Randomized Controlled Trial of Huanglian Jiedu Decoction in Improving Cognitive Function and Neuroinflammation in Patients with Vascular Dementia

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Abstract: Background and Objective: Huanglian Jiedu Decoction (HLJD) is commonly used for patients with vascular dementia (VaD) in China. Objective: To evaluate the clinical efficacy of HLJD through a randomized controlled trial (RCT). Methods: The control group received Donepezil Hydrochloride tablets, while the experimental group received Donepezil Hydrochloride tablets combined with HLJD. Both groups were treated for 8 weeks. The clinical efficacy and incidence of adverse reactions were compared between the two groups. The MMSE and MoCA scales were used to assess cognitive function. Inflammatory cytokines IL-6, IL-1β, TNF-α, and hs-CRP were also compared. Results: After treatment, the effective rate in the control group was 28.13%, while the effective rate in the experimental group was 56.67%, significantly higher than that in the control group ($P<0.05$). After treatment, the MMSE and MoCA scores of both groups increased significantly compared to baseline ($P<0.01$). The MMSE score in the experimental group was higher than that in the control group ($P<0.01$), and the MoCA score in the experimental group was also higher than that in the control group ($P<0.05$). After treatment, the levels of inflammatory cytokines IL-6, IL-1β, TNF-α, and hs-CRP in both groups decreased significantly compared to baseline ($P<0.01$). The experimental group showed better results in reducing the levels of these inflammatory cytokines than the control group ($P<0.01$). Additionally, the total clinical efficacy rate in the experimental group was 96.00%, higher than the 82.00% in the control group ($P<0.05$). Conclusion: HLJD combined with Donepezil can provide symptomatic benefits for patients with mild to moderate VaD.

***Keywords*:** Vascular dementia, Huanglian Jiedu Decoction, Randomized Controlled, TrialInflammatory factors, Cognitive function

1. Background

Vascular dementia (VaD) is a major cause of dementia after Alzheimer's disease [1]. As global population aging intensifies, the prevalence of VaD continues to rise worldwide, exerting significant economic pressure on the global economy[2, 3]. Currently, Western medicine lacks specific drugs for VaD, and long-term use of Western pharmaceuticals can cause severe side effects. Conversely, traditional Chinese medicine formulas can intervene in the complex pathogenesis of VaD through multi-target, multi-pathway, and multi-system approaches, with minimal toxic and side effects, and have achieved remarkable therapeutic effects.

HLJD is a traditional herbal medicine that meets this need. Multiple studies have confirmed that HLJD and its active components can improve dementia memory and psychiatric behavioral symptoms, but the mechanism of action has not yet been clarified [10]. This study aims to further explore the impact of HLJD on cognitive and inflammatory indicators in patients with mild to moderate VaD.

2. Experiment

2.1 Participants

2.1.1 Inclusion criteria

Patients aged 45-85 years and eligible with the diagnosis of probable or suspected VaD had a duration of 6 months[4]. VaD diagnosis considered clinical and radiographic evidence of cerebrovascular disease, evidence of ischemic stroke on MRI[5]. Other inclusion criteria were as follows: (1) MMSE score of 14 to 26; (2) MoCA scale score <26; (3) Clinical dementia rating scale CDR = 1.0 and 2.0; (4) those who signed informed consent; and (5) stable caregivers.

2.1.2 Exclusion criteria

(1) Medical history of other types of dementia, Such as Alzheimer's disease, Parkinson's disease dementia, etc.;[13] The acute phase of cerebral hemorrhage or subarachnoid hemorrhage; Hypothyroidism; Drug or alcohol abuse; History of epilepsy; History of myasthenia gravis; (2) Severe cardiovascular disease ; (3) Severe hepatic or renal dysfunction ; (4) No history of allergy to any type of drug used in this study; (5) No other TCM preparations with educational effect and heat-clearing and detoxification effect during the study, Such as ginkgo biloba leaf preparation, Qingkailing injection, Angong Niuhuang pill, etc.; (6) Do not use other western medicines with improved cognition.

2.2 Research on drug

The control group was given donepezil hydrochloride (Chongqing Zhien Pharmaceutical Co., LTD., national approval: H20010723, specification 5mg 7 tablets / box), the dosage of 5mg, once a day, taken before bed. Test group: Donepezil hydrochloride and copanjiedu soup.

Huanglian detoxification soup: Huanglian 9g, Scutellaria baicalensis 6g, Huangbai 6g, Gardenia 9g, Traditional Chinese medicine granule preparation (one side Chinese medicine granule in Guangzhou).

2.3 Efficacy assessment

2.3.1 Traditional Chinese medicine syndrome

Before and after 8 weeks of treatment, the clinical efficacy of patients was evaluated according to the TCM syndrome integral scale.

2.3.2 Cognitive function

The MMSE scale and the MoCA scale were evaluated for improved cognitive function.

2.3.3 Inflammatory factor indicators

The levels of IL-6, IL-1β, TNF-α, and hs-CRP were tested in the blood before and after 8 weeks.

2.4 Safety assessment

(1) Vital signs tests; (2) ECG; (3) laboratory parameters including complete blood count, urine routine, fecal routine and occult blood tests, liver and kidney function, coagulation; (4) any possible adverse events, including type of adverse events, timing, duration, treatment, and assessment of correlation between the drug tested, and adverse events ; the severity of adverse events (mild, moderate and severe) must be assessed.

2.5 Randomization

According to the computer-generated random numbers, they were divided into trial group and control group.

2.6 Statistical treatment

Clinically collected data were entered into an electronic computer to create the database and perform statistical analysis of the data using SPSS26.0.

3. Result

A total of 62 patients followed the study protocol, including 32 patients in the control group and 30 patients in the test group. The experimental flow is shown in Figure 1.

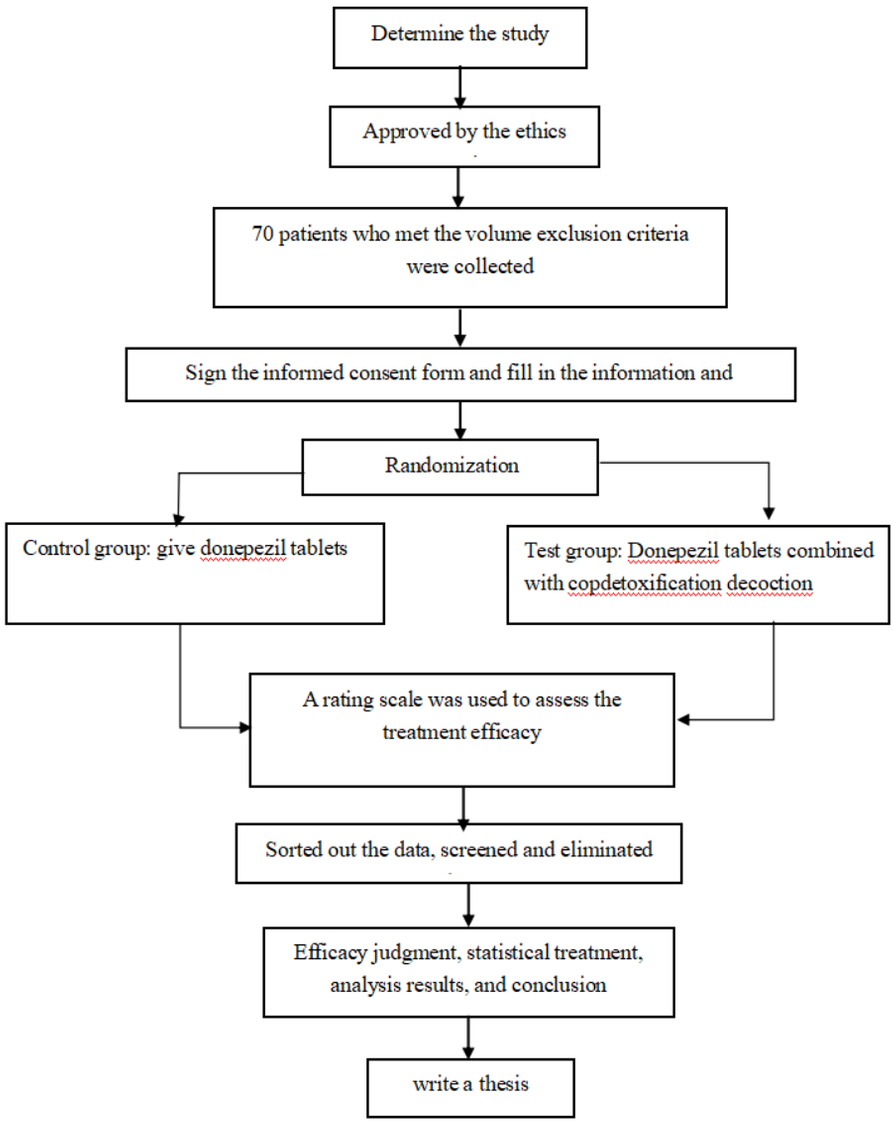

Figure 1. Technical roadmap

3.1 Comparison of the baseline data before treatment

After analysis by χ2 test, P> 0.05, gender, age, education, disease duration, and dementia, thus could be compared.(See Table 1)

Table 1. Comparison of baseline data

Group	Control group (32)	Test team (30)	P
Man	14	16	0.45
Woman	18	16	
Age (year)	69.50±5.18	69.76±5.29	0.842
Illiteracy	13	12	0.45
Primary school	12	8	
Junior high school and above	7	10	
Course of disease	5.17±0.45	5.43±6.53	0.460
Mild	18	16	0.818
Moderate	14	14	
Serious	0	0	

3.2 Pretherapy Comparison of cognitive function

After analysis by independent sample t-test, P> 0.05, not statistically significant, and thus comparable.(See Table 2)

Table 2. Comparison of cognitive function

Group	Control group (32)	Test team (30)	P
MMSE (Mean ± standard deviation)	15.22±2.71	16.20±2.23	0.126
MoCA (Mean ± standard deviation)	14.72±2.95	15.20±2.58	0.612

3.3 Pretherapy Comparison of TCM syndrome points

P>0.05, not statistically significant and comparable by independent sample t-test.(See Table 3)

Table 3. Comparison of Traditional Chinese Medicine Syndrome Scores

Group	n	Mean ± standard deviation	P
Control group	32	16.63±3.22	0.836
Test team	30	16.47±2.74	

3.4 Pretherapy Comparison of inflammatory factors

P> 0.05, not statistically significant and comparable.(See Table 9 and Table 10)

Table 4. Comparison of IL-6, I-1β, NF-α and hs-CRP Levels

Group	Control group (32)	Test team (30)	P
IL-6	17.53±1.40	18.31±1.78	0.059
IL-1β	0.25±0.02	0.15±0.03	0.912
TN F-α	3.62±0.47	3.40±0.39	0.06
hs-CRP	8.91±1.85	9.33±2.62	0.467

4. Evaluation of efficacy indicators

4.1 Efficacy evaluation of TCM

After treatment, the TCM symptoms of both groups improved (P <0.05), and the treatment effect was better than that of the control group (P <0.01).(See Table 5)

Table 5. Comparison of TCM syndrome points

Group	Pretherapy	Post-treatment
Control group	16.63±3.22	12.06±4.38*
Test team	16.47±2.74	9.07±3.29*▲

Note: *Intragroup comparison is indicated, P<0.05;▲comparison among groups, P<0.01.

After treatment, the overall response rate was 28.13% in the control group and 56.67% in the test group. The rank sum test showed the efficacy in the test group (P <0.05).(See Table 6)

Table 6. Comparison of Therapeutic Effects on Traditional Chinese Medicine Syndrome

Group	Efficacy of TCM symptoms			Total effective rate
	Excellence	Effective	Be of no effect	
control group	1	7	24	28.13%
test team	3	14	10	56.67%

Note: P <0.05 for the comparison between the two groups.

4.2 Comparison of the cognitive function

By paired t-test, cognitive function improved in both groups after treatment (P <0.01); the difference was statistically significant, and the test group was better able to improve cognition than the control group (P <0.01).(See Table 7)

Table 7. Comparison of MMSE scale scores before and after treatment

Group	Pretherapy	Post-treatment
Control group	15.22±2.71	18.63±1.81*
Test team	16.20±2.23	19.87±2.35*▲

Note: *Intragroup comparison is indicated, P<0.01;▲comparison among groups, P<0.01.

After paired t-test, cognitive improvement in both groups after treatment (P <0.01); the control group (P <0.05).(See Table 8)

Table 8. Comparison of MoCA scale scores before and after treatment

Group	Pretherapy	Post-treatment
Control group	14.72±2.95	17.91±2.5*
Test team	15.20±2.58	18.17±2.57*#

Note:*Within-group comparisons,P<0.01;#comparison among groups,P<0.05.

After paired t-test analysis, comparison among groups, P <0.01, indicating that the level of post-treatment inflammatory factor decreased; P<0.01, indicating that test team was more effective in inhibiting inflammatory response and reducing inflammatory factor level.(See Table 9)

Table 9. Comparison of IL-6, IL-1β, TNF-α, and hs-CRP levels after treatment

Group	IL-6	IL-1β	TNF-α	hs-CRP
Control group	14.1±1.14*	0.22±0.02*	3.12±0.41*	5.68±2.19*
Test team	8.02±1.28*▲	0.19±0.01*▲	2.10±0.31*▲	3.21±1.74*▲

Note: * indicates within-group comparison, P <0.01; ▲, P <0.01

4.3 Safety evaluation

No adverse reactions occurred in either group during the trial, and the treatment process was safe and reliable.

5. Discussion

Researchers have discovered that inflammatory mechanisms are key factors leading to VaD[7].The ischemia and hypoxia caused by long-term chronic hypoperfusion can excessively activate neuroinflammation,which can initiate or exacerbate the occurrence and development of VaD[8].A number of clinical studies and animal experiments[9-11]have found that Huanglian detoxification soup can improve the cognitive function of VaD patients. It was found that if Coptis chinensis detoxification soup was used in the acute stage of ischemic stroke, the cognitive function and behavioral impairment[12] of multiple cerebral infarction artery model rats could be alleviated by reducing inflammatory factors. In addition, Coptis chinensis detoxification soup can also inhibit intestinal flora disorders and the accumulation of A, reduce neuroinflammatory response, and improve cognitive function[13]. In addition,Flavonones, the active ingredients in Scutellaria baicalensis and cypress, can enhance cognitive[14]; the active ingredients in gardenia, such as glycoside and glycoside, have the functions to reduce inflammation and protect brain tissue[10]; berberine improves the spatial memory damage in senile rats[15].

In this study, no adverse reactions were found in the treatment of VaD and the safety was good.

6. Conclusion

In conclusion, the decoction can effectively improve the clinical symptoms of patients with VaD, improve the cognitive function of patients, reduce the level of inflammatory factors, and improve the quality of daily life of patients.

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