limiting factors of conventional treatment, which may cause adverse reactions such as intracranial hemorrhage and cannot guarantee the life safety of patients.[19] Therefore, it has become the focus of clinicians to find a treatment plan for ACI with exact efficacy and small side effects.

Edaravone is a free radical scavenger that inhibits lipid peroxidation, and n-acetyl aspartate (NAA) is a specific marker of neuron survival. Studies have found that the use of edaravone significantly increases the content of NAA, indicating that edaravone has a vital role in reducing the damage of nerve cells along with increasing the survival of neurons.[20] Edaravone should be used with caution in the elderly with liver insufficiency, mild to moderate renal dysfunction and heart disease. The adverse reactions of edaravone include increased blood pressure, heat sensation, increased cholesterol and triglyceride, increased or decreased platelet, increased total bilirubin, increased creatinine, allergic reaction, etc.[21]

Butylphthalide, its active ingredient is racemic-3-n-butylphthalide, is a kind of L-apigenin methylene racemate isolated from celery seed, which can be synthesized artificially, is a volatile oily component, is a new class I drug independently developed in China for the treatment of ACI and is currently widely used in the treatment of ACI patients in clinical practice.[22] Studies have shown that butylphthalide can protect the structure and function of mitochondria by inhibiting the generation of intracellular free radicals and enhancing the activity of antioxidant enzymes, thus improving the state of energy metabolism of nerve tissue cells under hypoxic ischemia and showing particularly significant clinical efficacy in ACI patients.[23] There are few adverse reactions of butylphthalein, a few can see elevated serum aminotransferase, occasionally nausea, abdominal discomfort, mental symptoms (mild hallucination), can return to normal after withdrawal. In clinical trials, drug-related adverse reactions were: elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), mild hallucinations, and digestive discomfort. The safety of butylphthalein in pregnant or lactating women is unclear and is not recommended.[24]

In our study, the outcomes displayed that the total effective rate of the combination group presented elevation when relative to the CG, which suggested that butylphthalide injection combined with edaravone had better clinical efficacy in elderly patients with ACI. Similarly, many studies have reported that butylphthalide combined with other drugs has a better therapeutic effect in ACI.[25]

The progression of ACI is linked to many factors, including cytokines, vascular endothelial function, and oxidative stress.[26] Among the cytokines, TNF-α, IL-6, IL-8, IL-18, IL-1β as well, as IL-10 are a class of cytokines with immunomodulatory functions and effects, mainly produced by mononuclear macrophages and T lymphocytes, and their concentration changes are involved in the pathological changes of cerebrovascular diseases.[27] In our study, the

results displayed that after therapy, TNF-α, IL-6, IL-8, IL-18, IL-1β as well as IL-10 levels declined in both groups and those in the combination group presented lower relative to the CG, which implied that butylphthalide injection combined with edaravone could better inhibit the inflammatory response in elderly patients with ACI. Consistently, previous literature has proven that butylphthalide combined with edaravone can obviously inhibit levels of cytokines in acute ischemic stroke patients.[28] ACI patients usually have vascular endothelial function impairment.[29] NO is an important vasodilator which can inhibit monocyte adhesion, smooth muscle cell proliferation, and free radical production.[30] VEGF is an important angiogenic factor, mainly through specific binding to endothelial cells, so as to promote the formation of blood vessels and endothelial cell proliferation.[31] Studies have revealed that VEGF is involved in pathological angiogenesis in diverse diseases such as atherosclerosis and ACI.[32,33] In our study, we observed that after therapy, NO in the combination group presented elevated relative to the CG. In contrast, VEGF in the combination group presented lower relative to the CG, reflecting that butylphthalide injection in combination with edaravone could better improve the vascular endothelial function of elderly ACI patients, which was in line with previous studies.[34,35] In oxidative stress, MDA, GSH-Px, and SOD are important indexes to evaluate oxidative stress, which is of great significance for evaluating the therapeutic effect as well as prognosis of ACI.[36] Among them, GSH-Px and SOD are the markers of free radical scavenging ability in the body, while MDA detection is mainly to understand the degree of lipid peroxidation.[37,38] In our study, we observed that after therapy, GSH-Px and SOD of the combination group presented elevated relative to the CG, while MDA of the combination group presented declined relative to the CG, implying that butylphthalide injection combined with edaravone could better inhibit the oxidative stress in elderly patients with ACI. Consistently, it has been reported that butylphthalide, in combination with other drugs, can reduce oxidative stress in ACI patients.[39] The reason may be that butylphthalein can stimulate the synthesis of nitric oxide and prostaglandin in vascular endothelium, reduce the level of arachidonic acid and the concentration of cellular calcium, inhibit the peroxide stress reaction, improve brain inflammation and brain edema, protect neurons and alleviate nerve function injury.[8]

In addition, our study proved that after therapy, the NIHSS score in the combination group presented lower when compared with the CG, while the ADL score in the combination group presented elevated relative to the CG. It is suggested that butylphthalide injection combined with edaravone could effectively restore the neurological function of patients and promote their ability to daily life, which was similar to the relevant reports.[40-43] The reason may be that butylphthalein is one of the commonly used drugs in the treatment of acute cerebral infarction. It is an artificial racemate of butylphthalein, and its structure is the same as that of L-apicone in celery seed, which can inhibit platelet aggregation, improve cerebral ischemic microcirculation, reduce infarction area and improve nerve function.[10]

However, due to time constraints, this study still has some shortcomings, mainly in the following aspects: First, this study did not track the long-term effects of the two treatment regimens on ACI, so the long-term effect of drug treatment on patients is still unclear. Second, this study did not include a larger sample may lead to bias in statistical results, and more subjects need to be recruited in future studies. We hope to carry out large randomized controlled trials in the follow-up study and carry out long-term follow-up to improve our research conclusions. In addition, our study will investigate the effects of these drugs on different subtypes of ACI and explore the mechanisms of action of butylphthalide injection and edaravone in ACI.

In conclusion, butylphthalide injection in combination with edaravone can effectively inhibit the inflammatory response and oxidative stress, promote vascular endothelial function, improve daily behavior ability and promote the neurological function of elderly ACI patients. Our study provides a clinical combined treatment protocols or guidelines for elderly ACI patients.

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