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The Effect of Ginkgo Biloba Leaf Dropping Pill Combined with Butylphthalide Capsule on Cognitive Dysfunction in Patients after Acute Ischemic Stroke and Its Impact on Serum Cytokines

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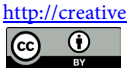

Abstract

Objective: To investigate the therapeutic effect of Ginkgo biloba extract dropping pills combined with butylphthalide capsules on cognitive dysfunction in patients after acute ischemic stroke (AIS) and its impact on serum cytokines CRP, IL-6, and Hcy. **Methods:** This study selected 76 patients with cognitive dysfunction after ischemic stroke who were hospitalized at Zhuji People's Hospital from January 2023 to January 2024. The patients were divided into two groups. The control group was treated with butylphthalide capsules, while the combination group received Ginkgo biloba extract dropping pills in addition to the treatment given to the control group. The neurological function, cognitive function, activities of daily living, and levels of serum cytokines CRP, IL-6, and Hcy were compared between the two groups after 1 month and 3 months of treatment. **Results:** The NIHSS scores, MMSE scores, ADL scores, and levels of CRP, IL-6, and Hcy in both groups showed statistically significant differences compared to before treatment ($P < 0.05$) after 1 month and 3 months of treatment. After 1 month and 3 months of treatment, the NIHSS scores in the combination group were significantly lower than those in the control group ($P < 0.05$), the MMSE scores and ADL scores in the combination group were significantly higher than those in the control group ($P < 0.05$), and the levels of CRP, IL-6, and Hcy in the combination group were significantly lower than those in the control group ($P < 0.05$). **Conclusion:** The combination of Ginkgo biloba extract dropping pills and butylphthalide capsules has a better therapeutic effect on cognitive dysfunction in patients after ischemic stroke. It can improve the neurological

function and cognitive function of patients, enhance their ability to perform daily activities, and reduce inflammatory responses.

Keywords

Acute Ischemic Stroke, Ginkgo Biloba Leaf Drop Pills, Butylphthalein, Cognitive Impairment

1. Introduction

Acute ischemic stroke (AIS) is the most common type of acute brain injury with a high incidence rate in China, mainly due to ischemia, hypoxia, and even necrosis of brain tissue around the infarcted vessel, which leads to related neurological dysfunction and seriously affects patients' cognitive function and cognitive status [1]. Therefore, it is very necessary to take active intervention measures for patients with AIS-induced cognitive dysfunction. Dibetes is a neuroprotective agent that can improve the activity of antioxidant enzymes in vivo and has been widely used in the pathogenesis of various ischemic stroke [2]. Ginkgo biloba drops are an effective traditional Chinese medicine preparation that can eliminate free radicals and enhance body immunity [3]. Based on this, this study will fully utilize the advantages of integrated traditional Chinese and Western medicine treatment, enhance their synergistic effect, explore an effective new treatment plan for cognitive dysfunction after AIS, and investigate the influence of Ginkgo biloba drops combined with dibetes on serum cytokines. The study will establish a database to provide new evidence-based basis for the clinical treatment of patients with AIS.

2. Methodology

2.1. Research Objects

The 76 AIS patients admitted to Zhuji People's Hospital from January 2023 to January 2024 were divided into two groups, with 38 patients in each group. Both clinical data were insignificant ($P > 0.05$) and were comparable, as shown in **Table 1**. This study was approved by the hospital ethics committee.

2.2. Inclusion and Exclusion Standards

Inclusion standards: 1) met the diagnostic criteria for stroke and for post-stroke cognitive dysfunction [4]; 2) the age was 65 years; 3) the patients and their families were aware of the study and signed informed consent.

Exclusion standards: 1) patients allergic to the study drug; 2) previous cognitive dysfunction; 3) traumatic brain injury and Parkinson's syndrome and other diseases affecting cognitive function; 4) severe hepatic and renal dysfunction; 5) severe mental disorders; 6) brain tumors or other malignant tumors; 7) To receive thrombolytic therapy.

2.3. Treatment Methods

In both groups, antitherapy, blood pressure control, blood glucose lowering and lipid regulation, the patients should sleep regularly, do more physical exercise, and maintain a healthy diet and lifestyle to promote microcirculation and anti-platelet aggregation. The control group took oral butylphthalide soft capsules (produced by Enbipu Pharmaceutical Co., Ltd., 3 times/d, 0.2 g/times), and the combined group took oral ginkgo biloba drop pills (produced by Zhejiang Wanbang Pharmaceutical Co., Ltd., 3 times/d, 5 pills/time, 60 mg/pill). Both groups were administered continuously for 3 months.

2.4. Index Observation Test

2.4.1. National Institutes of Health Stroke Scale (NIHSS)

The NIHSS score was in the range of 0 to 42 points, which was divided into 11 items, including upper limb motor function, lower limb motor function, language, visual field, and limb coordination function. A higher score indicates a more severe neurological deficit.

2.4.2. Cognitive Function Scale (MMSE)

It is divided into directional force, computing force, attention, delayed recall, immediate memory and other aspects. The score is in the range of 0 to 30 points, and the higher the score indicates a better cognitive ability.

2.4.3. Daily Life Scale (ADL)

The score of ADL is from 0 to 100, 0 - 20 refers to a state of life can not take care of themselves, 21 - 40 refers to a state of life needs great help, 41 - 60 refers to a state of life needs help, 61 - 80 is a state that can basically take care of themselves, 81 - 100 is a normal way of life.

2.4.4. Cytokines

C-reactive protein (CRP), interleukin 6 (IL-6) and homocysteine (Hcyn) levels were measured by enzyme-linked immunosorbent method before and 1 month and 3 months after treatment.

2.5. Statistical Process

The present data were collated, counted and analyzed using SPSS 26.0 software. All measurement data were tested by normal distribution. Normal distribution data are represented by (± s), independent t-test and paired t-test; non-normal distributed data are represented by M (IQR), Mann-Whitney test and Wilcoxon test, N and chi-square test. Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Comparison of Basic Patient Information between the Two Groups

Table 1 shows that the age of both groups was tested by normal distribution

(Shapiro-Wilk combination = 0.939, P combination = 0.038 < 0.05; Shapiro-Wilk control = 0.972, P control = 0.436 > 0.05), using the Mann-Whiteny test, Z = −0.406, P = 0.685 > 0.05; age > culture, gender, hypertension, diabetes P > 0.05 in the two groups.

Table 1. Basic information of patients in the two groups.

Group	Age	Education Level			sex		hypertension		diabetes	
		illiterate	primary school	junior middle school	male	female	no	yes	no	yes
Joint group	72.5 (61.75, 83)	5	24	9	25	13	6	32	30	8
control group	73 (63.25, 79.5)	0	29	9	19	19	5	33	27	11
Z/χ2	−0.406		5.472		1.943		0.106		0.632	
P	0.685		0.065		0.163		0.744		0.427	

3.2. Comparison of the NIHSS Scores between the Two Patient Groups

Non-normal menstrual distribution (Shapiro-Wilk combination = 0.901, 0.853, 0.781, P joint = 0.003, 0.000, and 0.000 < 0.05; Shapiro-Wilk control = 0.804, 0.826, 0.828, P control = 0.000, 0.000, and 0.000 < 0.05), Therefore, the comparison of NIHSS scores between the two groups was performed by Mann-Whiteny test, Z = −0.183, −2.370, −3.102, respectively, P = 0.854, 0.018, 0.002, Table 2 suggested that there was no significant difference in NIHSS scores between the two groups (P > 0.05), The NIHSS score in the combined group was significantly lower than that of the control group (P < 0.05). The difference between NIHSS scores at 1 month and March and before the Wilcoxon test (P < 0.05).

Table 2. Comparison of NIHSS scores between two groups of patients.

Group	n	Before Treatment (median, IQR)	1 Month After Treatment (median, IQR)	3 Months After Treatment (median, IQR)
Combination	38	3 (2, 5.25)	1 (0, 3)*	0 (0, 2)*
Control	38	3 (1.75, 4.25)	3 (0, 4)*	3 (0, 4)*
Z		−0.183	−2.370	−3.102
P		0.854	0.018	0.002

Note: *P < 0.05.

3.3. Comparison of the MMSE Scores between the Two Patient Groups

Distribution of MMSE scores before, January and March (Shapiro-Wilk combination = 0.949, 0.938, 0.896, P joint = 0.080, 0.037, and 0.002; Shapiro-Wilk

control = 0.973, 0.966, 0.960, P control = 0.467, 0.302, and 0.185), Therefore, the MMSE scores of the two groups were compared by the Mann-Whiteny test, Z = −0.052, −2.380, −3.133, respectively, P = 0.958, 0.017, 0.002, Table 3 suggested that there was no significant difference in MMSE scores between the two groups (P > 0.05), The MMSE score was significantly higher than that of the control group (P < 0.05). The difference between MMSE scores between January and March and Wilcoxon test before treatment (P < 0.05).

Table 3. Comparison of the MMSE scores between the two patient groups.

Group	n	Before Treatment (median, IQR)	1 Month After Treatment (median, IQR)	3 Months After Treatment (median, IQR)
Combination	38	20 (17.75, 22)	22 (20, 24)*	22 (21, 25)*
Control	38	20 (17, 22)	20 (17.75, 22)*	20.5 (17.75, 22)*
Z		−0.052	−2.380	−3.133
P		0.958	0.017	0.002

Note: *P < 0.05.

3.4. Comparison of the ADL Scores between the Two Patient Groups

Table 4 indicates that the normal distribution of ADL scores before, 1 month and 3 months (Shapiro-Wilk combination = 0.962, 0.969, 0.950, P joint = 0.218, 0.377, and 0.088; Shapiro-Wilk control = 0.954, 0.948, 0.949, P control = 0.120, 0.075, 0.084), Therefore, the two groups were compared by independent t-test, And t = 1.523, 2.404, and 2.515, respectively, P = 0.132, 0.019, 0.014, There was no significant difference in ADL scores between the two groups (P > 0.05), The ADL score in the combination group was significantly higher than that in the control group (P < 0.05).

The ADL scores were significant from the paired t-test (P < 0.05).

Table 4. Comparison of the ADL scores between the two patient groups.

Group	n	Before Treatment (mean ± SD)	1 Month After Treatment (mean ± SD)	3 Months After Treatment (mean ± SD)
Combination	38	71.18 ± 16.78	75.79 ± 15.18*	79.08 ± 14.04*
Control	38	64.34 ± 22.03	65.39 ± 21.91*	68.82 ± 20.87*
t		1.523	2.404	2.515
P		0.132	0.019	0.014

Note: *P < 0.05.

3.5. Comparison of Cytokine Levels in the Two Patient Groups

Normal distribution of CRP before, 1 month and March (Shapiro-Wilk combination = 0.952, 0.959, 0.965, P joint = 0.105, 0.173, and 0.275; Shapiro-Wilk control = 0.987, 0.973, 0.984, P control = 0.932, 0.464, 0.837), Therefore, the CRP contrast between the two patient groups was performed using an independent t-test, And t = −1.320, −5.241, and −9.385, respectively, P = 0.191, <0.001, <0.001, Show that there was no significant difference in CRP contrast between the two groups (P > 0.05), CRP was significantly lower in 1 month and 3 month than in the control group (P < 0.05).

Normal distribution of IL-6 before, 1 month and 3 months in both groups (Shapiro-Wilk combination = 0.976, 0.955, 0.985, P joint = 0.574, 0.134, 0.894; Shapiro-Wilk control = 0.981, 0.973, 0.966, P control = 0.736, 0.481, and 0.288), Thus the IL-6 contrast between both groups was performed by independent t-test, And t = 0.233, −6.714, and −7.977, respectively, P = 0.816, <0.001, <0.001, There indicates no significant difference in IL-6 contrast between the two groups (P > 0.05), IL-6 was significantly lower than the control group (P < 0.05).

Normal distribution of Hcy before, January, and March (Shapiro-Wilk combination = 0.988, 0.971, 0.963, P joint = 0.959, 0.416, and 0.234; Shapiro-Wilk control = 0.973, 0.966, 0.955, P control = 0.470, 0.289, and 0.130), Therefore, the two groups were tested by independent t-test, And t = 0.427, −7.329, and −12.602, respectively, P = 0.671, <0.001, <0.001, show that there was no significant difference in Hcy contrast between the two groups (P > 0.05), Hcy was significantly lower than that in the control group (P < 0.05).

CRP, IL-6, Hcy and paired t-test before treatment (P < 0.05):

Table 5 suggests significant reductions in CRP, IL-6 and Hcy levels in both groups at 1 and 3 months after treatment. However, combined treatment with ginkgo biloba drip leaves and butylphthalide capsules significantly reduced these inflammatory and metabolic markers compared with control subjects. These results suggest that the combination therapy is more effective in reducing systemic inflammatory and metabolic risk factors in patients with acute ischemic stroke.

Table 5. Comparison of cytokine levels between two groups of patients.

C-Reactive Protein (CRP)				
Group	n	Before Treatment (mean ± SD)	1 Month After Treatment (mean ± SD)	3 Months After Treatment (mean ± SD)
Combination	38	11.85 ± 2.51	4.84 ± 1.30*	2.69 ± 0.89*
Control	38	12.65 ± 2.75	6.55 ± 1.53*	4.57 ± 0.86*
t		−1.320	−5.241	−9.385
P		0.191	<0.001	<0.001

Continued

Interleukin-6 (IL-6)				
Group	n	Before Treatment (mean ± SD)	1 Month After Treatment (mean ± SD)	3 Months After Treatment (mean ± SD)
Combination	38	18.25 ± 2.40	9.73 ± 1.63*	6.27 ± 1.21*
Control	38	18.13 ± 2.03	12.04 ± 1.35*	8.66 ± 1.39*
t		0.233	−6.714	−7.977
P		0.816	<0.001	<0.001
Homocysteine (Hcy)				
Group	n	Before Treatment (mean ± SD)	1 Month After Treatment (mean ± SD)	3 Months After Treatment (mean ± SD)
Combination	38	23.36 ± 4.14	12.70 ± 2.23*	8.98 ± 1.14*
Control	38	22.99 ± 3.18	16.53 ± 2.33*	12.96 ± 1.58*
t		0.427	−7.329	−12.602
P		0.671	<0.001	<0.001

Note: Compared to before treatment, *P < 0.05.

4. Discussions

The latest data report that the lifelong risk of stroke in China has reached 40%, ranking first in the world. The incidence of stroke is increasing year by year, and the disease burden is increasing. The proportion of acute ischemic stroke (AIS) patients in the total number of cerebrovascular disease patients in China is about 70% [5] [6]. Studies have shown that about half of the stroke survivors have some cognitive impairment, and this impairment has a great impact on the quality of life and prognosis of patients in [7] [8]. The core reason for the significant decrease in the quality of life of patients with acute ischemic stroke (Acute ischemic stroke-induced cognitive impairment, AIS-ICI) is the obvious impact of on multiple life aspects such as social interaction, physical activity and emotional state [9]. Therefore, looking for an effective therapy has an important practical significance for the diagnosis and treatment of the disease.

In this study, we found that compound Ginkgo biloba dropping pills and butyphthalin capsules could significantly improve the NIHSS score of AIS-ICI patients and improve their MMSE and daily living ability. The main components of ginkgo biloba dropping pills are ginkgo biloba extract, the active ingredients are altinactone, ginkolide and ginkgo flavonoids, which can play the role of scavenging free radicals, antioxidation, is a natural platelet activating factor receptor antagonist [10]. Buryphthalide is a common AIS treatment, which reduces the edema in cerebral ischemic area, promotes the edema regression of cerebral

infarction site, protects the nerve cells in the ischemic position, and significantly improves the nerve function [11]; Ginkgo biloba dropping pill has the effect of reducing cerebral artery resistance, promoting blood supply, promoting brain blood circulation, and protects the structure and function of brain cells [12]. Modern pharmacological studies show that Ginkgo biloba extract can improve dementia symptoms, delay the development of dementia and improve their daily activities, and is a very safe drug [13]. Ginkgo biloba drop pill and butyphthalin capsule play a synergistic role to promote the recovery of patients 'neural function and cognitive function, and then improve the patient's daily living ability. Some scholars used buphthalin combined with Ginkgo biloba drop pills to treat cognitive impairment in ischemic stroke patients. The results found that the combination of the two could significantly reduce the NIHSS score and improve the MoCA score, which is similar to the results of this study [14].

Inflammatory response is closely related to the development of AIS-ICI. IL-6 is an important inflammatory factor that increases IL-6 levels after stroke, thus accelerating the inflammatory response to [15]. Hyperhomocysteine (Hcy) can induce the production of a large number of oxygen free radicals, trigger inflammatory reactions, and cause the damage and apoptosis of vascular endothelial cells [16]. Increasing Hcy level is proved to be an independent risk factor for stroke, and stroke can lead to cognitive dysfunction [17]. C-reactive protein (CRP) is a common inflammatory factor that can aggravate brain cell injury [18]. Studies show that elevated CRP levels are associated with a wide spectrum of brain dysfunction, with the most strongly associated with general intellectual ability, abstract reasoning ability [19]. CRP levels negatively correlated with the composite score of executive function and processing speed [20] and predicted poor memory performance [21]. This study found that the combination of Chinese medicine compound Ginkgo biloba dropping pill and butyphthalide could significantly reduce the inflammation index of AIS, suggesting that the combination of the two has certain clinical application value. The reasons are as follows: It can relieve the spasm of vascular tissue, eliminate free radicals, inhibit inflammatory reactions, and protect the blood vessels and nerves; the flavonoids in the key activating proteins and transcription factors block the downstream signaling by exerting anti-inflammatory effects [22]; Ginkgo terpenoids include Ginkgo golides A, B, C, J, K, M and terpene lipids. Ginkgo terpenoids are a natural inhibitor of platelet activating factor (PAF) receptor, which can inhibit platelet aggregation induced by PAF, while PAF can affect inflammatory response by activating signaling pathways such as MAPK and PI3K [23]. Some studies have shown that ginkgolide K can prevent the loss of myelin, hinder the activation of microglia, and downregulate the expression of pro-inflammatory cytokine IL-6 [24]. The reason may be that ginkgo tablet has a protective effect on neurons, can inhibit surrounding cell apoptosis, help to reduce the inflammatory response in patients with post-stroke cognitive dysfunction, and has a certain nutritional nerve effect, so as to repair the damaged neuron [25].

5. Conclusion

The combination of Ginkgo biloba leaf dropping pills and butylphthalide capsules is more effective in treating cognitive dysfunction in AIS patients compared to butylphthalide alone. This combined therapy improves neurological and cognitive functions, daily living activities, and reduces inflammatory responses, providing a promising treatment strategy for AIS-induced cognitive dysfunction.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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