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Evaluation of butylphthalide combination with sertraline on depression in ischemic stroke

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ABSTRACT

Objective: *This study aimed to explore the efficacy of butylphthalide combined with sertraline in the treatment of post-stroke depression after ischemic stroke.*

Methods: *A retrospective analysis was conducted on the clinical data of 90 patients with post-stroke depression admitted to a tertiary hospital in a certain city in China from March 2021 to March 2023. The patients were divided into an observation group and a control group, each consisting of 45 cases, based on different medication methods. The control group received sertraline treatment only, while the observation group was treated with butylphthalide combined with sertraline. Both groups completed an 8-week treatment course. The data after treatment were compared to systematically evaluate and compare the differences between the two groups in terms of clinical efficacy, levels of inflammatory factors, improvement in mood, and the incidence of adverse reactions.*

Results: *The observation group performed significantly better than the control group in terms of inflammatory indicators, treatment effects, and mood states, with a lower incidence of adverse reactions and a higher overall effective rate. The differences between the groups were statistically significant ($P < 0.05$). During the treatment period, the incidence of adverse reactions in the observation group was 6.67%, and the overall effective rate was 84.44%; while in the control group, the incidence of adverse reactions was 11.1%, and the overall effective rate was 68.88%. The observation group not only had a lower risk of adverse reactions but also showed more significant therapeutic effects, indicating a significant difference in the efficacy of drug intervention between the two groups, which was statistically significant ($P < 0.05$).*

Conclusion: *The combination of butylphthalide and sertraline is effective in treating post-stroke depression after ischemic stroke, improving multiple indicators of patients, enhancing their quality of life, and has high safety, presenting a promising clinical application prospect.*

Keywords: Butylphthalide; Sertraline; Ischemic stroke; post-stroke depression; Efficacy evaluation

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Introduction

Ischemic stroke, a prevalent neurological disorder, is associated with multiple risk factors including chronic lifestyle habits such as sleep deprivation, smoking, alcohol abuse, and physical inactivity, along with stress, anxiety, and obesity (Dan & Pei et al., 2025). This condition affects various bodily systems and often leads to complications during recovery, with hemiplegia, neurological deficits, and depression being particularly common (Zhou & Lansberg et al., 2023).

The prevalence of post-stroke depression (PSD) is approximately 31%, with the highest incidence occurring within 3 to 6 months after stroke onset (Hu and Ma et al., 2020). PSD not only affects patients' psychological well-being but also significantly hinders neurological recovery, compromises rehabilitation outcomes, exacerbates neurological damage, substantially reduces quality of life, and ultimately impacts long-term prognosis.

For the clinical treatment of post-ischemic stroke depression (PSD), a comprehensive intervention model combining standard neurology therapies with sertraline is commonly adopted (Dong Chuanzhan & Wang Lichun, 2021). While sertraline plays a pivotal role in depression management by effectively alleviating depressive and anxiety symptoms, its monotherapy approach presents significant individual variability in efficacy and potential side effects including nausea and insomnia (Zheng Shugong, 2021).

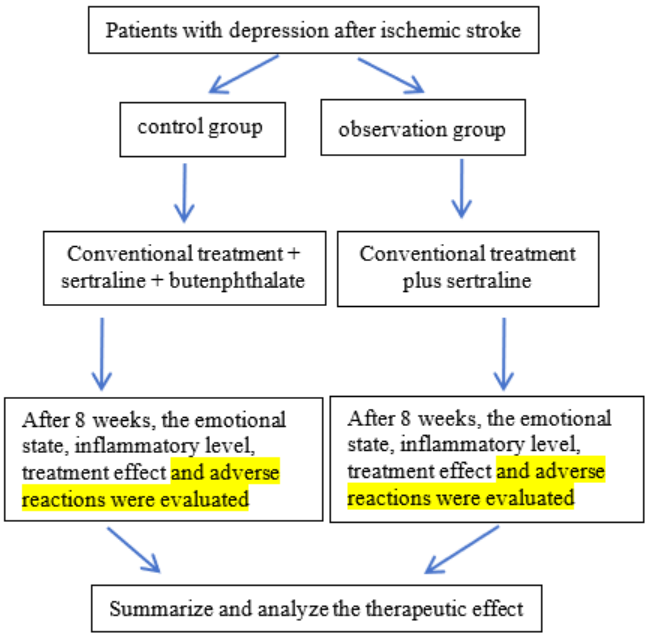
Benzylphthalide, a novel cerebral function protector, demonstrates multiple therapeutic effects including improving cerebral microcirculation, antioxidant properties, suppressing inflammatory responses, inhibiting platelet aggregation, and preventing thrombosis (Liu Juan et al., 2024). Research indicates its dual benefits of reconstructing microcirculation and enhancing mitochondrial function, while also suppressing neuronal apoptosis and exhibiting antidepressant properties (Wang Ting, 2020). This study investigates the efficacy and safety of benzylphthalide combined with sertraline in treating post-stroke depression (PSD), aiming to provide therapeutic guidance for patients with post-stroke depression.

1. Data and methods

1.1 General information and grouping

This prospective study enrolled 90 ischemic stroke patients with post-stroke depression treated at a tertiary hospital between March 2021 and March 2023. Using a randomized block design, the participants were divided into two groups of 45 cases each. Analysis of baseline characteristics including gender, age, body mass index (BMI), blood pressure, risk factors, and infarct location showed no statistically significant differences between groups ($P>0.05$), confirming their comparability. The study was approved by the hospital's ethics committee. All patients participated voluntarily and provided informed consent.

1.2 Research design



1.3 Inclusion and exclusion criteria

Inclusion criteria: (1) Meet the standards established in the "Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018": acute onset with localized or generalized neurological deficits, confirmed ischemic lesions on cranial CT or MRI, exclusion of non-vascular causes and hemorrhagic stroke; (2) Adhere to the post-stroke depression criteria outlined in the "Chinese Expert Consensus on Clinical Practice for Post-Stroke Depression"; Exclusion criteria: (1) Women in lactation or pregnancy; (2) Patients with severe cardiac, hepatic, renal dysfunction or organ failure; (3) Individuals with malignancies or autoimmune diseases; (4) Subjects with communication impairments or altered consciousness; (5) Those with documented psychiatric disorders (e.g., depression, schizophrenia); (6) Participants with concurrent cardiovascular or cerebrovascular diseases; (7) Those allergic to components of donepezil or sertraline.

1.4 Treatment methods

Control group: Conventional treatment + oral sertraline 50 mg daily, three times daily, for 8 weeks.

Observation group: Conventional treatment + oral sertraline 50 mg/day + butylphthalide soft capsules 200 mg/day for 8 weeks.

1.5 Observation indicators

1.5.1 Mood State Assessment: This study employed the Hamilton Depression Rating Scale (HAMD) to evaluate participants' emotional states. Widely adopted in clinical depression diagnosis and treatment evaluation (Cheng Xingyong, 2024), HAMD systematically quantifies depressive symptom severity in adults through multiple items, with a scoring range of 0 to 64 points. The scale categorizes scores as follows: 0-7 indicates no significant depressive features; 8-17 reflects mild depressive tendencies; 18-24 signifies moderate to severe depression; and scores above 24 indicate extremely severe depression. Higher scores correspond to more pronounced depressive symptoms.

1.5.2 Inflammatory Markers: Fasting venous blood

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samples were collected from subjects at both the start and end of treatment to measure inflammatory markers. After centrifugation to obtain serum, interleukin-8 (IL-8) levels were detected using the enzyme-linked immunosorbent assay (ELISA), and C-reactive protein (CRP) concentrations were measured. This systematic evaluation assessed the degree of inflammatory activity and its dynamic changes in the body.

1.5.3 Efficacy Evaluation: Compare the reduction rate and overall effectiveness rate of the Hamilton Depression Rating Scale (HDRS) before and after intervention. The reduction rate is calculated as [(Initial Score-Post-intervention Score)/Initial Score] × 100%. The overall effectiveness rate is determined by: (Number of fully recovered cases + Number of significantly improved cases + Number of partially improved cases) / Total sample size × 100%. Criteria for recovery: ≥75% reduction rate; Significant improvement: 50% ≤ reduction rate <75%; Partial improvement: 25% ≤ reduction rate <50%; No improvement: <25% reduction rate.

1.5.4 Adverse reactions: During the intervention, we should pay close attention to whether patients have adverse symptoms such as nausea, vomiting and anorexia, including the frequency and duration of these symptoms, and make detailed records for subsequent analysis.

1.6 Statistical methods

Statistical analysis was performed using SPSS 25 software. Quantitative data Xwere presented as mean ± standard deviation (±s). Independent samples t-tests were used for group comparisons, while paired t-tests were employed for intra-group comparisons. Categorical data were expressed as frequency or percentage (%) with X^2 tests for intergroup analysis. Significant differences were defined as P <0.05.

2. Experimental results

2.1 Comparison of emotional state before and after treatment in two groups

Before treatment, there was no significant difference in the Hamilton Depression Scale (HAMD) scores between the two groups (P>0.05). After 8 weeks of intervention, the HAMD scores of the observation group decreased significantly, and the HAMD scores of the control group decreased significantly, with a significant difference between the two groups (P<0.05), as shown in Table 1.

Table 1: Comparison of emotional status before and after treatment in two groups

group	n	HADM grade			
		pretherapy	post-treatment	t	*P*
control group	45	19.70±2.07	9.06±1.33*	29.720	<0.001
observation group	45	19.46±2.13	7.27±1.13*	34.385	<0.001
t		0.536	7.344		
P		0.591	<0.001		

Note: The difference between the two groups was statistically significant (*P <0.05)

2.2 Comparison of inflammation levels before and after treatment in two groups

Prior to treatment, no significant differences were observed in CRP and IL-8 concentrations between the observation group and control group (P>0.05). After 8 weeks of intervention, both groups showed reduced inflammatory markers. The observation group demonstrated a more pronounced decrease in CRP and IL-8 levels compared to the control group, with statistically significant differences (P<0.05). See Table 2.

Table 2: Comparison of inflammation levels before and after treatment in two groups

group	n	CRP/（mg/L）				IL-8/（mg/L）			
		pretherapy	post-treatment	*t*	*P*	pretherapy	post-treatment	*t*	*P*
control group	45	22.44±4.36	11.05±2.14*	16.421	<0.001	41.03±6.33	23.93±3.26*	16.155	<0.001
observation group	45	22.17±4.53	9.64±2.05*	19.061	<0.001	40.66±6.82	21.07±4.91*	17.122	<0.001
t		0.362	4.614			0.102	3.110		
P		0.701	<0.001			0.916	0.002		

Note: The difference between the two groups was statistically significant (*P <0.05)

2.3 Comparison of treatment effects before and after treatment in two groups

After 8 weeks of intervention, the total effective rate of treatment in the observation group was significantly higher than that in the control group, and the difference was statistically significant (P <0.05). See Table 3.

Table 3: Comparison of treatment effects before and after treatment in two groups

group	Number of cases	cure	excellence	valid	of no avail	total effective rate (%)
control group	45	7 (15.55)	14 (31.11)	10 (22.22)	16 (35.55)	31 (68.88) *

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observation group	45	13 (28.88)	16 (35.55)	9 (20.00)	7 (15.55)	38 (84.44) *
χ Value of 2						4.765
P price						0.024

Note: The difference between the two groups was statistically significant (*P <0.05)

2.4 Adverse reactions during treatment of the two groups

During the treatment period, 3 cases (3/45) in the observation group reported adverse reactions with a total incidence rate of 6.67%, including 1 case of nausea, 1 case of decreased appetite, and 1 case of vomiting. The control group showed a higher incidence rate of 11.1% (5/45), with 1 case of nausea, 2 cases of vomiting, and 2 cases of reduced appetite. The chi-square test analysis revealed no statistically significant difference in adverse reaction rates between the two groups (P=0.710), as shown in Table 4.

Table 4: Comparison of adverse reactions before and after treatment in two groups

divide into groups	n	untoward effect			Overall incidence (%)	*P*
		feel like vomiting	vomit	anorexia		
control group	45	1	2	2	11.1%*	0.710
observation group	45	1	1	1	6.67%*	

Note: There was no statistically significant difference between the two groups (P> 0.05)

3. Discussion

3.1 Comparison of treatment effect on emotional state between the two groups

As shown in Table 1, the combination therapy demonstrates significantly enhanced effects on improving patients 'emotional states. Further analysis reveals that sertraline, as an antidepressant and selective serotonin reuptake inhibitor (SSRIs), primarily works by specifically inhibiting serotonin (5-HT) reuptake in the central nervous system. This mechanism increases 5-HT concentration in synaptic clefts, playing a crucial role in stabilizing mood and alleviating depressive symptoms (Zhong Xia, 2024). On the other hand, butylphthalazine focuses on optimizing brain tissue microenvironment by enhancing cerebral blood circulation, promoting collateral circulation generation, and providing adequate nutritional support to damaged neurons. It also protects mitochondrial function and inhibits neuronal apoptosis, thereby indirectly improving emotional state (Zheng Shugong, 2021). The combined use of these two agents creates synergistic effects by regulating the 5-HT and norepinephrine (NE) systems, effectively intervening in central nervous system activity to improve neurological deficits, cognitive abilities, and daily living skills. Additionally, this approach more effectively alleviates depressive symptoms and enhances patients' quality of life (Wang Mixiang et al., 2021).

3.2 Comparison of the effect of inflammation control between the two groups

Prior to implementing the intervention, no statistically significant differences were observed in baseline serum C-reactive protein (CPR) and interleukin-8 (IL-8) levels between the two patient groups (P>0.05). As the intervention progressed, both groups showed a downward trend in CPR and IL-8 levels. However, the observed group demonstrated a more pronounced reduction compared to the control group, with this difference reaching statistical significance (P<0.05).

Dibenzylphthalide can reshape the metabolic pathways and functional states of immune cells, inhibit the release of inflammatory mediators, regulate the expression of CRP and IL-8, and exert anti-platelet aggregation and antioxidant stress effects by intervening in arachidonic acid metabolism (Dong Chuanzhan & Wang Lichun, 2021). Shetuline can modulate immune cell functions and influence the secretion levels of inflammatory factors such as IL-8. The combined use of these two drugs can significantly reduce patients' inflammatory responses, jointly decrease the production of pro-inflammatory factors, optimize clinical efficacy, and enhance therapeutic outcomes (Shang Xiaofeng & Zhang Ying et al., 2020).

As a selective serotonin reuptake inhibitor (SSRI), sertraline not only directly affects the central nervous system but also influences immune cell activities such as activation, proliferation, and apoptosis through intricate interactions within the neuroendocrine-immune network (Cheng Xingyong, 2024). Various neurotransmitters like serotonin and norepinephrine modulate immune cell functions via specific signaling pathways, indirectly altering systemic inflammatory responses and ultimately affecting related cytokine levels. Additionally, sertraline increases serotonin concentration in synaptic clefts, activating serotonin receptors on immune cells to regulate inflammatory signaling pathways (Meng Yuqing, 2024). This significantly inhibits pro-inflammatory factor secretion and reduces C-reactive protein (CRP) production in the liver. The serotonin receptors on immune cells constrain the activation of key effector cells like monocytes and macrophages, thereby exerting their anti-inflammatory properties. Similarly, butylphthalide demonstrates protective effects against cerebral ischemia-reperfusion injury (Wang Ting, 2020) by directly intervening in inflammatory cell activity and suppressing inflammatory factor expression, leading to decreased CRP and IL-8 levels. These findings highlight the complex interplay between neurotransmitters and immune responses.

3.3 Comparison of treatment effects between the two groups

Among the 45 patients in the observation group, 16 showed significant improvement after combined therapy, while 7 were ineffective, achieving a total effective rate of 84.44%. In the control group of 45 patients treated with sertraline alone, 14 demonstrated significant improvement and 16 showed no effect, with a total effective rate of 68.88%. Statistical analysis revealed a statistically significant difference in efficacy between the two groups (P<0.05). Further investigation indicated that the combined therapy in the observation group exhibited superior comprehensive therapeutic effects compared to monotherapy. The inflammatory response and oxidative stress caused by ischemic stroke can cause dual damage to the nervous system and exacerbate depressive symptoms. Bintaniprole has shown remarkable efficacy in improving neurological deficits (Zhang Ping & Chen Lei et al., 2023), while sertraline also demonstrated some effectiveness in this regard (Wei Zhisheng & Yang Qiyun et al., 2021). When used in combination,

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both drugs can more comprehensively counteract neurotoxic effects induced by inflammation and oxidative stress, mitigate nerve tissue damage caused by free radical injury, and achieve efficient control of depressive symptoms (Li Ting, 2021).

3.4 Comparison of adverse reactions between the two groups

As shown in Table 4, the adverse reactions caused by sertraline were predominantly gastrointestinal, with symptoms such as nausea, vomiting, and diarrhea being relatively common. These may also be accompanied by psychiatric symptoms like anxiety or agitation. In the control group, the incidence of adverse drug reactions was 11.1%, including 1 case of nausea, 2 cases of vomiting, and 2 cases of reduced appetite. During treatment, the observation group reported 6.67% adverse reactions to the medication, comprising 1 case of nausea, 1 case of vomiting, and 1 case of reduced appetite. After data processing, this difference showed no statistically significant significance (P>0.05).

4. Conclusion

In conclusion, the combination of Bintanipal and sertraline effectively inhibits inflammatory factors, improves neurological function, and alleviates cognitive impairment in post-ischemic stroke depression patients. This combined therapy demonstrates significant therapeutic efficacy with high safety profiles. It is recommended to conduct regular psychological assessments within 3-6 months after ischemic stroke, enhance screening for post-stroke depression (PSD), and promptly initiate treatment when symptoms such as low mood, reduced interest, fatigue, sleep disturbances, or appetite changes are observed. Implementing this integrated medication approach can effectively promote the recovery of cognitive and neurological functions.

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