Tropical Journal of Pharmaceutical Research April 2022; 21 (4): 887-892
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i4.28

Original Research Article

Effect of cognitive rehabilitation training combined with butylphthalide soft capsules and ginkgo-leaf tablets on patients with mild Alzheimer's disease

Yuanyuan Zhong[1], Jiaoping Chen[2]*
[1]Ward 2, Department of Internal Medicine, Zhuji Central Hospital of Zhejiang Province, [2]Department of Internal Neurology, Zhuji Traditional Chinese Medical Hospital of Zhejiang Province, Shaoxing 311800, China

For correspondence:* ***Email:* *ppnh55@163.com*

Sent for review: 7 October 2021 *Revised accepted: 27 March 2022*

Abstract

Purpose: *To study the impact of a combination of cognitive rehabilitation training, butylphthalide soft capsules and ginkgo-leaf tablets on patients with mild Alzheimer's disease (AD).*
Methods: *One hundred and twenty-eight (128) mild AD patients were randomly assigned to medication treatment group (MT group, n = 64) and joint training group (JT group, n = 64). Both groups were treated with butylphthalide soft capsules and ginkgo-leaf tablets, while the JT group additionally received cognitive rehabilitation training. Therapeutic effects and adverse drug reactionsin the two groups were assessed.*
Results: *Total effectiveness was significantly higher in JT patients (84.38 %) than in MT patients (60.94 %; χ^2 = 8.9320). After treatment, Mini-Mental State Exam (MMSE), Activity of Daily Living (ADL) and ADAS-cog scores in the JT group were significantly better than those in the MT group, ($p < 0.05$). There were significantly lower plasma NO, serum VEGF and MDA levels in JT patients than in MT patients. CRP and Hcy levels were markedly lower in JT than in MT patients. The incidence of adverse reactions in both groups was comparable ($p > 0.05$).*
Conclusion: *Rehabilitation training in combination with butylphthalide soft capsule and ginkgo-leaf tablets produce significant therapeutic impact on mild AD patients. The combination therapy delays cognitive decline and memory loss in AD patients, improves their serological indicators, and lowers the incidence of adverse reactions.*

Keywords: *Cognitive rehabilitation training, Butylphthalide soft capsules, Ginkgo-leaf tablets, Mild Alzheimer's disease*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Mild Alzheimer's disease (AD) is a degenerative disease of the nervous system characterized by memory impairment, changes in behavioral pattern, executive dysfunction and other aspects of global dementia [1,2]. Investigations have found that the population of AD patients in China exceeds 10 million, with AD incidence reaching 0.7 %. At present, the pathogenesis of AD is not yet clearly understood. Its clinical treatment focuses mainly on delaying memory loss and

intellectual deterioration in patients, as well as improving their cognitive ability and activities of daily living [3,4]. Ginkgo-leaf tablet is a Chinese patent medicine consisting of ginkgo biloba extract. It activates blood circulation, removes blood stasis and *dredges the collaterals* [5]. Butylphthalide soft capsule is a prescription drug for the treatment of mild and moderate acute ischemic stroke. Both drugs improve blood perfusion and energy metabolism in brain tissue, and they produce good therapeutic effect in the clinical treatment of patients with cerebral infarction. Some investigations have confirmed that the combination of butylphthalide soft capsules and ginkgo-leaf tablets produced relatively ideal therapeutic effect by improving the cognitive function and slowing down the memory loss of AD patients [6]. It has been reported that cognitive function training such as memory training and reasoning training can effectively delay the conditions of AD patients, and effectively improve their cognitive function and memory ability. In this study, the clinical effect of combined use of cognitive rehabilitation training and butylphthalide soft capsules and ginkgo-leaf tablets was determined in 128 mild AD patients.

METHODS

General patient information

The study followed the guidelines of Declaration of Helsinki [7]. The 128 mild AD patients were randomly assigned to medication treatment (MT) group (n = 64) and joint training (JT) group (n = 64). No statistically significant differences were observed in gender, age, disease course, MMSE score, ADAS-cog score, Clinical Dementia Rating (CDR) scale, and Activity of Daily Living (ADL) score on comparison of both groups.

Inclusion/exclusion parameters

Inclusion parameters

Subjects included were those who were diagnosed with AD via reference to the *Diagnostic and Statistical Manual of Mental Disorders* [8], patients aged 50 - 84 years, mild AD (with ADL scores > 26 points), patients with educational level above primary school, patients with stable conditions and clear consciousness, those who had family members to supervise their adherence to the drugs, and patients with no severe organic diseases in heart, lung and kidney.

Exclusion criteria

Patients with a history of brain surgery and brain trauma, those with poor cooperation, patients with mental diseases such as schizophrenia and depression, and patients with drug dependence, were excluded.

The study was approved by the Ethics Committee of Zhuji Central Hospital of Zhejiang Province (approval no. 20171039), and followed international guidelines for human studies. Written and signed informed consents were obtained from the patients and/or guardians.

Treatments

Patients in the two groups were treated with butylphthalide soft capsules and ginkgo-leaf tablets. The patients orally took butylphthalide soft capsules (approval number: H20050299; CSPC NBP Pharmaceutical Co. Ltd.) on an empty stomach (2 capsules 3 times/day). Ginkgo-leaf tablets (National Medical Products Administration approval number: Z20027949; Yangtze River Pharmaceutical Group Co. Ltd.) were administered orally (2 tablets 2 times/day) and were taken continuously for 6 months.

In addition, the JT group patients received cognitive rehabilitation training. The main components comprised the following:

(A) *Orientation training:* With clocks hung in patients' movement areas, patients' orientation was enhanced through recognition of time, memorizing places and identifying photos.

Table 1: General data for both groups

Parameter		MT group (n=64)	JT group (n=64)	χ^2/t	*P*-value
Sex	Male	31	33	0.1250	>0.05
	Female	33	31		
Age (years)		68.74±5.85	69.02±5.96	0.268	>0.05
Disease course (years)		2.69±0.85	2.85±0.92	0.309	>0.05
MMSE (points)		16.86±2.04	16.95±1.96	0.800	>0.05
ADAS-cog (points)		38.74±3.86	38.82±3.73	0.881	>0.05
CDR (points)		2.25±0.79	2.23±0.82	0.889	>0.05
ADL (points)		36.87±2.35	37.14±2.14	0.498	>0.05

(B) *Thought training:* Patients were allowed to arrange, classify or solve puzzles, or number cards regularly.

(C) *Memory training:* Some stuff or pictures familiar to patients were chosen for them to recognize as a way of carrying out the memory training. Reading newspapers or watching TV enabled patients to understand and remember news events. Besides, for memory training, patients were asked to recall some detailed plots after watching TV plays.

(D) *Intelligence training*: The stimulus-response method in vision and hearing was adopted. This involved comparing the similarities and differences between two pictures, answering detailed questions after listening to stories, and finding out the designated symbols in cards so as to improve patients' discernment and memory ability.

(E) *Activity of Daily Living (ADL) training*: Family members and nursing staff recorded patients' daily activities, supervised their regular work and rest, placed commonly used items such as wallets and keys in a fixed and conspicuous place, and taught them to dress, eat, sweep the floor, clean the table, and other things within their ability so as to improve their self-care ability. Patients received cognitive rehabilitation training for 45 min twice a day.

Evaluation of parameters

The therapeutic effect on AD was evaluated according to the *Guidelines for Clinical Research of Traditional Chinese Drug Research* [9]. If the Mini-Mental State Exam (MMSE) score increased by more than 20 %, the treatment was markedly effective, and if the MMSE score increased by 10 - 20 %, the treatment was effective. However, if the MMSE score increased by less than 10 %, the treatment was ineffective. The total treatment effectiveness was obtained from the formula in Eq 1.

$$TE = (ME + E)/T \times 100\ \% \quad \text{..... (1)}$$

where TE = total treatment effectiveness; ME = number of markedly effective cases; E = number of effective cases; T = total number of cases.

The MMSE score was used to evaluate patients' orientation, memory and intelligence. The full score was 30 points, and higher scores indicated better cognitive levels [10]. The ADL score [11] was used to evaluate the patients' daily living ability, with a total score of 100 points. Higher scores indicated better self-care ability. The ADAS-cog score [12] was employed for assessment of patients' cognitive function such as memory and language, with a total score of 75 points. Lower scores indicated lower cognitive impairment.

Venous blood (5 mL) was collected before and after treatment, and plasma was obtained after centrifugation. Then, plasma nitric oxide (NO) level was determined using nitrate reductase assay. Venous blood (3 mL) was collected before and after treatment, into test tubes and blood coagulation was allowed to take place under low temperature. After coagulation, the supernatant (serum) was carefully aspirated and stored in other clean containers. Then, ELISA method was used to determine serum vascular endothelial growth factor (VEGF) level, while thiobarbituric acid (TBA) method was adopted to determine malondialdehyde (MDA). Serum C-reactive protein (CRP) was determined with nephelometry immunoassay, while homocysteine (Hcy) was determined using enzymatic cycling assay. Adverse reactions during treatment were recorded.

Statistical analysis

The results were subjected to analysis using SPSS 19.0. Measured data are presented as mean

± SD; two-group comparison was done with *t*-test. Counted data are presented as numbers and percentages. They were compared using chi square test. Values of $p < 0.05$ indicated significant differences.

RESULTS

Treatment effects

Table 2 shows that the total effectiveness in JT patients (84.38 %) was significantly higher than that in MT patients (60.94 %, $p < 0.05$, $\chi^2 = 8.9320$).

Effect of treatments on MMSE, ADL and ADAS-cog scores

Before treatment, MMSE, ADL and ADAS-cog scores were comparable in both groups. However, post-treatment scores for MMSE, ADL and ADAS-cog were markedly better in JT patients than in MT patients (Figure 1). As shown in Figure 1, prior to treatment, MMSE, ADL and ADAS-cog scores were comparable in both groups, but there were improvements in post-treatment MMSE and ADL scores in both groups.

Table 2: Therapeutic effects in both groups

Group	Markedly effective	Effective	Ineffective	Total effectiveness
JT (n=64)	21	33	10	84.38%
MT (n=64)	14	25	25	60.94%
χ^2				8.9320
P-value				<0.05

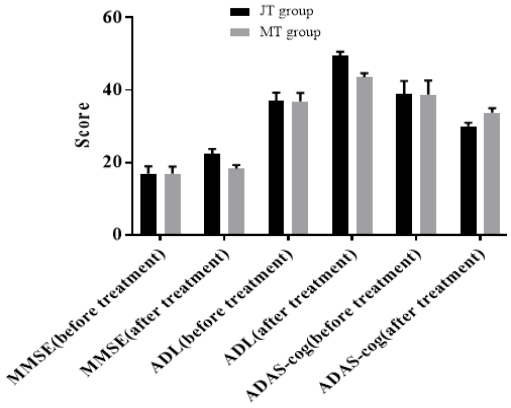

Figure 1: Comparison of MMSE, ADL and ADAS-cog scores in both groups

However, MMSE and ADL scores were markedly higher in JT patients than in MT patients. In addition, there were post-treatment decreases in ADAS-cog scores in JT and MT patients, while the ADAS-cog score in the JT group was significantly lower than that in the MT group.

Plasma NO and serum VEGF and MDA levels

Table 3 shows that prior to treatment, plasma NO and serum VEGF and MDA levels in JT and MT groups were comparable. After treatment, plasma NO, and VEGF and MDA levels in serum were better in JT group than in MT group, with statistical differences ($p < 0.05$).

CRP and Hcy levels

Prior to treatment, CRP and Hcy levels in the two groups were comparable ($p > 0.05$). However, after treatment, the CRP and Hcy levels in the JT group were significantly lower than those in the MT group ($p < 0.05$), as shown in Table 4.

Adverse reactions

The incidence of adverse reactions was similar in the two groups, as shown in Table 5.

Table 3: Plasma NO, serum VEGF and MDA levels in the two groups before and after treatment

Group	NO (μmol/L)		VEGF (ng/L)		MDA (μmol/L)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
JT (n=64)	31.45±0.63	46.45±1.21	145.63±6.45	185.34±8.56	4.53±0.54	2.25±0.35
MT (n=640)	31.38±0.58	39.57±1.02	145.71±6.51	167.24±8.73	4.49±0.53	3.19±0.42
t	0.654	34.779	0.070	11.843	0.423	13.755
P-value	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Table 4: Comparison of CRP and Hcy levels between the two groups before and after treatment

Group	CRP (mg/L)		Hcy (μmol/L)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
JT (n=64)	7.14±1.14	5.36±0.86	16.93±1.65	13.67±1.21
MT (n=64)	7.11±1.17	6.25±0.97	16.89±1.67	14.94±1.38
t	0.147	5.492	0.136	5.536
P-value	>0.05	<0.05	>0.05	<0.05

Table 5: Incidence of adverse reactions in both groups

Group	Gastrointestinal reaction	Dizziness and headaches	Insomnia	Transaminase elevation	Incidence
JT (n=64)	1	1	0	0	3.13%
MT (n=64)	0	1	1	1	4.69%
χ^2					0.2081
P-value					>0.05

DISCUSSION

Alzheimer's disease (AD) patients experience declines in memory, cognitive function, intelligence and self-care ability, which greatly reduce their quality of life, leading to a heavy burden on the family and society. At present, the pathogenesis of AD remains unclear, and there is no effective prevention and treatment in clinical practice. Thus, the need for identification of an effective treatment method has become the focus of clinical treatment of AD [13]. Recently, some studies have found that the metabolism of Hcy, and over-activation of inflammatory factors and oxidative reactions are the pathological factors involved in the occurrence of AD [14]. Moreover, these factors are also related to the occurrence of cardiovascular and cerebrovascular diseases [14]. Therefore, the key to the treatment of AD is to improve patients' cerebral tissue circulation and blood perfusion.

Butylphthalide, a drug frequently used for the treatment of mild and moderate acute ischemic stroke, improves the clearance of neurotoxic substances such as amyloid-β (Aβ), free radicals and inflammatory factors. It protects mitochondria by improving microcirculation in brain tissues, thereby effectively improving AD patients' cognitive and memory functions [15]. Ginkgo-leaf tablet, a drug used in traditional Chinese medicine for improving cerebral blood perfusion, significantly enhances cerebral tissue circulation and improves blood perfusion. Several studies have shown that combination of Ginkgo-leaf tablets and butylphthalide soft capsules produced significant therapeutic effects on AD, with positive impact by slowing down cognitive decline and memory loss, as well as improving patients' self-care ability [16]. In the *Philosophy of Animals*, Lamarck, a French biologist, proposed that the organs of an organism become well-developed when used regularly, but will gradually degenerate if not used regularly. In clinical treatment in AD patients, cognitive function, memory ability and self-care ability are exercised through cognitive rehabilitation training to slow down cognitive decline and enhance the quality of life of patients.

In the present study, the clinical effect of cognitive rehabilitation training in combination with butylphthalide soft capsules and ginkgo-leaf tablets was determined in 128 selected mild AD patients. The results showed markedly higher total effectiveness in JT patients (84.38%) than in MT patients (60.94 %). After treatment, the MMSE, ADL and ADAS-cog scores in the JT group were significantly better than those in the MT group. The results of this study are consistent with those of a previous study [17]. Therefore, combination of rehabilitation training with butylphthalide soft capsules and ginkgo-leaf tablets effectively delayed AD patients' cognitive decline and significantly improved their intelligence and self-care ability, with better therapeutic effect than drug treatment alone.

Comparison of serological indexes between the two groups showed that after treatment, the plasma NO, serum VEGF and MDA levels were marked reduced in JT patients. This is consistent with the results of a study by Baranowski *et al* [18]. These results suggest that the combination of butylphthalide soft capsules and ginkgo-leaf tablets with cognitive rehabilitation training significantly improved serological indicators in AD patients. The comparison of serum inflammatory factor levels between the two groups revealed that after treatment, the CRP and Hcy concentrations were markedly reduced in JT group. This confirms that combining butylphthalide soft capsules and ginkgo-leaf tablets with cognitive rehabilitation training reduced the release of inflammatory factors in AD patients and alleviated brain inflammatory response. The incidence of unwanted reactions was similar in both groups, indicating that the combination of butylphthalide soft capsules, ginkgo-leaf tablets and cognitive rehabilitation training is safe and effective, and it can achieve significant therapeutic effects without increasing the incidence of adverse reactions.

CONCLUSION

The combination of rehabilitation training with butylphthalide soft capsules and ginkgo-leaf tablets produces significant therapeutic benefits in mild AD patients. The combination therapy delays AD patients' cognitive decline and memory loss, improves their serological indicators, and lowers inflammatory response, without increasing the incidence of adverse reactions. This treatment approach will find application in enhancing the quality of life in mild AD patients, but further clinical trials are required.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We 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 the authors. Yuanyuan Zhong and Jiaoping Chen conceived and designed the study, collected, analyzed and interpreted the experimental data, drafted the manuscript and revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

REFERENCES

1. *Rai SP, Krohn M, Pahnke J. Early cognitive training rescues remote spatial memory but reduces cognitive flexibility in Alzheimer's disease mice. J Alzheimers Dis 2020; 75: 1301-1317.*
2. *Alanazi FK, Radwan AA, Aou-Auda H. Molecular scaffold and biological activities of anti-Alzheimer agents. Trop J Pharm Res 2022; 21: 439-451.*
3. *Simon SS, Castellani M, Belleville S, Dwolatzky T, Hampstead BM, Bahar-Fuchs A. The design, evaluation, and reporting on non-pharmacological, cognition-oriented treatments for older adults: Results of a survey of experts. Alzheimers Dement (NY) 2020; 6: e12024.*
4. *Wang J, Caprio TV, Simning A, Shang J, Conwell Y, Yu F, Li Y. Association between home health services and facility admission in older adults with and without Alzheimer's disease. J Am Med Dir Assoc 2020; 21: 627-633.e9.*
5. *Geddes MR, O'Connell ME, Fisk JD, Gauthier S, Camicioli R, Ismail Z; Alzheimer Society of Canada task force on dementia care best practices for COVID-19. Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada task force on dementia care best practices for COVID-19. Alzheimers Dement (Amst) 2020; 12: e12111.*
6. *Khatun S, Morshed BI, Bidelman GM. A Single-Channel EEG-based approach to detect mild cognitive impairment via speech-evoked brain responses. IEEE Trans Neural Syst Rehabil Eng 2019; 27: 1063-1070.*
7. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
8. *Imbeault H, Langlois F, Bocti C, Gagnon L, Bier N. Can people with Alzheimer's disease improve their day-to-day functioning with a tablet computer? Neuropsychol Rehabil 2018; 28: 779-796.*
9. *Kosenko E, Tikhonova L, Alilova G, Urios A, Montoliu C. The erythrocytic hypothesis of brain energy crisis in sporadic Alzheimer disease: Possible consequences and supporting evidence. J Clin Med 2020; 9: 206.*
10. *Jia L, Fu Y, Shen L, Zhang H, Zhu M, Qiu Q, Wang Q, Yan X, Kong C, Hao J, et al. PSEN1, PSEN2, and APP mutations in 404 Chinese pedigrees with familial Alzheimer's disease. Alzheimers Dement 2020; 16: 178-191.*
11. *Kim JH, Han JY, Park GC, Lee JS. Effects of electroacupuncture combined with computer-based cognitive rehabilitation on mild cognitive impairment: study protocol for a pilot randomized controlled trial. Trials 2019; 20: 478.*
12. *Kim HG, Park S, Rhee HY, Lee KM, Ryu CW, Lee SY, Kim EJ, Wang Y, Jahng GH. Evaluation and prediction of early Alzheimer's disease using a machine learning-based optimized combination-feature set on gray matter volume and quantitative susceptibility mapping. Curr Alzheimer Res 2020; 17: 428-437.*
13. *Cheng X, Wang H, Liu C, Zhong S, Niu X, Zhang X, Qi R, Zhao S, Zhang X, Qu H, et al. Dl-3-n-butylphthalide promotes remyelination process in cerebral white matter in rats subjected to ischemic stroke. Brain Res 2019; 1717: 167-175.*
14. *Zhou H, Ye M, Xu W, Yu M, Liu X, Chen Y. DL-3-n-butylphthalide therapy for Parkinson's disease: A randomized controlled trial. Exp Ther Med 2019; 17: 3800-3806.*
15. *Liao Z, Cheng L, Li X, Zhang M, Wang S, Huo R. Meta-analysis of Ginkgo biloba preparation for the treatment of Alzheimer's disease. Clin Neuropharmacol 2020; 43: 93-99.*
16. *Wallin C, Friedemann M, Sholts SB, Noormägi A, Svantesson T, Jarvet J, Roos PM, Palumaa P, Gräslund A, Wärmländer SKTS. Mercury and Alzheimer's disease: Hg(II) ions display specific binding to the amyloid-β peptide and hinder its fibrillization. Biomolecules 2019; 10: 44.*
17. *Won DY, Byun SJ, Jeong JS, Shin JY. Association between acetylcholinesterase inhibitors and osteoporotic fractures in older persons with Alzheimer's disease. J Am Med Dir Assoc 2020; 21: 1128-1133.e1.*
18. *Baranowski BJ, Marko DM, Fenech RK, Yang AJT, MacPherson REK. Healthy brain, healthy life: a review of diet and exercise interventions to promote brain health and reduce Alzheimer's disease risk. Appl Physiol Nutr Metab 2020; 45: 1055-1065.*