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Original Article

Efficacy of butylphthalein injection combined with alteplase thrombolysis in patients with acute cerebral infarction and its impact on Lp-PLA2 and CXCL16 levels

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Abstract: Objective: To evaluate the efficacy of butylphthalein injection combined with alteplase thrombolysis in patients with acute cerebral infarction (ACI) and its effects on lipoprotein-associated phospholipase A2 (Lp-PLA2) and CXC chemokine ligand 16 (CXCL16) levels. Methods: A total of 127 ACI patients admitted to Shandong Provincial Third Hospital between March 2020 and June 2023 were included and divided into a butylphthalein group (n = 67) and a control group (n = 60) based on their treatment regimen. All patients received basic treatment. Additionally, the control group underwent intravenous thrombolysis with alteplase, while the butylphthalein group received butylphthalein injection combined with alteplase thrombolysis. Both groups were treated for two consecutive weeks. Results: The overall clinical efficacy rate in the butylphthalein group was significantly higher than that in the control group ($P < 0.05$). After treatment, cerebral infarction size and National Institutes of Health Stroke Scale (NIHSS) scores were significantly reduced in both groups (both $P < 0.05$), with greater reductions observed in the butylphthalein group (both $P < 0.05$). The peak systolic velocity (Vs) of the posterior cerebral, vertebral, and basilar arteries increased significantly in both groups after treatment compared with baseline (all $P < 0.05$), with higher values in the butylphthalein group (all $P < 0.05$). The resistance index (RI) of these arteries decreased significantly in both groups after treatment ($P < 0.05$) and was lower in the butylphthalein group than in the control group ($P < 0.05$). Serum levels of IL-6, TNF-α, CRP, Lp-PLA2, and CXCL16 were significantly lower after treatment in both groups (all $P < 0.05$), with greater reductions in the butylphthalein group (all $P < 0.05$). There was no significant difference in adverse effects between the two groups ($P > 0.05$). Conclusion: The combination of butylphthalein injection and alteplase intravenous thrombolysis is effective in improving clinical outcomes, reducing neurological deficits, enhancing microcirculation, and lowering serum Lp-PLA2 and CXCL16 levels in patients with ACI. This therapy is worth clinical promotion.

Keywords: Butalbital injection, alteplase, acute cerebral infarction, Lp-PLA2, CXCL16

Introduction

Acute cerebral infarction (ACI) occurs due to the narrowing or occlusion of arterial lumens, leading to thrombus formation and subsequent obstruction of cerebral blood flow [1]. Current clinical treatments for ACI focus on relieving the obstruction through intravenous thrombolysis or mechanical thrombus removal to restore cerebral blood flow. However, patients often experience complications such as plaque rupture, microthrombosis, inflammation, and postoperative restenosis, making follow-up medication-assisted therapy essential [2, 3].

Alteplase, a novel thrombolytic agent, offers distinct advantages in drug specificity, thrombolytic efficacy, and a favorable half-life. Clinical reports indicate that intravenous thrombolysis with alteplase effectively repairs the ischemic penumbra in brain tissue, restoring cerebral blood supply and mitigating neurological damage [4-6]. In addition, butylphthalide, a neuroprotective agent developed in China for ACI, has demonstrated efficacy in improving functional status, enhancing collateral circulation and blood flow, reducing the accumulation of local metabolic byproducts, regulating oxidative enzyme activity, and protecting brain mitochon-

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dria. These effects collectively contribute to neuronal protection [7-9].

Despite the efficacy of alteplase in thrombolysis, the lack of effective neuroprotective drugs remains a challenge in ACI treatment. To further enhance clinical outcomes and improve patient prognosis, this study conducted a retrospective analysis to evaluate the clinical efficacy of butylphthalide injection combined with alteplase thrombolysis. The findings aim to provide evidence-based support for optimizing the clinical management of ACI.

Information and methods

Clinical data

This retrospective study included 127 patients with ACI admitted to Shandong Provincial Third Hospital between March 2020 and June 2023. Patients were divided into the butylphthalide group (n = 67) and the control group (n = 60) based on their treatment regimens. The study was approved by the Ethics Committee of Shandong Provincial Third Hospital.

Inclusion and exclusion criteria

Inclusion criteria: Patients met the diagnostic criteria for ACI outlined in the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke [10] and were diagnosed using clinical evaluations and imaging studies. Time from disease onset to hospital admission was ≤ 6 hours. First occurrence of ACI. Age between 18 and 80 years.

Exclusion criteria: Comorbidities such as malignant tumors, hematologic disorders, or infectious diseases. Combined hepatic, renal, or cardiac dysfunction. Allergy to study drugs. Presence of arteriovenous malformations or intracranial tumors. Coagulation disorders. Recent major trauma or surgery. History of mental illness.

Methods

Control Group: Patients received basic treatments including oxygen therapy, maintenance of water and electrolyte balance, and anti-platelet aggregation therapy. Additionally, patients underwent intravenous thrombolysis with alteplase (Boehringer Ingelheim Pharma GmbH & Co. KG, SJ20160054) at a dose of 0.9 mg/kg. The initial 10% of the dose was administered as a bolus within 10 minutes, followed by infusion of the remaining dose over 60 minutes.

Butylphthalide Group: In addition to the above treatments, patients were administered butylphthalide injection (Stone Pharmaceutical Group Enbipu Pharmaceutical Co., Ltd., H2010-0041) 6 hours after alteplase thrombolysis. Butylphthalide was given intravenously at 100 ml/day in two divided doses. All treatments were continued for two weeks.

Observation indicators

Cerebral Infarction Area: Patients underwent MRI using the Philips Achieva TX 1.5 T system before and after treatment. Infarct areas were calculated using relevant software.

Neurological Function [11]: Neurological deficits were assessed using the National Institutes of Health Stroke Scale (NIHSS). This scale evaluates 11 parameters, including consciousness, motor function, and speech, with scores ranging from 0 to 42. Higher scores indicate more severe impairment.

Activities of Daily Living (ADL) [12]: Patients' daily living abilities were measured using the ADL scale, which includes 11 items such as eating, bathing, and mobility. Scores range from 0 to 100, with higher scores indicating better functional status.

Posterior Circulation Hemodynamics: Color Doppler ultrasound was used to measure systolic peak velocity (Vs) and resistance index (RI) in the posterior cerebral, vertebral, and basilar arteries.

Serum Inflammatory Markers: Peripheral venous blood samples (5 ml) were collected before and after treatment. Serum levels of IL-6, TNF-α, and CRP were measured using enzyme-linked immunosorbent assay (ELISA). Kits were purchased from Wuhan Jilide Biotechnology Co., Ltd. (J20252, J20223, J21212).

Serum Lp-PLA2 and CXCL16 Levels: Peripheral venous blood (5 ml) was collected and centrifuged to measure Lp-PLA2 and CXCL16 levels

Table 1. Comparison of the general data

Clinical information	Butylphthalide group (n = 67)	Control group (n = 60)	t/x^2	*P*
Gender				
Male	41	36	0.019	0.891
Female	26	24		
Age (years, x ± s)	60.35±10.97	61.05±9.83	0.377	0.707
Site of infarction				
Basal ganglia	29	26	0.521	0.771
Frontal parietal lobe	18	19		
Other sites	20	15		

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

Group	Number of cases	Basically cured	Remarkable effect	Effective	Invalid	Overall effectiveness rate (%)
Butylphthalide group	67	29 (43.28)	18 (26.87)	15 (22.39)	5 (7.46)	92.53
Control group	60	16 (26.67)	14 (23.33)	18 (30.00)	12 (20.00)	80.00
Z/X^2	-	7.046				4.291
P	-	0.070				0.038

using ELISA. Kits were procured from Wuhan Jilide Biotechnology Co., Ltd. (J21096, J20184).

Adverse Reactions: Drug-related adverse reactions during treatment were observed and recorded in both groups.

Clinical efficacy

Clinical efficacy was assessed based on established standards [11]: Basically healed: Symptoms and signs largely disappeared, with no disability and full independence in daily activities. The NIHSS score decreased by 91% to 100% compared to pre-treatment. Remarkable effect: Symptoms and signs significantly improved, but the patient still required assistance. NIHSS scores decreased by 46% to 90% compared to pre-treatment. Effective: Symptoms improved, but the patient remained dependent on others. NIHSS scores decreased by 18% to 45% compared to pre-treatment. Invalid: No change or deterioration in symptoms and signs, with complete dependence on others. NIHSS score decreased by < 18% or even increased. The overall effective rate of treatment = basic cure rate + remarkable effect rate + effective rate.

Statistical analysis

Data analysis was analyzed using SPSS 27.0. Measurement data were compared using a t-test, qualitative data with the chi-square test, and rank data with the rank sum test. A *P*-value < 0.05 was considered statistically significant.

Results

Comparison of general information

The butylphthalide group included 41 males and 26 females (mean age: 60.35±10.97 years), with infarct locations as follows: basal ganglia (29 cases), frontal parietal lobe (18 cases), and others (20 cases). The control group consisted of 36 males and 24 females (mean age: 61.05±9.83 years), with infarct sites as: basal ganglia (26 cases), frontal parietal lobe (19 cases), and others (15 cases). There were no statistically significant differences in general information between the two groups (all P > 0.05) (**Table 1**).

Comparison of clinical efficacy

The clinical efficacy in the butylphthalide group was significantly better than in the control group (P < 0.05) (**Table 2**).

Comparison of cerebral infarct size before and after treatment

Before treatment, there was no significant difference in the area of cerebral infarction between the two groups (P > 0.05). After treat-

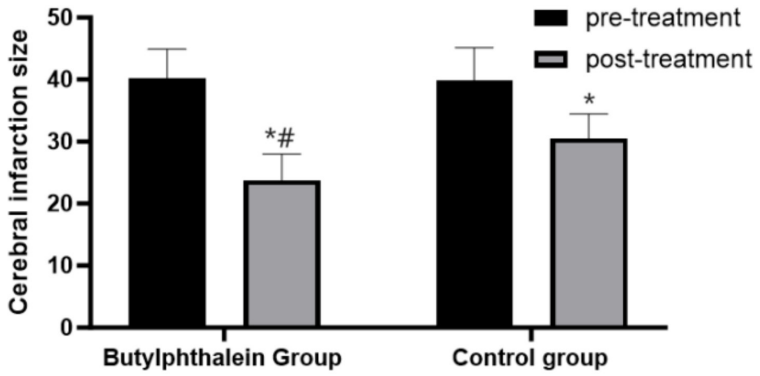

Figure 1. Comparison of cerebral infarct area before and after treatment in both groups (cm^2). Note: Compared with the group before treatment, *P < 0.05; Compared with the control group, #P < 0.05.

ment, the cerebral infarct area decreased significantly in both groups (P < 0.05), with the butylphthalide group showing a significantly smaller infarct area compared to the control group (P < 0.05) (**Figure 1**). MRI images of typical cases before and after treatment are shown in **Figure 2**.

Comparison of NIHSS scores

There was no significant difference in pre-treatment NIHSS scores between the two groups (P > 0.05). Post-treatment NIHSS scores were significantly lower than pre-treatment scores in both groups (P < 0.05), with the butylphthalide group showing significantly lower post-treatment NIHSS scores compared to the control group (P < 0.05) (**Figure 3**).

Comparison of ADL scores

No significant difference in ADL scores was observed between the two groups before treatment (P > 0.05). Post-treatment ADL scores decreased in both groups compared to pre-treatment (P < 0.05), with the butylphthalide group showing significantly lower ADL scores compared to the control group after treatment (P < 0.05) (**Figure 4**).

Comparison of posterior circulatory hemodynamics

Before treatment, there were no significant differences in Vs and RI of the posterior cerebral artery, vertebral artery, and basilar artery between the two groups (all P > 0.05). After treatment, Vs in both the posterior cerebral artery, vertebral artery, and basilar artery increased significantly compared to pre-treatment (all P < 0.05), with the butylphthalide group showing higher Vs compared to the control group (all P < 0.05). Additionally, the RI of these arteries decreased significantly post-treatment (all P < 0.05), and the butylphthalide group had lower RI values than the control group (all P < 0.05) (**Table 3**).

Comparison of serum inflammatory factors

There was no statistically significant difference in serum IL-6, TNF-α, and CRP levels between the two groups before treatment (all P > 0.05). After treatment, IL-6, TNF-α, and CRP levels decreased significantly in both groups compared to pre-treatment (all P < 0.05). Moreover, IL-6, TNF-α, and CRP levels in the butylphthalide group were significantly lower than those in the control group (all P < 0.05) (**Table 4**).

Comparison of serum Lp-PLA2 and CXCL16 levels before and after treatment

There was no statistically significant difference in Lp-PLA2 and CXCL16 levels between the two groups before treatment (all P > 0.05). Post-treatment, both Lp-PLA2 and CXCL16 levels were lower in both groups compared to pre-treatment (all P < 0.05). Additionally, the Lp-PLA2 and CXCL16 levels in the butylphthalide group were significantly lower than those in the control group after treatment (all P < 0.05) (**Table 5**).

Comparison of adverse reactions

In the butylphthalide group, 2 cases of gingival bleeding and 4 cases of nasal bleeding occurred during the treatment period, yielding an adverse event rate of 8.96% (6/67). In the control group, 1 case had mucosal bleeding, 2 had gingival bleeding, and 2 had epistaxis, with an adverse event rate of 8.33% (5/60). There was

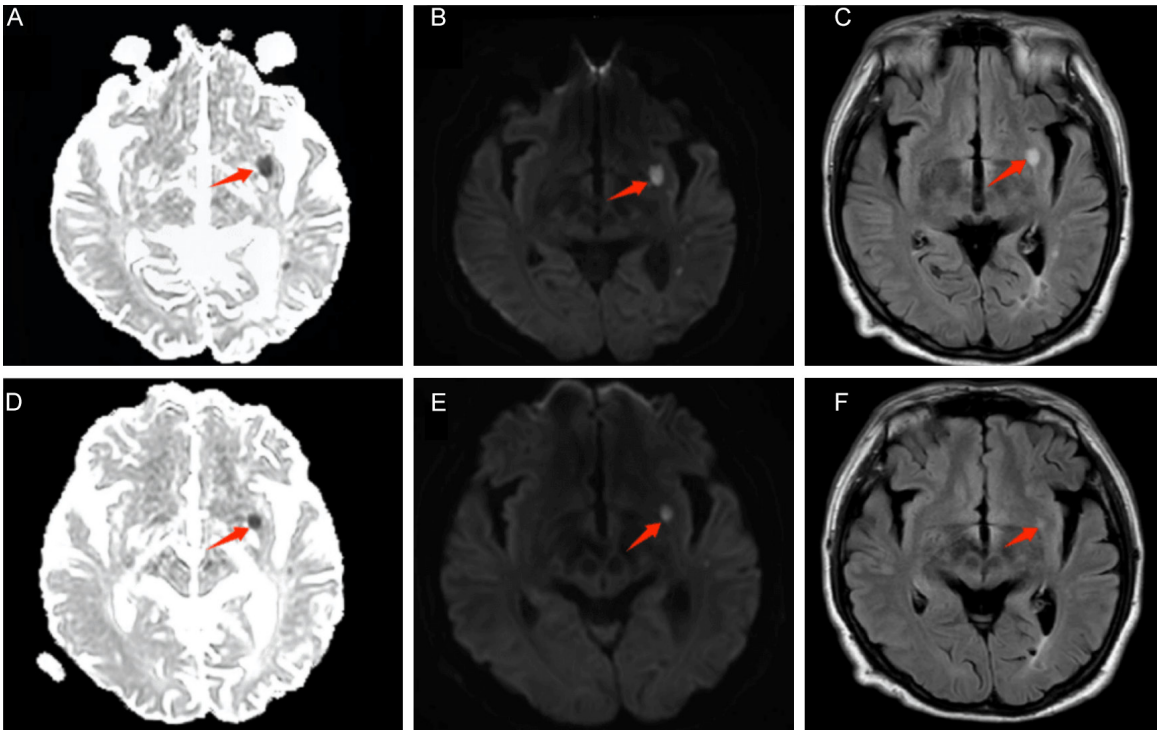

Figure 2. MRI images before and after treatment in a typical case. Male, 68 years old. A-C: ADC map, DWI sequence, and FLAIR sequence before treatment, with an infarct diameter of approximately 8 mm. D-F: ADC map, DWI sequence, and FLAIR sequence after treatment with tingbaiti and alteplase intravenous thrombolysis, with an infarct diameter reduced to 6 mm. ADC, Apparent Diffusion Coefficient; DWI, Diffusion Weighted Imaging; FLAIR, Fluid Attenuated Inversion Recovery.

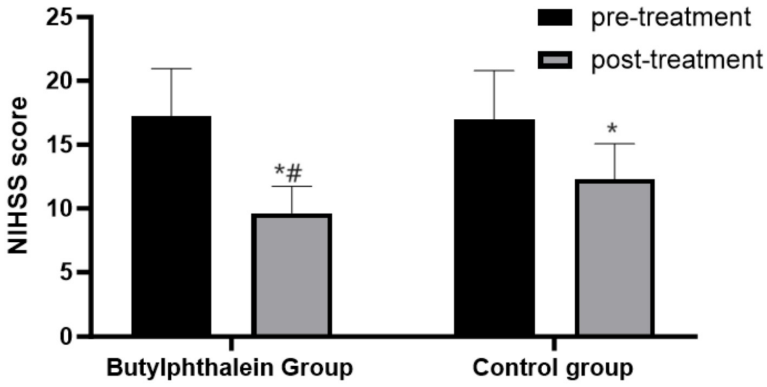

Figure 3. Comparison of NIHSS scores before and after treatment between the two groups (points). Note: Compared with the same group before treatment, *P < 0.05; Compared with the same control group, #P < 0.05. NIHSS, National Institute of Health stroke scale.

no statistically significant difference in adverse reactions between the two groups (P > 0.05).

Discussion

In recent years, with changes in lifestyle and increased life pressure, the incidence of cerebral infarction in China has been rising. The recurrence rate, mortality rate, and disability rate among ACI patients remain high, and patients often become disabled after the onset of the disease, severely affecting their quality of life and health [13].

Cerebral ischemic injury can lead to a series of pathophysiological changes. During ischemia, a large number of oxygen free radicals are generated, damaging cell membranes and organelles, which ultimately leads to the death of neurofunctional cells [14, 15]. The lesion in ACI typically consists of an ischemic core surrounded by a penumbra. The ischemic core, where blood supply is completely blocked, is necrotic and often results in severe neurological deficits in patients [16, 17]. Blood vessels in the ischemic penumbra may still be functional,

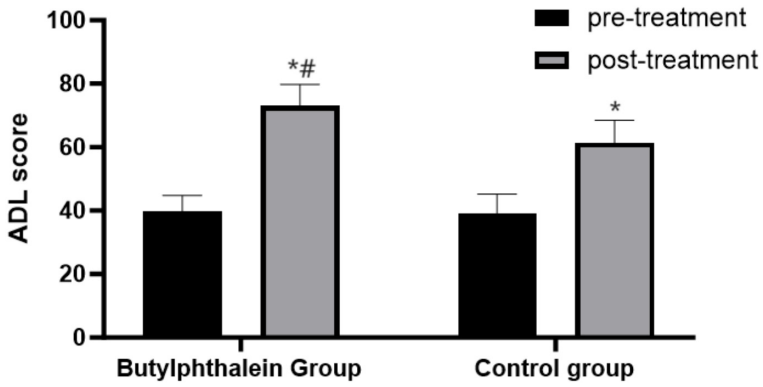

Figure 4. Comparison of ADL scores before and after treatment (points). Note: Compared with the same group before treatment, $^{*}P < 0.05$; Compared with the same control group, $^{\#}P < 0.05$. ADL, Activities of Daily Living Scale.

allowing for the potential recovery of blood flow. If therapeutic measures are applied in time, circulation in the ischemic penumbra can be restored, aiding the recovery of damaged brain tissue and improving the clinical prognosis [18, 19]. However, if untreated, the penumbra gradually shrinks, leading to further neuronal death and irreversible loss of neurological function. In contrast, timely and effective treatment can help restore blood flow, reduce free radical release, and promote the recovery of neural function in the ischemic penumbra region [20, 21].

Intravenous thrombolysis is the most direct and effective treatment for ACI. The thrombolytic drug commonly used for ACI is alteplase, which effectively restores blood flow by unblocking occluded blood vessels, rapidly supplying oxygen to brain tissues, salvaging ischemic tissue, and reducing the ischemic penumbra, thus improving patient prognosis [22, 23]. However, intravenous thrombolysis is limited by the "time window" after symptom onset and can lead to vascular occlusion and neuronal damage following treatment. Therefore, it is recommended to combine neuroprotective agents with thrombolysis [23, 24]. Butylphthalide, a neuroprotective agent used in ACI treatment, dilates blood vessels, improves cerebral microcirculation, enhances energy metabolism in the brain, and protects neurons by reducing the accumulation of local metabolites, regulating oxidase activity, and protecting brain mitochondria [25, 26].

This study investigated the efficacy of combining butylphthalide injection with alteplase thrombolysis in treating ACI, aiming to further explore its impact on improving clinical outcomes. The results showed that the therapeutic efficacy in the butylphthalide group was superior to that in the control group. Specifically, the reduction in infarct size, improvement in NIHSS scores, and increase in ADL scores were significantly better in the butylphthalide group compared to the control group. Furthermore, the posterior cerebral artery, vertebral artery, and basilar artery velocities after treatment in the butylphthalide group were higher, while the RI was lower compared to the control group. These findings align with previous studies [27, 28], suggesting that the combination of thrombolytic treatment with alteplase effectively reduces the infarct area in ACI, improves neurological function, and enhances daily living activities. Additionally, the use of butylphthalide promotes cerebral blood circulation, further improving treatment efficacy.

Lp-PLA2 is a pro-inflammatory enzyme that hydrolyzes LDL by breaking down oxidized lecithin and plays a role in regulating blood lipids. Lp-PLA2 also stimulates endothelial cells to release adhesion factors that promote plaque formation and rupture. It has been found that Lp-PLA2 is significantly positively correlated with the degree of neurological deficits in ACI patients and can serve as an indicator of disease severity [29-31]. CXCL16, a newly discovered chemokine, plays a key role in the inflammatory response and atherosclerosis through its chemotactic and adhesive properties [32]. Studies have shown that microcirculatory disturbances in ACI lead to immune cell activation, triggering an inflammatory response and the release of mediators. Endothelial cell damage exacerbates this inflammation, impairing neuronal function [33]. These inflammatory mediators can also upregulate CXCL16 expression, accelerating disease progression [34]. The results of this study demonstrated that Lp-PLA2 and CXCL16 levels were significantly reduced in both groups post-treatment, with the butylphthalide group showing a more pronounced decrease compared to the control group. This

Table 3. Comparison of posterior circulation hemodynamic indexes before and after treatment between the two groups ($\bar{x}$±s)

Index		Butylphthalide Group (n = 67)				Control Group (n = 60)			
		Pre-treatment	Post-treatment	t	P	Pre-treatment	Post-treatment	t	P
Vs	Posterior cerebral artery	44.21±3.06	57.64±3.97*	21.931	< 0.001	44.64±3.64	51.20±4.17	9.180	< 0.001
	Vertebral artery	39.86±3.86	48.65±4.03*	12.893	< 0.001	39.47±3.12	44.51±3.67	8.105	< 0.001
	Basilar artery	28.13±3.24	39.64±3.77*	18.953	< 0.001	28.33±3.20	35.21±3.47	11.290	< 0.001
RI	Posterior cerebral artery	0.73±0.11	0.55±0.09*	10.367	< 0.001	0.76±0.14	0.64±0.08	5.765	< 0.001
	Vertebral artery	0.68±0.08	0.54±0.07*	10.780	< 0.001	0.71±0.09	0.61±0.10	5.758	< 0.001
	Basilar artery	0.71±0.09	0.52±0.08*	12.915	< 0.001	0.72±0.10	0.62±0.07	6.356	< 0.001

Note: *P < 0.05 vs. control group for the same period. RI, Blood Flow Resistance Index.

Table 4. Comparison of serum inflammatory factor levels before and after treatment in the two groups ($\bar{x}$±s)

Group	Stage	IL-6 (pg/ml)	TNF-α (pg/ml)	CRP (mg/L)
Butylphthalide Group (n = 67)	Pre-treatment	83.24±9.72	60.14±7.35	24.52±3.71
	Post-treatment	42.67±8.64*	21.04±5.97*	10.24±2.96*
	t	25.535	33.799	24.628
	P	< 0.001	< 0.001	< 0.001
Control Group (n = 60)	Pre-treatment	85.61±12.15	59.87±7.98	24.10±2.96
	Post-treatment	50.33±7.93	34.50±6.71	15.67±3.04
	t	18.835	18.848	15.390
	P	< 0.001	< 0.001	< 0.001

Note: *P < 0.05* compared to contemporaneous controls. TNF-α, tumor necrosis factor-α; CRP, C-reactive protein.

Table 5. Comparison of serum Lp-PLA2 and CXCL16 levels before and after treatment in the two groups (ng/ml, $\bar{x}$±s)

Group	Stage	Lp-PLA2	CXCL16
Butylphthalide Group (n = 67)	Pre-treatment	261.52±31.05	3.86±1.03
	Post-treatment	180.67±23.84*	2.21±0.65*
	t	16.905	11.089
	P	< 0.001	< 0.001
Control Group (n = 60)	Pre-treatment	257.16±30.64	3.98±1.12
	Post-treatment	207.54±25.76	2.85±0.87
	t	9.602	6.172
	P	< 0.001	< 0.001

Note: *P < 0.05 compared to contemporaneous controls. Lp-PLA2, lipoprotein-associated phospholipase A2; CXCL16, CXC chemokine ligand 16.

suggests that combining butylphthalide with alteplase intravenous thrombolysis effectively reduces Lp-PLA2 and CXCL16 levels in ACI, attenuating the inflammatory response, protecting endothelial and neuronal cells, and slowing the formation of atherosclerotic plaques, thereby improving clinical outcomes. However, due to the small sample size, the study results may be biased, and further studies can expand the sample size to obtain more accurate research results. In conclusion, the combination of butylphthalide and alteplase intravenous thrombolysis effectively improves clinical outcomes in ACI by enhancing neurological function, alleviating blood microcirculation disorders, and reducing serum Lp-PLA2 and CXCL16 levels. This treatment is worthy of further clinical promotion.

Disclosure of conflict of interest

None.

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