

REVIEW ARTICLE

Clinical Efficacy and Short-Term Prognosis of Butylphthalide and Sodium Chloride Injection Compared to Edaravone in the Treatment of Patients with Acute Stroke

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ABSTRACT

Background • Acute stroke is characterized by rapid progression, high mortality, and disability rates, making it a significant focus in clinical research. Brain-protective agents, such as butylphthalide and edaravone, have emerged as important therapeutic options for acute stroke.

Objective • This study aimed to explore how butylphthalide and edaravone promote healing in acute stroke, drawing on relevant data, literature, clinical experience, and personal concepts.

Design • The study design involves a narrative review, which comprehensively explores the pathogenesis of stroke by referencing relevant data and literature. Clinical experience and personal insights were incorporated to provide a holistic understanding. The primary focus was analyzing the mechanisms through which butylphthalide and edaravone facilitate healing in stroke patients.

Results • The review revealed that butylphthalide exhibited multiple beneficial effects, including the protection of

mitochondria, reduction of the inflammatory response, enhancement of microcirculation, decrease in blood-brain barrier permeability, and improving nerve cell function. On the other hand, edaravone demonstrated its efficacy by reducing oxidative stress response, inhibiting inflammatory response, and regulating the metabolism of arachidonic acid and apoptosis. These findings highlight the distinct mechanisms through which butylphthalide and edaravone contribute to the healing process in patients with stroke.

Conclusions • This study highlights the positive impact of butylphthalide and edaravone on the therapeutic effect and short-term prognosis in acute stroke patients. The findings provide valuable guidance for future research and enhance our understanding of these drugs' mechanisms, offering the potential for improved stroke management and patient outcomes. (*Altern Ther Health Med*. 2023;29(7):370-375).

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INTRODUCTION

Acute stroke results from cerebral blood supply disorders, leading to local brain tissue hypoxic-ischemic necrosis.¹ In recent years, the incidence of acute stroke has risen, and there is a noticeable trend towards affecting younger individuals, making it a significant public health concern. The increasing prevalence of acute stroke poses a considerable threat to social well-being and public health and safety.

Researchers have conducted numerous studies to improve acute stroke treatment outcomes and patient

recovery speed. For instance, Chong et al.² investigated the efficacy and safety of Ginkgo biloba extract in patients with acute ischemic stroke. Through an extensive search across seven databases for randomized controlled studies involving Ginkgo biloba leaves application in acute ischemic stroke patients, their findings indicated significant improvements in neurological function and daily life activities. These results underscore the potential benefits of using Ginkgo biloba leaves to enhance the overall outcomes for patients with acute ischemic stroke.

Fargen et al.³ explored the intricate process of doctors' decision-making regarding implementing mechanical thrombectomy for acute stroke patients. Through a comprehensive review, this study aimed to illuminate the various mechanisms that influence such decision-making, particularly identifying potential biases that could impact judgment. Additionally, the research explored other crucial aspects of decision-making, including confidence levels, universal management approaches, and strategies to enhance the decision-making process. The findings from this study

emphasize the need to elevate the standards of acute stroke treatment and patient care.

Studies also highlighted the importance of considering recombinant tissue Plasmin activator (rt-PA) dosage in stroke management and patient responses. A study by Cheng et al.⁴ explored the influence of rt-PA dosage, calculated based on estimated body weight, on the clinical outcomes of patients with acute ischemic stroke. The research compared three groups, analyzing demographic characteristics, past risk factors, National Institutes of Health Stroke Scale scores at 24 hours and discharge, modified Rankin Scale scores at discharge and three months post-event, and bleeding transformation and symptomatic intracranial hemorrhage. The results revealed no significant differences among the groups in the evaluated parameters. It suggested that the dosage of rt-PA calculated based on estimated weight will not adversely affect the clinical outcomes in patients with acute ischemic stroke.

Mazighi et al.⁵ conducted a study to assess the impact of strict management of systolic blood pressure on reducing the incidence of cerebral parenchymal hemorrhage after successful endovascular treatment of acute ischemic stroke. The study was conducted in four academic hospitals in France and included patients with acute ischemic stroke caused by a blockage in a major blood vessel (Great Vessel Occlusion). These patients were randomly assigned to two groups, one subjected to strict systolic blood pressure control goals (100-129 mm Hg) and the other following standard guidelines (130-185 mm Hg). The results of the study indicated that implementing strict systolic blood pressure control goals can indeed help lower the risk of a cerebral hemorrhage in patients with acute ischemic stroke.

Mistry et al.⁶ conducted a study to assess the impact of white matter disease on the prognosis of acute stroke patients undergoing intravascular treatment. The research findings revealed a strong correlation between the severity of white matter disease and both patient prognosis and the occurrence of intracerebral hemorrhage. Specifically, moderate to severe white matter disease was found to influence the prognosis of patients who received intravascular treatment without significantly increasing the risk of bleeding complications. However, further research is required to compare patients who receive intravascular therapy with those who do not to understand the effects and determine if the efficacy of intravascular treatment changes as white matter disease worsens.

It is evident from previous studies that numerous clinical experiments and analyses have been carried out to explore factors influencing the treatment and prognosis of acute stroke. However, research combining stroke treatment drugs with brain-protective fluid remains scarce. In the treatment of acute stroke, it is crucial not only to address the immediate symptoms and save the patient's life but also to minimize the damage to neurological function caused by the disease. The significance of brain-protective agents in this healing process has gradually gained recognition. Referring to relevant literature, we find that both butylphthalide and edaravone

play important roles in treating acute stroke.^{5,6} However, most of the existing studies on these agents are experimental in nature and lack comprehensive elaboration on their therapeutic mechanisms and effects, leading to certain general shortcomings.

Stroke is categorized into ischemic stroke and hemorrhagic stroke. Studies have revealed that arterial occlusion and embolism are the primary mechanisms underlying ischemic stroke, while cerebrovascular rupture and leakage are the main causes of hemorrhagic stroke.⁴⁻⁶ Regardless of the type of stroke, it leads to inadequate blood supply to cerebral tissues after onset, resulting in cerebral hypoxic-ischemic injury and various symptoms. Additionally, hypoxia can induce abnormal mitochondrial structure in brain tissues, ultimately causing a rapid depletion of brain energy.⁶ Finally, ischemia can trigger an inflammatory response, producing numerous inflammatory factors in brain tissues. This, in turn, induces the expression of intercellular adhesion molecules, enhancing the adhesion between leukocytes and vascular endothelial cells, which plays a significant role in the development and progression of stroke.

This review aims to address these limitations and provide a more comprehensive understanding of the therapeutic potential of butylphthalide and edaravone in acute stroke treatment. The purpose of this study is to investigate the clinical efficacy and short-term prognosis of combining butylphthalide sodium chloride injection with edaravone in patients with acute stroke based on previous research findings.

MECHANISM OF BUTYLPHTHALIDE IN ACUTE STROKE

Protection of Mitochondria

Butylphthalide is considered to influence factors in the apoptosis signaling pathway of mitochondrial organelle cells, such as programmed cell death factor 5 (PDCD5), B lymphocytoma-2 gene (Bcl-2), and apoptosis-related factor (FAS). These interactions contribute to reducing neuronal cell death caused by brain ischemia, thereby playing a protective role in mitochondrial organelles and preventing further brain tissue damage.

Previous research has shown that butylphthalide can safeguard the mitochondrial function of endothelial cells under hypoxia-ischemia conditions, enhancing the clearance of intracellular reactive oxygen species and ultimately decreasing their production within mitochondria. This protective action effectively reduces mitochondrial damage. Additionally, butylphthalide directly impacts ischemic tissue mitochondria, increasing the activity of respiratory chain complex enzyme IV and elevating adenosine triphosphate and phosphocreatine levels. Consequently, it diminishes mitochondrial damage caused by depletion.

In animal experiments, mice were subcutaneously injected with butylphthalide, and after 20 minutes, the mice were decapitated to establish an ischemic model. This model demonstrated a reduction in increased lactate and adenosine triphosphate, as well as an increase in decreased phosphocreatine. These findings further confirm that

butylphthalide plays a protective effect on mitochondria and reduces brain tissue damage.

Reducing Inflammatory Responses

Inflammatory response plays a crucial role in the development and progression of acute stroke, and ischemia exacerbates this response, leading to increased damage to vascular endothelial cells. However, butylphthalide can effectively decrease the number of inflammatory cells and mitigate the inflammatory response, thereby protecting endothelial cells from damage caused by inflammatory factors. Additionally, it inhibits the adhesion of neutrophils to endothelial cells and hampers their accumulation at inflammatory sites, thus decreasing inflammation progression.

Animal experiments involving a rat model of intracerebral hemorrhage demonstrated that tumor necrosis factor- α (TNF- α) expression was significantly reduced in the perihematomal brain tissue after the injection of butylphthalide. It suggests that butylphthalide can effectively inhibit the expression of inflammatory factors. As the inflammatory response is intricately involved in the occurrence and progression of a stroke, butylphthalide proves beneficial in preventing further damage to brain tissue by reducing this inflammatory response.

Enhancing Microcirculation

In the healing of acute stroke, the early restoration of blood supply to the ischemic penumbra is critical for improved patient outcomes. Butylphthalide plays a significant role in this process by increasing the nitric oxide (NO) level in vascular endothelial cells, resulting in vasodilation. This action accelerates the reconstruction of microcirculation in the ischemic area, promoting the opening of blood vessels and restoring cerebral blood circulation at an early stage, thereby enhancing the microcirculation of brain tissue.⁷

Platelet activation plays a pivotal role in the onset and progression of stroke. Butylphthalide inhibits platelet aggregation and adhesion, consequently enhancing cerebral blood flow and facilitating the early recovery of neurological function. *Ex vivo* experiments have demonstrated that butylphthalide effectively inhibits human platelet aggregation and adenosine triphosphate release in a dose-dependent manner.⁸

Butylphthalide shows protective effects by reducing nuclear factor κ B/p65 expression. This factor enhances adhesion-promoting molecules, leading to microthrombi formation and luminal obstruction, exacerbating brain tissue damage. In animal experiments using a rat model of myocardial ischemia-reperfusion and administering butylphthalide injection, nuclear factor κ B/p65 expression decreased in the rat brain, further supporting the protective role of butylphthalide.⁹

In a domestic study¹⁰ utilizing a rat model of cerebral ischemia and injecting butylphthalide and its derivatives, researchers observed remarkable increases in the diameter and blood flow velocity of cerebral arterioles after injection. It indicates the effective enhancement of cerebral

microcirculation and confirms the potential use of butylphthalide and its derivatives in treating arterial thrombotic diseases.

Reducing Blood Brain Barrier Permeability

Rho family proteins, a group of intracellular signaling molecules, play a crucial role in regulating cytoskeletal dynamics and influencing endothelial cell permeability. It possesses GTPase activity, controlling cytoskeletal reorganization and influencing endothelial cell permeability. In stroke pathogenesis analysis, these proteins become activated in response to inflammatory factors, leading to blood-brain barrier disruption and exacerbation of neural tissue edema, contributing to the pathogenesis of the condition. However, animal experiments have revealed that butylphthalide injection can mitigate the activation of Rho family proteins induced by inflammatory factors. In a hypoglycemic and hypoxic environment, butylphthalide decreases myosin light chain phosphorylation. It helps to reduce blood-brain barrier permeability, ultimately lessening brain edema and injury.¹¹

Enhancing the Function of Nerve Cells

Nerve growth factor (NGF) plays a vital role in the growth and development of neurons, facilitating the repair of nervous system injuries. In rat experiments, after establishing a cerebral ischemia-reperfusion model, researchers observed increased expression of nerve growth factor and brain-derived neurotrophic factor in the peri-infarct tissue following butylphthalide injection. It is beneficial as it promotes the survival and growth of nerve cells, effectively enhancing their function.

Resting potential serves as the foundation for ensuring proper nerve cell functioning. In *in-vitro* cell experiments, butylphthalide intervention demonstrated its ability to inhibit the abnormal expression of TREK-1 channels in cells, thereby maintaining the normal resting membrane potential and ensuring the proper functioning of nerve cells.¹²

MECHANISM OF EDARAVONE IN ACUTE STROKE

Reducing Oxidative Stress

Peroxidative damage caused by reactive oxygen species is a significant factor in the pathogenesis of acute stroke. However, edaravone plays a crucial role in counteracting this damage. It has the ability to identify and reduce DPPH free radicals, thus decreasing oxidative stress. Additionally, edaravone inhibits the activity of xanthine and hypoxanthine oxidase, leading to increased prostacyclin production. It interferes with the metabolism of arachidonic acid and inhibits the capture of hydroxyl radicals, effectively quenching reactive oxygen species and reducing peroxidation damage to tissue cells.

Furthermore, when edaravone molecules enter the body, they transform into anions, converting reactive oxygen radicals into oxidation-inactive groups. This mechanism enables edaravone to effectively scavenge oxygen radicals, reducing the harmful effects of oxygen on brain tissue.¹³

Additionally, edaravone can inhibit the peroxidation of membrane lipids caused by free radicals, reducing the toxic effects of hydroxyl radicals on cells. In animal experiments, edaravone was found to effectively inhibit the process of peroxidation of linoleic acid, which leads to the generation of harmful oxygen radicals. This further confirms the ability of edaravone molecules to reduce peroxidation.¹⁴

Reviewing relevant data shows that edaravone can increase superoxide dismutase activity, significantly inhibiting the detrimental effects of oxygen-free radicals. This action ultimately reduces nerve cell damage and death following a stroke event.¹⁵ In animal experiments, edaravone was administered after reperfusion by creating a rat reperfusion model after ischemia. Notably, no neuronal loss was observed in the CA1 region of the hippocampus, which can be attributed to edaravone's ability to act on free radicals and peroxy groups, thereby inhibiting lipid peroxidation and reducing cell injury. It has been observed that edaravone, at a specific concentration, does not impact superoxide anion. However, it remarkably reduces the hydroxylation of salicylic acid, effectively scavenging free radicals. Studies on animal experiments in other countries have supported and confirmed this discovery.¹⁶

Inhibition of Inflammatory Responses

Edaravone has anti-inflammatory properties that help modulate the production of inflammatory factors after a stroke and reduce delayed neuronal death. Following acute stroke, inflammatory factors such as TNF- α , IL-1 β , IL-6, and IL-8 significantly increase. However, these levels remarkably decrease after edaravone treatment, indicating its ability to combat inflammation.¹⁷

Elevated IL-8 triggers liver stimulation, leading to the generation of high-sensitivity-C reactive protein (hs-CRP), complement activation, and the release of inflammatory mediators, resulting in inflammatory responses in blood vessels. In contrast, edaravone reduces hs-CRP levels, effectively inhibiting the inflammatory response.

MMP-9, which plays a role in the inflammatory response, shows high expression in ischemic brain tissue areas. In a foreign study,¹⁸ patients with ischemic stroke who received early edaravone treatment had lower MMP-9 levels compared to those who did not receive edaravone after 2 weeks. These findings confirm the effective anti-inflammatory response of edaravone.¹⁸⁻¹⁹

Regulation of Apoptosis

Neuronal apoptosis plays a significant role in causing neurological impairment, and the expression of apoptosis-related genes influences this process. Lab experiments have confirmed that activated microglia can produce NO, leading to the death of cortical neurons. However, edaravone can counteract this effect by inhibiting NO production, thereby protecting neurons and reducing apoptosis.

In a recent study,²⁰ edaravone was administered to rats after cerebral ischemia-reperfusion. After 24 hours, the researchers observed a decrease in the number of apoptotic

cells around the infarcted area. Additionally, the expression of genes related to inhibiting apoptosis increased, while the expression of genes associated with inducing apoptosis decreased. Moreover, there was a remarkable improvement in the score of neurological function. The Fas/FasL signaling pathway is a crucial mechanism that regulates apoptosis. Edaravone has the ability to inhibit the expression of genes in the Fas/FasL pathway, resulting in reduced neuronal apoptosis. It, in turn, helps in minimizing neuronal injury and apoptosis after a stroke, ultimately protecting neurological function.

APPLICATIONS OF BUTYLPHTHALIDE AND EDARAVONE IN ACUTE STROKE

Clinical Efficacy

Butylphthalide is a new anti-cerebral ischemia drug known for effectively reducing pathological damage caused by ischemia. On the other hand, edaravone acts as a free radical scavenger, reducing oxidative stress damage caused by free radicals. Multiple domestic and international studies have highlighted the high clinical efficacy of combining butylphthalide and sodium chloride injection with edaravone in treating acute stroke.

In one domestic study,²¹ 600 patients with acute cerebral infarction were selected, with the control group receiving conventional treatment plus edaravone and the observation group receiving the combination of butylphthalide and sodium chloride injection alongside edaravone. The observation group showed a significantly higher effective rate (91.67%) compared to the control group (78.67%). Another study²² involved 150 patients with acute cerebral infarction receiving different treatment methods (details in Table 1). The total effective rate in group C (94.00%) was higher than that in groups A (78.00%) and B (74.00%). It further supports the notion that combining different treatments in acute cerebral infarction leads to higher clinical efficacy compared to using any drug alone.

Short-Term Prognosis

Acute cerebral infarction leads to irreversible neurological impairment, impacting daily activities to

Table 1. Treatment methods for three groups of patients in Guo et al²²

Group	Healing Method
Group A	Aspirin Enteric-coated Tablets, oral, 100 mg/d Atorvastatin calcium tablets, oral at bedtime, 20 mg/time, once a day Butylphthalide and Sodium Chloride Injection, 100ml ivgtt bid
Group B	Aspirin Enteric-coated Tablets, oral, 100 mg/d Atorvastatin calcium tablets, oral, 20 mg/time, once a day Edaravone, 30 mg in 100 ml normal saline (0. 9%), intravenous drip, twice a day
Group C	Aspirin Enteric-coated Tablets, oral, 100 mg/d Atorvastatin calcium tablets, oral, 20 mg/time, once a day Edaravone, 30 mg in 100 ml normal saline (0. 9%), intravenous drip, twice a day Butylphthalide and Sodium Chloride Injection, 100ml ivgtt bid

Table 2. Treatment Plan for Each Group of Patients in Huan et al²³

Group	Treatment Duration	Conventional Therapy	Special Treatment
Control Group	14 days	Control blood sugar, blood pressure, blood lipids and other basic treatments, and carry out Symptomatic treatment such as improving cerebral circulation and nourishing Cranial nerves.	Oral aspirin enteric coated tablets, 0.1g each time, once daily.
Observers	14 days	Control blood sugar, blood pressure, blood lipids and other basic treatments, and carry out Symptomatic treatment such as improving cerebral circulation and nourishing Cranial nerves.	Based on the control group, 0.2 g of butylphthalide soft capsules were administered orally three times a day; Edaravone 30mg plus 100 mL of normal saline was given intravenously twice daily.

Table 3. Comparison of NIHSS scores and SF-36 scores of patients in each group before and after the experiment in Zhang et al²⁴

Experimental Time	Index	Control Group	Observers	<i>t</i>	<i>P</i> value
Before The Experiment	NIHSS Total Score	19.2 ± 2.6	20.4 ± 3.5	1.524	1.022
	SF-36 Total Score	426 ± 58	439 ± 62	1.733	1.257
After The Experiment	NIHSS Total Score	14.1 ± 2.4	17.1 ± 2.2	2.671	.008
	SF-36 Total Score	602 ± 53	527 ± 54	3.964	.002

Note: The data demonstrates the mean values ± standard deviations for each group. The “*t*” values represent the calculated *t* test statistics, and the “*P*” values indicate the level of significance.

varying degrees. The extent of nerve tissue injury can be assessed using the neurological deficit (NIHSS) score, which is negatively correlated with daily living activities and measures short-term prognosis for patients after stroke treatment. In a domestic study, 100 patients with acute cerebral infarction were selected and divided into a control and observation groups using a random number table method. The treatment methods received by the two groups of patients are outlined in Table 2.

After completing the experiment, the researchers conducted a statistical analysis of the NIHSS score and SF-36 score for both groups of patients. Before the experiment, the *t* test *P* values for the NIHSS score and quality of life score were greater than the significance level of .05, indicating no significant difference in the data. However, after the experiment, the NIHSS score of the observation group was lower than that of the control group, and the quality of life score was higher in the observation group. The *P* values of the *t* test were all less than .05, indicating a significant difference in the data. These findings suggest that combination therapy can effectively reduce neurological damage and improve the quality of life for patients.²³

Hemodynamic Enhancement and Prognostic Evaluation

Abnormal hemodynamic changes play a crucial role in the development and progression of acute stroke. Therefore, assessing the hemodynamics of patients after treatment can be used as an indicator to evaluate their prognosis. In a study²⁴ involving 285 patients with acute cerebral infarction, the participants were divided into two groups: the control group (treated with conventional therapy + edaravone) and the observation group (treated with conventional therapy + edaravone + butylphthalide). Before treatment, there were no significant differences in hemodynamics between the two

groups. However, after treatment, the study group showed improvements in whole blood viscosity, whole plasma viscosity ratio, and platelet aggregation rate compared to the control group, indicating that combined therapy was more effective in enhancing hemodynamics.²⁴ The study suggests that improving hemodynamics can lead to early restoration of blood perfusion in the ischemic area and penumbra, reduce the risk of thrombosis, and effectively lessen hypoxic-ischemic brain tissue injury, ultimately improving the prognosis of patients.

CONCLUSION

In conclusion, our study highlights the significant therapeutic potential of both butylphthalide and edaravone in the treatment of acute stroke. Butylphthalide demonstrates its efficacy through multiple mechanisms, including protecting mitochondria, reducing the inflammatory response, enhancing microcirculation, and reducing blood-brain barrier permeability. On the other hand, edaravone effectively reduces oxidative stress, inhibits inflammatory response, and regulates apoptosis and arachidonic acid metabolism.

Moreover, when combined, butylphthalide and edaravone synergistically enhance the overall treatment outcomes, offering a more promising approach to healing acute stroke patients. The combined therapy leads to improved nerve cell function, reduced neuronal injury, and enhanced hemodynamics, which collectively contribute to a more favorable prognosis for patients. Our findings underscore the importance of combining these two drugs for the effective management and treatment of acute stroke. The results provide valuable insights into potential therapeutic strategies that can lead to enhanced patient outcomes and pave the way for further advancements in acute stroke research and healing.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

DY, MZ, and JZ conceived the study design. DY and MZ performed the literature searches. DY, MZ, and XW screened the literature and extracted the data. MZ and XW summarized the data and performed the statistical analysis. DY, MZ, and JZ interpreted the data and drafted the manuscript. JZ helped revise the manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved its submission.

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