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Assessment of the impact of combining butylphthalide and atorvastatin on neurological function, quality of life and vascular endothelial function in individuals diagnosed with acute cerebral infarction

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Abstract: Acute cerebral infarction poses a significant health risk and effective treatment is crucial. This randomized controlled trial assessed the impact of combining Butylphthalide and Atorvastatin on neurological function, quality of life and vascular endothelial function in 124 individuals with acute cerebral infarction. Participants were randomized into control and experimental groups, with the latter receiving the combination therapy. Objective assessments using NIHSS, SS-QOL, MBI and MoCA scales, along with biochemical markers, demonstrated improved outcomes in the experimental group. This study provides evidence for the clinical benefits of the drug combination in managing acute cerebral infarction.

Keywords: Acute cerebral infarction, butylphthalide, atorvastatin, vascular endothelial function, neurological function, quality of life.

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INTRODUCTION

Stroke is a highly challenging global disease and ranks as the second leading cause of death worldwide (GBD 2019 Stroke Collaborators, 2021). Data reveals a 106% increase in the prevalence of stroke in China over the past 30 years, accompanied by a 32.3% rise in mortality rates, with ischemic stroke being a prominent subtype (Ma *et al*., 2021). Ischemic stroke, also known as cerebral infarction, occurs primarily due to stenosis or occlusion of cerebral arteries, resulting in diminished or halted blood supply to brain tissue. This leads to local tissue ischemia, hypoxia, and potential necrosis, ultimately resulting in severe dysfunction of the central nervous system (Zheng *et al.*, 2022). Common clinical manifestations of cerebral infarction include hemiplegia, cognitive impairment and language disorders (Guo, *et al.*, 2016). The high morbidity and mortality rates associated with this condition pose significant threats to patients' prognosis and overall well-being. The primary goal of clinical management in cerebral infarction is to mitigate neurological damage and enhance patients' quality of life (Yu *et al*., 2022). Consequently, the administration of anticoagulants, as well as drugs aimed at improving cerebral circulation, forms the mainstay of thrombolytic therapy within the optimal time window (Kanazawa *et al.*, 2019; Liu *et al.*, 2022). However, a thrombolytic treatment for cerebral infarction can be effective depending on when blood supplies to ischemic brain tissue are restored (Zhou *et al.*, 2019).

Atorvastatin is a widely utilized clinical anti-platelet aggregation drug known for its beneficial effects in reducing blood lipid levels and enhancing endothelial function. These properties contribute to its potential in stabilizing atherosclerotic plaques to some extent. Notably, research indicates that Atorvastatin demonstrates neuroprotective effects in mice with ischemic stroke, attributed to its antioxidative properties. Furthermore, it holds a traditional role in the prevention and treatment of ischemic stroke (Lu *et al.*, 2019; Fan *et al.*, 2022; Laufs *et al.*, 2000). Butylphthalide represents a novel drug utilized in the management of cerebrovascular diseases in recent years, exhibiting notable anti-ischemic effects.

Studies have highlighted its capacity to promote neovascularization in the ischemic area of cerebral infarction patients, leading to increased blood flow and improved microcirculation within the affected brain region. This subsequently decreases the magnitude of cerebral ischemic infarction and promotes the recovery of neurological function in individuals experiencing acute cerebral infarction (Han *et al.*, 2019; Zhao *et al.*, 2013; Zhang *et al.*, 2019; Du *et al.*, 2015). Due to their distinct application characteristics and benefits, Atorvastatin and Butylphthalide are commonly utilized in the clinical management of cerebral infarction. Combining these drugs in the treatment regimen holds the potential to

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synergistically enhance therapeutic outcomes for patients with cerebral infarction, thereby effectively improving their overall recovery. Based on these discoveries, the current study seeks to examine how the combination of butylphthalide and atorvastatin affects patients with cerebral infarction. The study seeks to further elucidate the clinical efficacy and underlying mechanisms of this drug combination in patients with cerebral infarction.

MATERIALS AND METHODS

Research design and intervention

The study was conducted as a randomized controlled trial (RCT) at The Affiliated Hospital of Southwest Medical University from January 2021 to December 2022. It was an interventional clinical trial where 145 individuals with acute cerebral infarction were initially screened. After applying the inclusion and exclusion criteria, 124 patients were randomly assigned to either the control group or the experimental group, with each group consisting of 62 participants. The randomization process was performed using a computer-generated random sequence to ensure allocation concealment and the groups were balanced for prognostic variables. The solicitation of the subjects and the treatment of patients in each group are shown in fig. 1.

Inclusion and exclusion criteria

The eligibility criteria for patient recruitment were as follows. (1) Patients were under 80 years of age; (2) diagnosis of cerebral infarction was confirmed based on relevant imaging test results, in accordance with diagnostic criteria; (3) patients presented with symptom onset within 48 hours; (4) patients demonstrated good compliance and provided informed consent, either personally or through their families, by providing their consent after reading and understanding the information provided in the consent form.

The criteria for excluding patients from the selection process were listed below. (1) Patients with symptom onset exceeding 3 d; (2) patients who passed away within 24 h after admission; (3) patients with concurrent severe conditions such as malignant tumors and (4) patients with incomplete data.

Sample collection and technique

The sample size was determined using a power analysis with an estimated effect size based on preliminary data, aiming for 80% power to detect a significant difference at the 5% significance level. Patients were included if they were under 80 years of age, had a confirmed diagnosis of cerebral infarction through imaging tests, presented with symptom onset within 48 hours and provided informed consent.

Exclusion criteria included symptom onset exceeding 72 hours, death within 24 hours after admission, concurrent severe conditions such as malignancies and incomplete data. The sample technique involved a consecutive sampling method, ensuring that all eligible patients within the study period were considered.

Diagnostic parameters

Diagnostic parameters were integral to the study conduct. All participants underwent a standardized diagnostic process that included neuroimaging (CT or MRI) to confirm the presence and location of cerebral infarction. Additional diagnostic parameters included clinical manifestations and laboratory tests to rule out mimic conditions and to assess the severity of the infarction.

Participant benefits

Participants in the study received standard treatment for acute cerebral infarction, which included anti-platelet aggregation, anticoagulation, and control of complications. The experimental group received an additional intervention with butylphthalide soft capsules, which they took orally at a dosage of 0.2g, three times a day. This intervention was hypothesized to provide additional benefits in terms of neurological recovery and quality of life.

Assessment scales and analysis

The primary outcomes measured included the National Institute of Health Stroke Scale (NIHSS), Stroke-Specific Quality of Life Scale (SS-QOL), Modified Barthel Index (MBI), and Montreal Cognitive Assessment (MoCA). Each scale was analyzed individually for each question, and comparative analyses were performed between the control and experimental groups using both parametric and non-parametric statistical tests as appropriate. This approach allowed for a detailed understanding of the impact of the intervention on various aspects of neurological function and quality of life.

Vascular and cerebral blood flow assessment

Vascular endothelial function was assessed by measuring serum levels of nitric oxide (NO), endothelin-1 (ET-1), and homocysteine (Hcy) using enzyme-linked immunosorbent assay (ELISA) kits. Cerebral blood flow was evaluated using transcranial Doppler ultrasound to measure peak systolic blood flow velocity (Vs), diastolic blood flow velocity (Vd), pulsatility index (PI) and resistance index (RI). These assessments were conducted at baseline and at the end of the study period to monitor changes in vascular health.

ETHICAL APPROVAL

This study was approved by the ethics committee of The Affiliated Hospital of Southwest Medical University (Approval No. SMU-21-021).

Table 1: Basic information and clinical data of the subjects

Variables		Total (n=124)	Control Group (n=62)	Experimental Group (n=62)	t/χ^2 value	P value
Age, [years, ($\bar{x}\pm s$)]		56.97±5.75	56.81±5.44	57.13±6.09	0.311	0.756
Gender, [n(%)]	Female	46(37.10)	24(38.71)	22(35.48)	0.138	0.710
	Male	78(62.90)	38(61.29)	40(64.52)		
BMI, [kg/m^2, ($\bar{x}\pm s$)]		24.26±3.33	24.13±3.20	24.40±3.47	0.455	0.650
Smoking, [n(%)]		80(64.52)	39(62.90)	41(66.13)	0.141	0.707
Alcohol, [n(%)]		49(39.52)	24(38.71)	25(40.32)	0.034	0.854
Comorbidities [n(%)]	Hypertension	75(60.48)	37(59.68)	38(61.29)	0.095	0.992
	Hyperlipidemia	55(44.35)	26(41.94)	29(46.77)		
	Diabetes	60(48.39)	30(48.39)	30(48.39)		
	Coronary heart disease atherosclerosis	71(57.26)	35(56.45)	36(58.06)		
Time from onset to hospital, [h, ($\bar{x}\pm s$)]		21.55±7.49	21.89±8.03	21.21±6.97	0.502	0.617
Infarct size, [cm^3, ($\bar{x}\pm s$)]		5.71±0.99	5.73±0.96	5.69±1.02	0.181	0.856
Infarct type [n(%)]	Lacunar infarction	31(25.00)	15(24.19)	16(25.81)	1.196	0.754
	Basal ganglia infarction	50(40.32)	23(37.10)	27(43.55)		
	Temporal lobe infarction	23(18.55)	12(19.35)	11(17.74)		
	Others	20(16.13)	12(19.35)	8(12.90)		

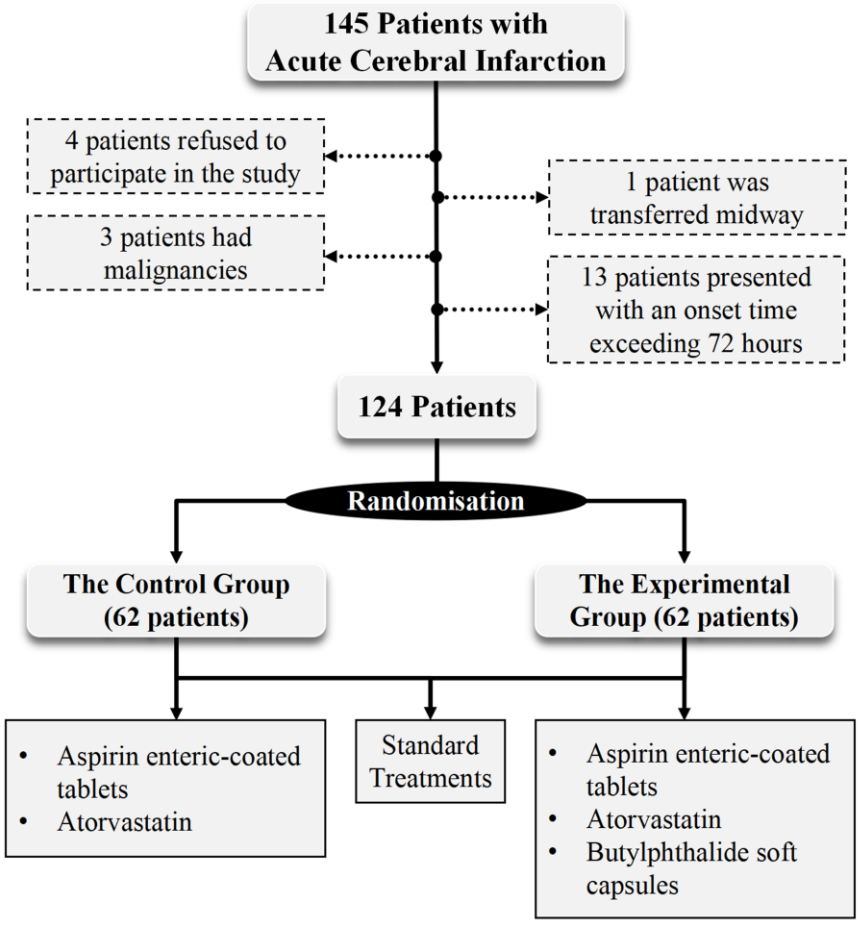

Fig. 1: Solicitation of research objects and related treatments.

Table 2: Clinical therapeutic effect of two groups [n(%)]

Effect	Control Group (*n*=62)	Experimental Group (*n*=62)	χ^2 value	*P* value
Basic cure	12(19.35)	22(35.48)		
Obvious effectiveness	23(37.10)	26(41.94)		
Effectiveness	14(22.58)	10(16.13)		
Ineffectiveness	13(20.97)	4(6.45)		
Total cure rate	12(19.35)	22(35.48)	4.052	0.044
Total effective rate	49(79.03)	58(93.55)	5.522	0.019

Table 3: Comparison of the detection results of SS-QOL, NIHSS, Barthel and MoCA between two groups at different time periods (x ± s)

Index	Time	Control Group (*n*=62)	Experimental Group (*n*=62)	*t* value	*P* value
SS-QOL	Before treatment	93.27±8.99	93.77±9.79	0.296	0.768
	7 d after treatment	104.26±9.26	106.42±14.62	0.983	0.328
	14 d after treatment	124.66±14.21▲	162.52±20.21▲	12.063	<0.001
NIHSS	Before treatment	9.47±1.64	9.60±1.56	0.449	0.654
	7 d after treatment	8.42±1.64	7.81±1.23	2.361	0.020
	14 d after treatment	7.53±1.74▲	5.61±1.55▲	6.477	<0.001
MBI	Before treatment	47.71±9.67	47.68±8.71	0.020	0.984
	7 d after treatment	52.47±10.88	70.90±13.59	8.341	<0.001
	14 d after treatment	72.35±7.74▲	84.63±6.36▲	9.645	<0.001
MocA	Before treatment	15.42±3.11	15.16±3.01	0.470	0.639
	7 d after treatment	16.02±1.90	17.19±2.58	2.893	0.005
	14 d after treatment	19.85±2.54▲	24.52±2.98▲	9.364	<0.001

▲ It was statistically significant compared with that before treatment, that is, P<0.05.

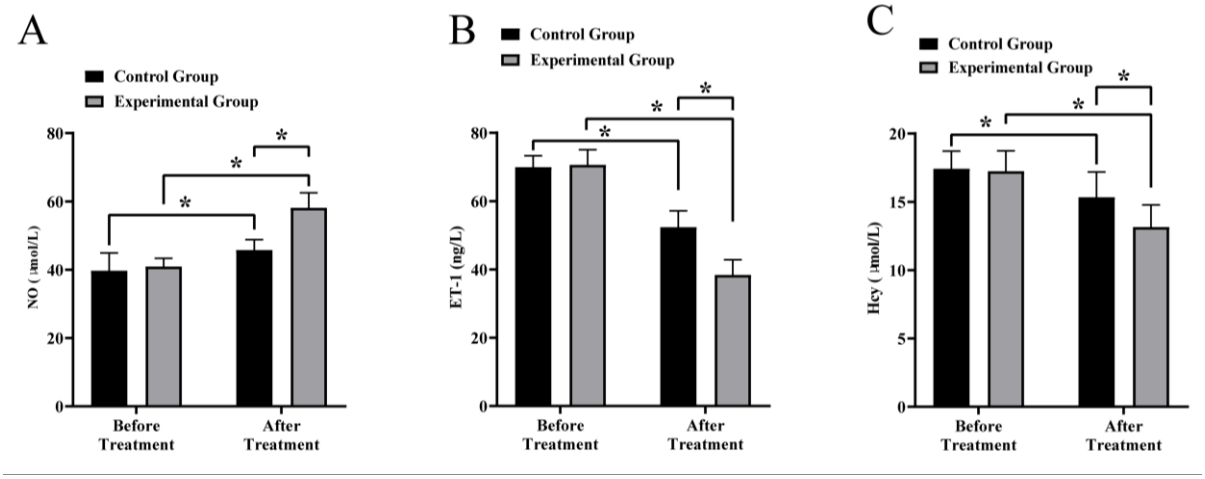

Fig. 2: Expression of vascular endothelial factor in two groups before and after treatment. (A) shows the results of nitric oxide (NO). (B) shows the results of endothelin-1 (ET-1). (C) shows the results of homocysteine (Hcy). *There are significant statistical differences between the two groups (P<0.05).

STATISTICAL ANALYSIS

Data analysis was performed using SPSS software, version 26.0. Continuous variables are presented as mean ± standard deviation ($\bar{x}$±s) and group comparisons were conducted using independent samples t-tests for normally distributed data or Mann-Whitney U tests for non-normally distributed data. Categorical variables were compared using chi-square tests. A p-value of less than 0.05 was considered statistically significant. The analysis included both intention-to-treat and per-protocol approaches to handle missing data and ensure the robustness of the study findings.

RESULTS

Basic information of the object of study

Table 1 presents the basic information and clinical data of all 124 patients. The patients' mean age was (56.97±5.75) years, and the male patients accounted for 78 individuals (62.9%). The average body mass index (BMI) was (24.26± 3.33) kg/m^2. Among the patients, 64.52% had a

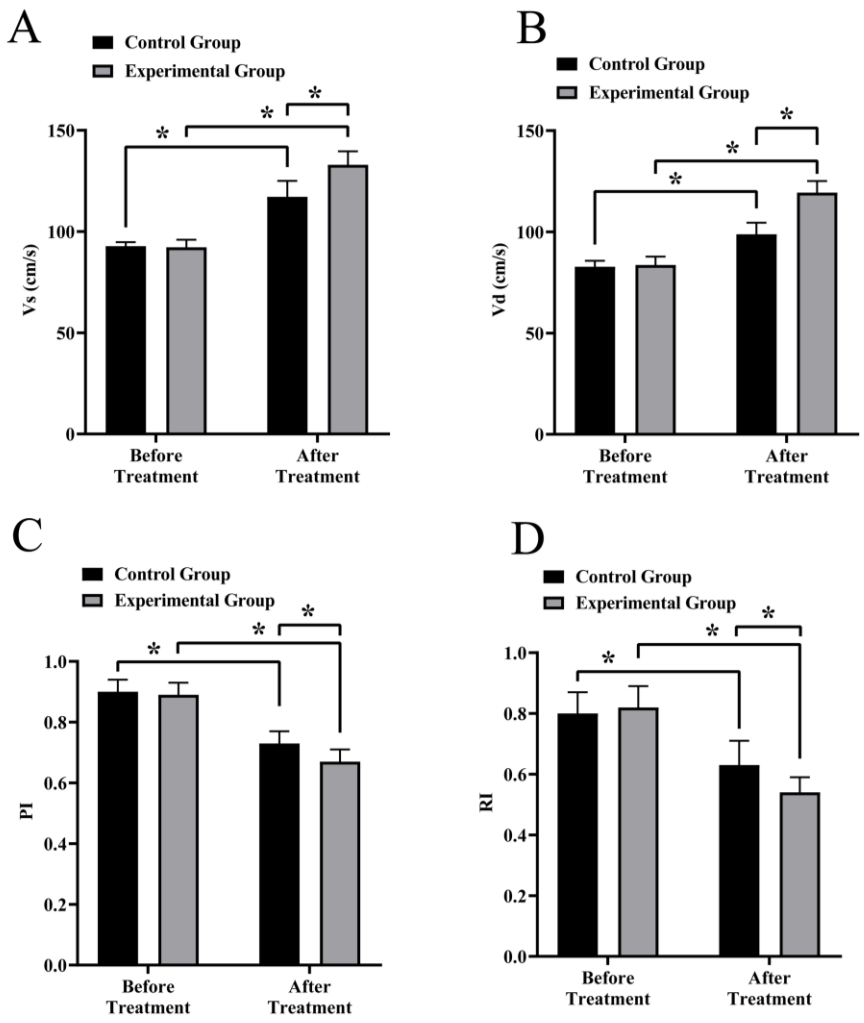

Fig. 3: Results of cerebral blood flow indexes in two groups of patients before and after treatment. (A) shows the results of peak systolic blood flow velocity (Vs). (B) shows the results of diastolic blood flow velocity (Vd). (C) shows the results of pulsatility index (PI). (D) shows the results of and occlusion index (RI). *There are significant statistical differences between the two groups (P<0.05).

smoking habit, while 39.52% had a drinking habit. In terms of comorbidities, 60.48% of the patients had hypertension, 57.26% had coronary heart disease and atherosclerosis, 48.39% had diabetes and 44.35% had hyperlipidemia. The study also revealed that the average time from symptom onset to admission was approximately (21.55±7.49). In terms of related examinations, the average infarct size was (5.71±0.99) m^3, with the majority of patients having basal ganglia infarction (40.32%), followed by lacunar infarction (25.00%). There were no notable disparities detected in the aforementioned data and clinical information between the two groups (*P*>0.05).

Comparison of therapeutic effects between two groups of patients

Table 2 displays the clinical therapeutic outcomes of both groups. The experimental group exhibited notably higher cure rate and treatment effective rate at 35.48% and 93.55%, respectively, compared to the control group's rates of 19.35% and 79.03% (*P*<0.05).

Comparison of the detection results of SS-QOL, NIHSS, Barthel, and MoCA between two groups at different time periods

Table 3 displays the scores of SS-QOL, NIHSS, MBI and MoCA before treatment at 7 d and at 14 d after treatment in both groups. Prior to the intervention, there were no notable disparities detected in the scores of the four scales between the experimental group and the control group (*P* >0.05). However, at 14 d after treatment, the scores of the four scales in both groups differed significantly from those before treatment.

Among the findings, it was observed that, on the seventh day after treatment, the scores of the NIHSS, MBI and MoCA scales in the experimental group were significantly different from those in the control group. On

the 14th day after treatment, the experimental group demonstrated significantly higher scores in SS-QOL, MBI, and MoCA compared with control group. However, the NIHSS score in the experimental group was significantly lower than that in the control group (P<0.05).

Comparison of the expression of vascular endothelial factor between the two groups

Fig. 2 illustrates the specific expression of vascular endothelial factors in the two groups. Prior to intervention, there were no significant disparities observed in the levels of nitric oxide NO, ET-1 and Hcy between the experimental group and control group. However, post-intervention revealed noteworthy alterations in the indices of patients from both groups when compared to their respective pre-treatment values (P<0.05).

The experimental group demonstrated a notable increase in NO levels compared to the control group, suggesting an enhancement in endothelial function and vasodilation. Conversely, the experimental group exhibited significantly reduced levels of ET-1 and Hcy when compared to the control group (P<0.05).

Comparison of the results of cerebral blood flow related indexes between the two groups

Fig. 3 displays the cerebral blood flow indexes of the two groups before and after treatment. Before the treatment, there was no noticeable disparity observed between the two groups (P>0.05). However, after treatment, notable differences were observed in the cerebral blood flow indexes of both groups compared to their pre-treatment values.

Upon analyzing the differences between the two groups, it was discovered that the experimental group demonstrated noticeably elevated levels of Vs and Vd after treatment, with values of (132.98±6.65) cm/s and (119.4±5.69) cm/s, respectively, compared to the control group (P<0.05). Moreover, the experimental group exhibited considerably reduced values in relation to both the PI and RI when compared to the control group (P<0.05).

DISCUSSION

The incidence of acute cerebral infarction is alarmingly high, characterized by rapid disease progression and significant rates of clinical disability and fatality (Sun *et al*., 2019). In the initial phases of acute cerebral infarction, the ischemic region within the brain consists of a central necrotic zone and an encompassing peripheral area with reduced blood flow. The brain cells within the central necrotic area often experience irreversible damage within a short timeframe, making clinical intervention challenging. However, the cells within the surrounding ischemic penumbra are still alive and with effective treatment to restore cerebral blood flow, it is possible to reverse the risk of cell death and improve neurological function in this specific brain region (Li *et al*., 2020; Sun, *et al*., 2015; Cheng, *et al.*, 2014).

Our study revealed the effectiveness of combining butylphthalide with atorvastatin in treating patients with cerebral infarction. The combination therapy demonstrated significantly improved clinical cure rates and effectiveness compared to treatment with atorvastatin alone. Our experimental findings demonstrated notable enhancements in the NIHSS scale, SS-QOL scale, modified Barthel index and MoCA scale among participants in the experimental group as compared to those in the control group. The NIHSS scale is a widely utilized measure for evaluating the degree of neurological dysfunction in individuals experiencing acute cerebral infarction (Peng *et al.*, 2022). Higher NIHSS scores indicate more severe cerebral infarction and more pronounced neurological impairment symptoms (Zheng, *et al*., 2022). So, the experimental findings indicated a significant enhancement in the neurological function of patients belonging to the experimental group.

To further evaluate the improvement in patients' neurological function, this study utilized the MBI and MoCA scale. The Barthel index is commonly employed to assess functional status and activities of daily living in various diseases, including cerebral infarction (Akezaki *et al.*, 2022). The MBI, an enhancement of the Barthel index, offers improved evaluation of the prognosis in patients with cerebral infarction and overcomes the limitations of the Barthel index in assessing patients with higher functional levels (Yang *et al*., 2021). And the MoCA scale is more sensitive in evaluating cognitive impairment (Li, *et al.*, 2021). Therefore, the observed advancements in the NIHSS, MBI, and MoCA scores within the experimental group indicate a notable improvement in neurological impairment levels. This research utilized the SS-QOL scale to assess patients' life quality, providing substantial evidence for the aforementioned discoveries. The SS-QOL scale proves to be a dependable, efficient and pragmatic tool for evaluating life quality among individuals with cerebral infarction (Wayessa *et al.*, 2023). Earlier research has established a noteworthy association between SS-QOL and NIHSS scores (Wei *et al.*, 2017). Therefore, when considering the neurological impairment scale alongside patients' quality of life, it becomes evident that the combination of butylphthalide and atorvastatin can substantially improve clinical neurological deficits in patients with cerebral infarction. This improvement holds positive significance in enhancing patients' daily living abilities and cognitive levels.

Furthermore, to investigate the underlying mechanism of the combination therapy, this study focused on the vascular endothelial factors and cerebral blood flow indexes, taking into account the characteristics of action of the two drugs and previous related studies. The experimental group showed significant enhancements in

the serum levels of NO, ET-1 and Hcy, indicating a positive impact on vascular endothelial function. These results strongly support the effectiveness of combining butylphthalide and atorvastatin in improving vascular health. In general, disturbances in cerebral vascular endothelial function can disrupt normal vasodilation, resulting in reduced micro vascular blood flow in the brain and potentially leading to blood-brain barrier dysfunction. Atorvastatin is a well-established statin and a classic blood lipid regulator that falls under the category of HMG-CoA reductase inhibitors. Its primary mechanism involves inhibiting cholesterol synthase activity, thereby reducing the synthesis of endogenous cholesterol. Moreover, Atorvastatin enhances the uptake of low-density lipoprotein in liver tissue, leading to reduced blood lipid levels and improved vascular endothelial function (Gavazzoni *et al.*, 2017; Liu *et al.*, 2018). Notably, Yang *et al.*'s research on a rat model of ischemic cerebral infarction demonstrated that Atorvastatin also plays a role in promoting brain blood barrier function and regulating endothelial function to facilitate vascular remodeling (Yang *et al.*, 2021). Butylphthalide, a relatively novel synthetic drug, has gained recognition as a common treatment option for acute cerebral infarction in clinical settings. Its efficacy stems from its ability to promote angiogenesis in ischemic brain tissue and enhance collateral vascular circulation, consequently improving cerebral microcirculation. These effects contribute to the rescue of the ischemic penumbra surrounding the brain, leading to a reduction in the area of cerebral ischemic infarction and ultimately aiding in the restoration of brain function (Du *et al*., 2015; Zhan *et al.*, 2022). The combination of atorvastatin and butylphthalide is believed to exert synergistic effects in preserving brain tissue. By restoring and maintaining blood circulation in the surrounding ischemic penumbra, this combination therapy holds potential in mitigating the consequences of acute cerebral infarction and fostering brain tissue recovery.

In support of our findings, we assessed cerebral blood flow parameters and found that the experimental group demonstrated significantly higher cerebral blood flow velocities compared to both their own pre-treatment measurements and the control group. Additionally, the values of the PI and RI were significantly decreased. These results indicate a notable improvement in the cerebral vasoconstriction and relaxation function in patients. Impaired regulation of cerebral blood flow in patients leads to decreased cerebral perfusion and blood flow, exacerbating the condition of those with cerebral infarction (Li *et al.*, 2022). Consequently, the findings suggest that the clinical efficacy of the combined administration of these two drugs appears to be associated with their impact on vascular endothelial factors, leading to enhanced blood circulation in cerebral vessels and consequent improvement in the microcirculation of the ischemic penumbra surrounding the brain.

CONCLUSIONS

The combination therapy of butylphthalide and atorvastatin has shown efficacy in the clinical management of individuals diagnosed with cerebral infarction. This efficacy can be attributed to the therapy's ability to effectively regulate vascular endothelial factor expression and improve cerebral blood flow in patients. These findings highlight the potential benefits of this combination treatment in improving the overall outcomes and enhancing the well-being and overall life satisfaction of individuals diagnosed with cerebral infarction.

CONFLICT OF INTERESTS

The authors declared no conflict of interest.

REFERENCES

GBD 2019 Stroke Collaborators (2021). Global, regional and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.*, **20**(10): 795-820.

Akezaki Y, Nakata E, Kikuuchi M, Sugihara S, Katayama Y, Katayama H, Hamada M and Ozaki T (2022). Association between overall survival and activities of daily living in patients with spinal bone metastases. *Healthcare-Basel.*, **10**(2): 350.

Costa D, Ielapi N, Perri P, Minici R, Faga T, Michael A, Bracale UM, Andreucci M and Serra R (2024). Molecular insight into acute limb ischemia. *Biomolecules*, **14**(7): 838.

Yan F, Tian Y, Huang Y, Wang Q, Liu P, Wang N, Zhao F, Zhong L, Hui W and Luo Y (2022). Xi-Xian-Tong-Shuan capsule alleviates vascular cognitive impairment in chronic cerebral hypoperfusion rats by promoting white matter repair, reducing neuronal loss, and inhibiting the expression of pro-inflammatory factors. *Biomed. Pharmacother.*, **145**: 112453.

Fan J, Zhang X and Chen R (2022). Atorvastatin alleviates oxidative damage by activating the nuclear factor erythroid 2-related factor 2 pathway after brain ischemia in mice. *Ann. Transl. Med.*, **10**(20): 1135.

Gavazzoni M, Gorga E, Derosa G, Maffioli P, Metra M and Raddino R (2017). High-dose atorvastatin versus moderate dose on early vascular protection after ST-elevation myocardial infarction. *Drug Des. Devel Ther.*, **11**: 3425-3434.

Guo S, Liu Y, Ma R, Li J and Su B (2016). Neuroprotective effect of endogenous cannabinoids on ischemic brain injury induced by the excess microglia-mediated inflammation. *Am. J. Transl Res.*, **8**(6): 2631-2640.

Han QY, Zhang H, Zhang X, He DS, Wang SW, Cao X, Dai YT, Xu Y and Han LJ (2019). dl-3-n-butylphthalide preserves white matter integrity and alleviates cognitive impairment in mice with chronic

cerebral hypoperfusion. *CNS Neurosci. Ther.*, **25**(9): 1042-1053.

Kanazawa T, Kurano T, Ibaraki H, Takashima Y, Suzuki T and Seta Y (2019). Therapeutic effects in a transient middle cerebral artery occlusion rat model by nose-to-brain delivery of anti-tnf-alpha sirna with cell-penetrating peptide-modified polymer micelles. *Pharmaceutics*, **11**(9): 478.

Siniscalchi C, Basaglia M, Riva M, Meschi M, Meschi T, Castaldo G and Di Micco P (2023). Statins effects on blood clotting: A review. *Cells*, **2**(23): 2719.

Li C, Zhu L, Dai Y, Zhang Z, Huang L, Wang TJ, Fu P, Li Y, Wang J and Jiang C (2022). Diet-induced high serum levels of trimethylamine-N-oxide enhance the cellular inflammatory response without exacerbating acute intracerebral hemorrhage injury in mice. *Oxid Med. Cell Longev.*, 1599747.

Li J, Tao T, Xu J, Liu Z, Zou Z and Jin M (2020). HIF-1alpha attenuates neuronal apoptosis by upregulating EPO expression following cerebral ischemia-reperfusion injury in a rat MCAO model. *Int. J. Mol. Med.*, **45**(4): 1027-1036.

Li N, Yang T, Ran W, Zhang X, Wang Y, Xu Z, Ren S, Zhao Q, Guo B, Wang S, Meng F and Chen Z (2021). A study on the characteristics of cognitive function in patients with multiple system atrophy in China. *Sci Rep-Uk.*, **11**(1): 4995.

Liu C, Gu J, Yao Y, Guo P and Hu H (2022). Correlation between retinol binding protein 4 and ct perfusion imaging and prognosis in patients with acute ischemic stroke based on cell imaging data analysis. *Contrast Media Mol I.*, 3055712.

Liu LY, Liu Y, Wu MY, Sun YY and Ma FZ (2018). Efficacy of atorvastatin on the prevention of contrast-induced acute kidney injury: A meta-analysis. *Drug Des Devel Ther*, **12**: 437-444.

Lu D, Shen L, Mai H, Zang J, Liu Y, Tsang CK, Li K and Xu A (2019). HMG-CoA reductase inhibitors attenuate neuronal damage by suppressing oxygen glucose deprivation-induced activated micro glial Cells. *Neural Plast.*, **2019**: 7675496.

Ma Q, Li R, Wang L, Yin P, Wang Y, Yan C, Ren Y, Qian Z, Vaughn MG, McMillin SE, Hay SI, Naghavi M, Cai M, Wang C, Zhang Z, Zhou M, Lin H and Yang Y (2021). Temporal trend and attributable risk factors of stroke burden in China, 1990-2019: An analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*, **6**(12): e897-e906.

Peng SJ, Chen YW, Yang JY, Wang KW and Tsai JZ (2022). Automated cerebral infarct detection on computed tomography images based on deep Learning. *Biomedicines*, **10**(1): 122.

Sun Y, Xu Y and Geng L (2015). Caspase-3 inhibitor prevents the apoptosis of brain tissue in rats with acute cerebral infarction. *Exp. Ther. Med.*, **10**(1): 133-138.

Sun Z, Xu Q, Gao G, Zhao M and Sun C (2019). Clinical observation in edaravone treatment for acute cerebral infarction. *Niger J. Clin Pract.*, **22**(10): 1324-1327.

Wayessa DI, Chala MB, Demissie SF, Abebe AB, Janakiraman B, Deme S and Gashaw M (2023). Cross-cultural translation, adaptation and validation of the stroke-specific quality of life (SSQOL) scale 2.0 into Amharic language. *Health Qual. Life Out*, **21**(1): 7.

Wei D, Xie D, Li H, Chen Y, Qi D, Wang Y, Zhang Y, Chen K, Li C and Zhang Z (2017). The positive effects of Xueshuan Xinmai tablets on brain functional connectivity in acute ischemic stroke: A placebo controlled randomized trial. *Sci. Rep-UK*, **7**(1): 15244.

Yang W, Zhang X, Li Z, Zhang Q, Xue C and Huai Y (2021). The effect of brain-computer interface training on rehabilitation of upper limb dysfunction after stroke: A meta-analysis of randomized controlled trials. *Front Neurosci-Switz*, **15**: 766879.

Yang Y, Yang LY, Salayandia VM, Thompson JF, Torbey M and Yang Y (2021). Treatment with atorvastatin during vascular remodeling promotes pericyte-mediated blood-brain barrier maturation following ischemic stroke. *Transl. Stroke Res.*, **12**(5): 905-922.

Yu Y, Zhang G, Han T, Liu H and Huang H (2022). A network meta-analysis of the clinical efficacy and safety of commonly used Chinese patent medicines in the auxiliary treatment of poststroke depression. *Evid-Based Compl Alt*, **2022**: 7265769.

Zhan L, Pang Y, Jiang H, Zhang S, Jin H, Chen J, Jia C, Guo H and Mu Z (2022). Butylphthalide inhibits TLR4/NF-kappaB pathway by upregulation of miR-21 to have the neuroprotective effect. *J. Healthc Eng.*, **2022**: 4687349.

Zhang XL, Dong YT, Liu Y, Zhang Y, Li TT and Hu FY (2019). Effects of dl-3-n-butylphthalide on serum lipoprotein-associated phospholipase A2 and hypersensitive C-reactive protein levels in acute cerebral infarction. *Brain Behav.*, **9**(12): e01469.

Zhao Y, Li J, Zhang P, Chen C and Li S (2013). Protective effects of dl-3n-butylphthalide against diffuse brain injury. *Neural Regen. Res.*, **8**(28): 2615-2624.

Zheng J, Luo S and Long Y (2022). Bioinformatic analysis and clinical diagnostic value of hsa_circ_0004099 in acute ischemic stroke. *Plos One*, **17**(11): e0277832.

Zheng Z, Liang S, Sun S, Liu P and Yu L (2022). Clinical observation of salvianolic acid combined with panax notoginseng saponins combined with basic nursing intervention on cerebral ischemia-reperfusion injury in rats. *J. Healthc. Eng*, **2022**: 8706730.

Zhou Z, Xu H, Liu B, Dun L, Lu C, Cai Y and Wang H (2019). Suppression of lncRNA RMRP ameliorates oxygen-glucose deprivation/re-oxygenation-induced neural cells injury by inhibiting autophagy and PI3K/Akt/mTOR-mediated apoptosis. *Bioscience Rep.*, **39**(6): BSR20181367.