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Original Research Article

Efficacy and safety of combining ginkgolide diterpene glucosamine injection with dual antibodies in elderly patients with acute ischemic stroke

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Abstract

Purpose: *To investigate the clinical effects and safety of ginkgo biloba diterpene lactone glucosamine injection, combined with dual antibiotic therapy for acute ischemic stroke in elderly individuals within a hyper thrombolytic time window.*
Methods: *100 elderly patients with acute ischemic stroke at Changsha First Hospital, Changsha, China from March 2022 to March 2023 were randomly and equally assigned to study and control groups (50 patients each). Study group received aspirin and clopidogrel, while control group received ginkgo biloba diterpene lactone glucosamine injection along with dual antibodies. Clinical efficacy, National Institutes of Health Stroke Scale (NIHSS) score, Instrumental Activities of Daily Living (IADL) score, cerebral hemodynamics, and safety were compared between the two groups.*
Results: *There was no significant difference in effective rate between the two groups ($p > 0.05$). However, following treatment, study group showed superior NIHSS and IADL scores compared to control group, with greater statistical significance as the disease progressed. Doppler ultrasound revealed that study group had smaller Pulsatility index (PI) values and larger mean cerebral artery blood flow velocity (Vm), and systolic value (Vs) compared to control group ($p < 0.05$). In study group, three adverse reactions were reported (gastrointestinal discomfort, abnormal liver/kidney function, and skin itching), whereas the control group experienced five adverse reactions (gastrointestinal discomfort, abnormal liver/kidney function, dizziness, and skin itching).*
Conclusion: *The combination of Ginkgo biloba diterpene lactone glucosamine injection and dual antibodies in elderly individuals with acute ischemic stroke within a super thrombolytic time window enhances intracerebral blood flow levels, effectively promotes neurological recovery, improves daily living abilities, and safety. Further research is needed to elucidate the exact pathways involved.*

Keywords: *Ginkgo biloba, Diterpene lactone, Glucosamine, Dual anti-treatment, Acute ischemic stroke, Thrombolytic time window*

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INTRODUCTION

Acute ischemic stroke (AIS) is a prevalent cerebrovascular disease characterized by high morbidity, disability, and mortality. It has a high incidence in middle-aged and elderly individuals [1-3]. Mainstream treatment protocol for AIS remains intravenous thrombolysis within 4.5 h of stroke onset, and intravascular mechanical embolectomy for patients with large artery

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occlusion within 6 h of symptom onset. However, some patients fail to receive timely thrombolysis due to various reasons in clinical practice [4,5].

Aspirin and clopidogrel are often used for patients with AIS beyond the thrombolysis time window, especially in elderly patients. Although, combination of Ginkgo biloba and clopidogrel effectively reduces risk of recurrence of ischemic stroke [3]. Long-term use of dual anti-treatment may cause varying degrees of physical damage. As a result, higher safety requirements are necessary for elderly patients' treatment effect.

Relevant medical studies have shown that ginkgo biloba diterpene lactone dextran injection blocks multiple pathological links associated with AIS while protecting patient brain tissue to some extent [3]. Its rate of clinical application has increased significantly in recent years as it resists platelet aggregation and improves circulation while blocking ischemic cascade reaction through multiple targets to achieve neuroprotective effects [5-7].

Hence, thus study was aimed at investigating ginkgo biloba diterpene lactone glucosamine injection, combined with dual antibiotic therapy for acute ischemic stroke in elderly individuals.

METHODS

General information

Clinical data of 100 elderly acute ischemic stroke patients admitted to Changsha First Hospital, Changsha, China from March 2022 to March 2023 who were beyond the thrombolytic time window were retrospectively analyzed. In study group, mean age was 68.45 ± 5.17 years, with 20 female cases (40 %) and 30 male cases (60 %). Body In control group, the age range was 62 - 79 years (69.53 ± 7.86 years). There were 21 female cases (42 %) and 29 male cases (58 %). General data between the two groups were not statistically significant ($p > 0.05$), indicating that the groups were comparable. This study was approved by the ethics committee of Changsha First Hospital (approval no. 20230088) and was performed in line with the Declaration of Helsinki [8]. Signed written informed consents were obtained from the patients and/or guardians.

Inclusion criteria

Patients that met the diagnostic criteria for cerebral infarction as outlined in the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018 [5], admitted within 6 - 72 h after onset, beyond the thrombolysis time window, ≥ 60 years of age, be conscious, exhibit good cooperation from either themselves or their family, and provided signed informed consent were included.

Exclusion criteria

Patients with severe stroke coma, a National Institutes of Health Stroke Scale (NIHSS) score greater than 20, presence of comorbidities such as severe cardiopulmonary disease, platelet and coagulation abnormalities, hepatic or renal insufficiency, malignancy, or gastrointestinal bleeding; psychiatric patients, known allergies or are allergic to the components of aspirin, clopidogrel, or ginkgo biloba diterpene lactone dextran injection; and patients who are currently receiving thrombolytic or anticoagulant therapy were excluded.

Safety indicators

Patients in both groups underwent regular monitoring of blood parameters, biochemical functions, ECG readings, and other vital signs before enrollment. Additionally, follow-up visits were conducted in the 2nd, 4th, and 6th weeks after medication initiation. Adverse events were monitored and recorded for both groups. The timing of adverse events was also documented, and measures taken to address these events as well as subsequent regression were also recorded.

Treatments

Control group were administered enteric-coated aspirin tablets (Shiyang Group Ouyi Pharmaceutical Co., Ltd., Guopharm Zhizhi H13023635) orally at a dosage of 100 mg once daily in combination with clopidogrel (Zhejiang Jingxin Pharmaceutical Co., Ltd., Guopharm Zhizhi H20213330) at a dosage of 75 mg once daily. Study group received intravenous injections of Ginkgo biloba diterpene lactone glucosamine (Jiangsu Kang Yuan Pharmaceutical Co., Ltd., State Drug Administration Z20120024) at a dose of 5 ml dissolved in 250 mL of 0.9 % sodium chloride solution once daily for two weeks.

For comorbid conditions, medication was administered symptomatically without affecting the determination of the efficacy of the tested drugs; during the treatment period. As confirmed by clinical trials, the enrolled patients were not allowed to take other Chinese medicines and proprietary Chinese medicines with preventive effects on stroke.

Evaluation of parameters/indices

Efficacy assessment criteria

The efficacy was classified as significantly effective (SE) (there was a significant improvement in symptoms of cerebral ischemia and hypoxia, accompanied by a decrease in NIHSS score ranging from 90 % to 100 %), effective (E) (there was an improvement in symptoms and a decrease in NIHSS score ranging from 18 % to 89 %), ineffective (I) (there was no improvement in symptoms, with a decrease in NIHSS score below 18 %). The total effective rate (TE) was calculated using Eq 1.

$$TE\ (\%) = \{(SE+E)/N\}100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

where N is the total number of cases

Instrumental Activities of Daily Living (IADL)

Higher scores indicate more significant functional impairment and a score of 14 represents normal functioning, while scores above 14 indicate varying degrees of functional decline.

Cerebral hemodynamics

Cerebral hemodynamics were assessed using transcranial Doppler ultrasound measurements, including pulsatility index (PI), mean cerebral artery blood flow velocity (Vm), and systolic value (Vs). Measurements were primarily taken from anterior, middle, and posterior cerebral arteries based on infarct location and intermediate values were recorded.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS) 20.0 (IBM, Armonk, NY, USA) and GraphPad Prism 9 (La Jolla, CA, USA) software for data processing and analysis. Measurement data were presented as mean ± standard deviation (SD), and the t-test was used for comparison. Count data were expressed as relative numbers and analyzed using chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Efficacy

There was no significant difference in efficacy between the two groups before and after treatment, but the overall efficacy rate of the study group was higher compared to control group (Table 1).

NIHSS and IADL scores

After 2, 4, and 6th week of treatment, both groups showed significant decrease in NIHSS scores compared to pre-treatment levels. Furthermore, study group exhibited significantly superior improvement in neurological deficits compared to control group ($p < 0.05$) (Table 2). The IADL scores of both groups decreased relative to baseline index, with study group exhibiting significant reduction compared to control group after 4, and 6th weeks of treatment ($p < 0.05$) (Table 3).

Table 1: Comparison of overall efficacy rate between two groups (n = 50)

Group	Significant effect (%)	Effective (%)	Ineffective (%)	Overall efficacy rate (%)
Study	14(28.00)	28(56.00)	8(16.00)	42(84.00)
Control	15(30.00)	19(38.00)	16(32.00)	34(68.00)
χ^2				3.5088
P-value				0.0610

Table 2: Comparison of NIHSS scores between the two groups (n = 50)

Group	Pre-treatment	2 weeks	4 weeks	6 weeks
Study	7.92±2.28	5.12±1.82$^{※}$	3.56±1.22$^{※}$	2.33±0.32$^{※}$
Control	8.06±2.33	6.47±2.31$^{*\#}$	4.05±1.82$^{*\#}$	3.93±0.42$^{*\#}$

$^{*}P < 0.05$ vs. between two groups, $^{※}p < 0.05$ vs. control group, $^{\#}p < 0.05$ vs. pre-treatment levels

Table 3: Comparison of IADL scores between the two groups (n = 50)

Group	Pre-treatment	2 weeks	4 weeks	6 weeks
Study	17.20±1.80	16.73±2.08	14.38±1.78$^{※}$	13.98±1.28$^{※}$
Control	17.16±1.51	16.82±1.26	16.02±1.34$^{*\#}$	15.73±2.34$^{*\#}$

$^{※}P < 0.05$ within each group before treatment, $^{\#}p < 0.05$ vs. study group

Table 4: Pulsatility index (PI) between the two groups (n = 50)

Group	Pre-treatment	2 weeks	4 weeks	6 weeks
Study	0.80±0.19	0.72±0.39	0.61±0.11※	0.53±0.23※
Control	0.78±0.21	0.75±0.36	0.70±0.16*#	0.68±0.16*#

※$P < 0.05$ within study group, #$p < 0.05$ within control group *$p < 0.05$ vs. study group

Table 5: Mean cerebral artery blood flow velocity (Vm) between the two groups (n=50)

Group	Pre-treatment	2 weeks	4 weeks	6 weeks
Study	46.8±1.8	50.3±1.8※	56±4.3※	61±4.0※
Control	45.7±2.4	49.9±5.4	54±4.2*#	59±3.4*#

※$P < 0.05$ compared within study group, #$p < 0.05$ compared within control group, *$p < 0.05$ vs. study group.

Table 6: Systolic values (Vs) between the two groups (n = 50)

Group	Pre-treatment	2 weeks	4 weeks	6 weeks
Study	79.0±7.8	81±7.7	85.5±6.3※	86.3±6.2※
Control	79.0±8.0	80±8.3	84.5±6.0#	84.0±5.8*#

※$P < 0.05$ within study group, #$p < 0.05$ within control group, *$p < 0.05$ vs. study group

Table 7: Comparison of the occurrence of adverse reactions in the two groups (n=50)

Group	Gastrointestinal reactions	Abnormal liver and kidney function	Headaches and dizziness	Itchy skin	Total incidence
Study	1(2.00)	1(2.00)	0	1(2.00)	3(6.00)
Control	2(4.00)	1(2.00)	1(2.00)	1(2.00)	5(10.00)

Hemodynamic indices

The PI values of both groups decreased after treatment. However, control group had significantly higher PI values compared to study group at 4th and 6th week after treatment ($p < 0.05$) (Table 4). Also, Vm and Vs increased after treatment (Table 5). Moreover, study group exhibited significantly smaller PI compared to control group, along with larger Vm and Vs values ($p < 0.05$). Also, as the disease progressed, disparity in PI and Vm values between the two groups became more significant at the 4th and 6th week ($p < 0.05$) (Table 6).

Incidence of adverse reactions

Total incidence rate of adverse reactions in study group was lower than that of control group, however the difference was not significantly significant ($p > 0.05$) (Table 7).

DISCUSSION

Etiology and treatment of Ischemic stroke, referred to as stroke in traditional medicine [6,7], is currently the subject of extensive research. The focus lies primarily on six aspects namely; wind, fire, phlegm, stasis, qi, and deficiency. Most clinical studies suggest that the interaction between wind, phlegm, and stasis is crucial during the acute stage of stroke; with phlegm and stasis being considered as the essence of this disease. Ginkgo biloba diterpene is a purely traditional Chinese medicine preparation derived mainly from *Ginkgo biloba* [9]. Its active component known as ginkgo biloba diterpene lactones (such as ginkgo biloba A, B, K), is obtained through purification [3]. The taste profile of these components is characterized by flatness along with hints of sweetness, bitterness, and astringency, and they belong to the lung and kidney meridians. *In vitro* studies have demonstrated that ginkgo diterpene lactones play significant roles in reducing blood-brain barrier permeability while also alleviating brain edema, improving brain metabolic disorders, and inhibiting neuronal apoptosis [10].

Currently, the primary treatment approach for an extended thrombolytic time window in elderly patients with acute ischemic stroke (AIS) is dual antiplatelet therapy. This involves administering a drug from the aspirin class and a drug belonging to the 2b3a receptor antagonist category to prevent platelet aggregation and treat cerebral infarction. However, traditional antiplatelet drugs like aspirin and clopidogrel have limitations such as slow onset of action, long half-life, resistance in some patients, and uncertain clinical efficacy in achieving effective treatment and prevention of AIS progression [11]. Recent studies have investigated the mechanism of action and pathways associated with ginkgolide diterpene glucosamine injection along with its active

components (such as ginkgolide A, B, K) through transcriptomic research.

These studies have demonstrated their ability to counteract oxygen-glucose deprivation by targeting key genes and signaling pathways involved in inflammation regulation, apoptosis inhibition, platelet activation modulation, among other biological processes. Downregulation of FcεRI, NOD-like receptors MAPK pathway VEGF signaling pathway interference with platelet activation phospholipase D signaling pathway may contribute to these effects [12]. Studies have indicated that combining dual antiplatelet therapy with ginkgolide diterpene glucosamine injection significantly reduces neurological deficits in AIS patients while enhancing their anti-inflammatory response and antioxidant capacity [13].

In this study, the study group utilized ginkgolide diterpene lactone glucosamine injection in combination with dual antibodies for treatment of acute ischemic stroke in elderly patients. Overall treatment efficacy was superior to that of control group, and this suggests that the efficacy may be attributed to the anti-inflammatory and neuroprotective effects of ginkgolide A, which is the active ingredient present in ginkgolide diterpene lactone glucosamine injection [14]. Doppler color ultrasound hemodynamic comparison revealed a decrease in beat index and an increase in mean cerebral arterial blood flow velocity as well as systolic values between both groups before and after treatment. This indicates a potential association with the anti-inflammatory, oxidative stress-controlling, and anti-platelet aggregation effects of ginkgolide B, along with the anti-ischemic brain injury effects of ginkgolide K [15]. Furthermore, this study demonstrated significant reduction in neurological deficits among patients in study group compared to control group at week 2, 4, and 6 of treatment.

This highlights the beneficial impact of ginkgolide on neurological function improvement among stroke patients. Additionally, at the 4^{th} and 6^{th} week of treatment, IADL scores along with PI and Vm values were significantly better in study group compared to control group. These findings indicate that combining ginkgo biloba diterpene glucosamine injection with dual antibodies for treating acute ischemic stroke in elderly patients effectively reduces oxidative damage and inflammation while promoting neurological function recovery and enhancing daily living abilities more effectively than dual antibodies alone.

Limitations of this study

The sample size was relatively small, which may limit the generalizability of the findings to a larger population, and the study only focused on elderly patients with acute ischemic stroke, so the results may not apply to younger patients or those with different types of strokes. Additionally, the study did not include a long-term follow-up to assess the sustainability of the observed effects. Also, the study did not investigate specific mechanisms underlying the observed outcomes. Lastly, the study relied on subjective measures such as neurological deficits and daily living abilities, which may introduce bias in the assessment.

CONCLUSION

Combination of Ginkgo biloba diterpene lactone glucosamine injection, aspirin enteric-coated tablets, and clopidogrel enhances neurological function, reduces stroke disability, and improves cerebral hemodynamic index. Further research is needed to elucidate the exact pathways involved in the observed outcomes.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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