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Yinao Capsules Combined with Memantine Hydrochloride in the Treatment of Alzheimer's Disease in the Elderly

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Abstract: *Objective:* To investigate the clinical efficacy of Yinao capsule combined with memantine hydrochloride in the treatment of Alzheimer's disease (AD) in the elderly, and to analyze its effects on cognitive function and quality of life of patients. *Methods:* A total of 84 elderly AD patients admitted to the hospital from June 2022 to June 2023 were randomly divided into an observation group (42 cases, Yinao capsule combined with memantine hydrochloride) and a control group (42 cases, memantine hydrochloride monotherapy), both of which were treated for 3 months. The Mini-Intelligent Mental State Scale (MMSE) was used to evaluate cognitive function, and the Quality of Life Scale for Alzheimer's Patients (QOL-AD) was used to evaluate the quality of life. *Results:* Before treatment, there was no significant difference in the MMSE AND QOL-AD scores between the two groups ($P>0.05$). After 3 months of treatment, the MMSE AND QOL-AD scores of both groups were significantly higher than those before treatment (both $P<0.001$), and the MMSE (24.70±3.70 points) and QOL-AD (31.60±3.59 points) scores in the observation group were significantly higher than those in the control group (21.24±3.33 points) and (28.44±3.26 points), both $P<0.001$. There were no serious adverse reactions in either group. *Conclusion:* Yinao capsule combined with memantine hydrochloride can significantly improve cognitive function and quality of life in elderly AD patients, and the efficacy is better than memantine hydrochloride monotherapy, and the safety is good.

Keywords: Alzheimer's disease dementia in the elderly; Yinao capsule; Memantine hydrochloride; Cognitive function; Quality of life

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1. Introduction

Alzheimer's disease dementia (AD) is a chronic neurological degenerative disease whose cause has not been fully determined, mainly characterized by progressive memory loss and cognitive dysfunction [1]. The prevalence of

AD increases significantly with age. The prevalence is approximately 0.20% among 59-year-olds and as high as 35.90% among those over 90, presenting a distinct age gradient [2]. It will not only lead to the gradual impairment of patients' ability to perform daily life and social activities, seriously reduce their quality of life, but also bring heavy care pressure and economic burden to the family and society [3]. There is currently no curative therapy, and clinical practice mainly relies on drugs (such as cholinesterase inhibitors, NMDA receptor antagonists, etc.) to delay disease progression, improve cognitive function, and daily living ability [4].

Memantine hydrochloride is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist that selectively blocks pathologically overactivated NMDA receptors and reduces glutamate-mediated excitotoxicity, thereby improving cognitive function and psychobehavioral symptoms in patients with moderate to severe AD [5]. A large number of clinical trials have shown that memantine significantly improves patients' cognitive scores, ability to perform daily living, and control of behavioral disorders, and is generally well tolerated [6]. However, memantine hydrochloride alone also has limitations. First, memantine only targets the glutamatergic system and fails to simultaneously regulate multiple pathological links, such as the cholinergic system, inflammatory response, and oxidative stress involved in the course of AD, resulting in limited clinical efficacy in some patients. Secondly, long-term medication may cause gastrointestinal discomfort (such as nausea, vomiting) and central nervous system side effects (such as dizziness, headache), and some patients may even experience a decrease in efficacy. Therefore, the combination of memantine with cholinesterase inhibitors or other neuroprotective agents is often considered clinically in order to achieve more comprehensive pathological intervention and longer-lasting efficacy [5–6].

In the theory of traditional Chinese medicine, AD belongs to the categories of "dementia" and "forgetfulness", and the pathogenesis is based on kidney essence deficiency, insufficient qi and blood, cerebral marrow dystrophy, phlegm turbidity, and blood stasis blocking the brain channel. As a proprietary Chinese medicine developed based on the theory of traditional Chinese medicine, Yinao capsule contains ginseng, codonopsis, Ganoderma lucidum, tortoiseshell gum, poria, and other multi-flavored traditional Chinese medicines, which have the effects of nourishing qi and yin, nourishing the kidney and brain, nourishing the mind, and calming the nerves. Ginsenosides in ginseng and other medicinal materials, Rg1 significantly increased the concentration of extracellular acetylcholine in the hippocampus of rats with an AD model, improving cognitive function [7–8]. Rg1 promotes Aβ degradation by upregulating the PPARγIDE pathway, reducing Aβ content in the hippocampus, and improving memory [9]. In APP/PS1 transgenic mice, Rg1 treatment significantly reduced Aβ142 and phosphorylated tau (pTau) levels and restored synaptic plasticity [10]. At the same time, Rg1 also showed the effect of inhibiting NLRP1 inflammasomes and reducing inflammatory mediators, further supporting its anti-inflammatory effects [11]. Ganoderma lucidum polysaccharide can significantly reduce the expression of pro-inflammatory cytokines such as TNFα and IL6, and improve cognitive impairment by modulating the inflammatory network of the brain-liver axis [12]. These mechanisms of action are complementary to the glutamate modulation of memantine hydrochloride, providing a theoretical basis for the combined application of the two in the treatment of AD.

2. Information and methods

2.1. General information

A total of 84 elderly patients with Alzheimer's disease dementia admitted to the hospital from June 2022 to June 2023 were selected as the research subjects. Inclusion criteria: Meet the diagnostic criteria for AD set by the National Institute of Neurological Disorders and Stroke-Alzheimer's and Related Disorders Association (NINDS-

ADRDA); Age ≥ 60 years; Patients and their families are informed and sign the informed consent form. Exclusion Criteria: Patients with severe dementia; Patients with cognitive impairment not caused by AD, such as vascular dementia and frontotemporal lobe dementia; Patients with impaired consciousness, severe physical diseases (such as severe heart, liver, and kidney failure), severe depression, speech disorders, and allergies. This study protocol was approved by the hospital ethics committee. The patients were divided into a control group and an observation group according to the random number table method, with 42 cases in each group. There were 27 males and 15 females in the control group; Age 60–82 years, mean 71.1±1.0 years; The duration of the disease was 0.5–16.1 years, with an average of 4.5±1.1 years. There were 30 males and 12 females in the observation group. Age 61–81 years, mean 70.9±1.1 years; The duration of the disease is 0.5–16.3 years, with an average of 4.6±1.2 years. The general data, such as gender, age, and disease course of the two groups, were compared, and the differences were not statistically significant (P>0.05), which were comparable.

2.2. Treatment

Both groups received basic interventions during treatment, including health publicity and education (guiding family members to master patient care skills) and simple cognitive training (such as memory games and language communication exercises). The control group was treated with memantine hydrochloride tablets (Guangzhou Baiyunshan Pharmaceutical Group Co., Ltd. Baiyunshan Pharmaceutical General Factory, Sinopharm Zhunzi H20090310), and the dose adjustment regimen was: 5 mg/time in week 1, 1 time/d (oral administration before going to bed); 10 mg/time, 1 time/day in week 2; 15 mg/time, 1 time/d in week 3; Maintain 20 mg/time, 1 time/d, for 3 months of continuous treatment at week 4 and beyond. The observation group was treated with Yinao Capsule (Guizhou Sanli Pharmaceutical Co., Ltd., Sinopharm Zhunzi Z52020035, 0.3g/capsule), 3 capsules/time, 3 times/d (oral administration after meals), and continued treatment for 3 months.

2.3. Observation indicators

The cognitive function and quality of life of the patients in the two groups before and after 3 months of treatment were observed, and the occurrence of adverse reactions (such as headache, vomiting, dizziness, etc.) during the treatment period was recorded.

2.4. Evaluation criteria

Cognitive function assessment: The Mini-Mental State Examination Scale (MMSE) was adopted, which covers orientation, memory, attention, calculation, language ability, and other dimensions, with a total score of 30 points. Quality of life assessment: The Quality of Life Scale for Alzheimer's Patients (QOL-AD) was adopted, which contains a total of 13 items in 4 domains, with a total score ranging from 13–52 points, with higher scores indicating a higher quality of life for patients.

2.5. Statistical methods

The data were processed by SPSS 20.0 software, and the measurement data were expressed in Mean ± SD, and the t-test was used for comparison before and after treatment within groups and between groups. Numerical data are expressed as frequencies (%), and the comparison is tested using the x^2 test. The difference was statistically significant in P<0.05.

3. Comparison of clinical efficacy between the two groups

3.1. Comparison of cognitive function (MMSE score) and quality of life (QOL-AD score) between the two groups before and after treatment

Before treatment, there was no difference in MMSE score (19.09±3.02 points) between the observation group and the control group (19.04±2.97 points) (P=0.936). After 3 months of treatment, the MMSE scores of both groups were significantly increased (24.70±3.70 points in the observation group and 21.24±3.33 points in the control group), and the score of the observation group was significantly higher than that of the control group (P<0.001). Before treatment, there was no difference in QOL-AD score (23.30±2.58 points) between the observation group and the control group (23.27±2.60 points) (P=0.953), and after 3 months of treatment, the QOL-AD score of both groups was significantly increased (observation group (31.60±3.59 points, control group 28.44±3.2 points), and the comparison within the group was P<0.001). The score of the observation group was significantly higher than that of the control group (P<0.001) (**Table 1**).

Table 1. MMSE, QOL-AD scores, and *P* values before treatment and after 3 months in the two groups

	MMSE score			QOL-AD score		
Constituencies	**Before treatment**	**After 3 months of treatment**	***P*-value before and after treatment**	**Before treatment**	**After 3 months of treatment**	***P*-value before and after treatment**
Observation group (*N*=42).	19.09±3.02	24.70±3.70	<0.001	23.30±2.58	31.60±3.59	<0.001
Control group (*N*=42).	19.04±2.97	21.24±3.33	<0.001	23.27±2.60	28.44±3.26	<0.001
P-value	0.936	<0.001		0.953	<0.001	

3.2. Security

During the treatment period, 1 case in the observation group had a mild headache, 1 case in the control group had nausea, and 1 case had dizziness, all of which were not treated for spontaneous relief, and no serious adverse reactions occurred (**Table 2**).

Table 2. The occurrence of adverse reactions

Constituencies	**Headache**	**Disgusting**	**Dizzy**	**Total incidence (%)**
Observation group	1 (2.38)	0 (0.00)	0 (0.00)	2.38
Control group	0 (0.00)	1 (2.38)	1 (2.38)	4.76
P-value	-	-	-	0.557

4. Discussion

The pathological process of AD involves multiple mechanisms, such as neuronal damage, neurotransmitter imbalance, and inflammation, and its core treatment goal is to delay cognitive decline and maintain the patient's quality of life. This study achieved significant results in improving cognitive function and quality of life through the combination of Yinao capsules with memantine hydrochloride.

As an NMDA receptor antagonist, memantine hydrochloride in AD pathology can specifically block neuronal excitotoxicity caused by overactivation of glutamate, reduce synaptic damage and neuronal loss,

and improve cognitive function in patients [13]. However, a single drug works only on the glutamate system and has limited intervention in the complex pathological network of AD [14]. In the formula of Yinao capsule, ginseng and codonopsis nourish qi and strengthen the spleen to transform qi and blood, Ganoderma lucidum and tortoise shell gum nourish the kidney and strengthen the brain to nourish the brain marrow, and Poria calms the mind and calms the mind to regulates the vitality. Modern pharmacological research has shown that Yinao capsules can synergize through multiple pathways. First, by promoting the synthesis and release of acetylcholine, cholinergic nerve function is enhanced [15]. Yinao capsule complements the glutamate regulation of memantine hydrochloride, comprehensively improving the balance of neurotransmitters in the brain. Second, Rg1 delays neuronal degeneration by restoring mitochondrial autophagy (PINK1Parkin pathway) by reducing Aβ plaques and attenuating tau phosphorylation [16]. Provides structural support for the "neuroprotective" effects of memantine hydrochloride. At the same time, Rg1 can also promote Aβ degradation by inhibiting the ERK/PPARγ phosphorylation pathway [17]. Third, in the APP/PS1 mouse model, Rg1 significantly downregulated the expression of TNFα and IL1β in the inflammasome of NLRP1 and its downstream, showing strong anti-inflammatory effects [18]. In addition, Rg1 further inhibits tau phosphorylation and mitigates oxidative stress by modulating the Wnt/GSK3β/βcatenin signaling pathway [7].

Ganoderma lucidum in the formula has a "nootropic and calming" effect. Ganoderma lucidum spore extract can inhibit NF-κB/NLRP3 inflammatory pathway and enhance GABAergic neuronal activity, thereby improving sleep disturbance and restoring cognitive function in rat models with AD [19]. In early models of AD, shelled Ganoderma lucidum spores significantly reduced microglial activation and inflammatory factor expression (TNF) in the hippocampus and prefrontal cortex-ATHE-1β), and elevated BDNF levels, exhibiting antidepressant and anxiolytic effects [20]. Molecular docking and kinetic simulations showed that glycyrrhizic acid A and mannitolic acid B in Ganoderma lucidum had a high affinity for MARK4 (microtubule affinity-regulated kinase 4), which could inhibit its activity, thereby blocking the key pathway of abnormal phosphorylation of tau protein [21]. In addition, liquid-fermented Ganoderma lucidum (GANO99) can remodel the gut microbial structure of AD transgenic mice, reduce Aβ plaque deposition, and improve memory behavior [21]. Ganoderma lucidum is anti-inflammatory, antioxidant, and anti-inspired Aβ and anti-tau pathology, making it promising in AD prevention and treatment [22].

The above multi-target mechanism is similar to that of memantine hydrochloride. Glutamate regulation is complementary: memantine primarily reduces NMDA receptor-mediated excitotoxicity, while Yinao capsules can repair damaged neurons at the structural level and improve overall neural network function by enhancing cholinergic delivery, scavenging Aβ, inhibiting tau pathology, and inhibiting inflammation. For this reason, the combination of the two has shown better improvements in cognitive function, daily living ability, and quality of life in this clinical observation. To be a potential strategy to optimize AD treatment options. The quality of life of AD patients is not completely linearly correlated with cognitive function, and factors such as emotional state and behavioral abnormalities can also directly affect their ability to live. The "nootropic and calming" effect of the Yinao capsule can reduce the decline in life ability caused by mental symptoms by regulating central nervous system function and relieving patients' mental and behavioral symptoms, such as anxiety and paranoia [23–26]. This is also an important driver of improved QOL-AD scores.

Clinical manifestation of TCM toxicity reduction and efficiency. In this study, the total incidence of adverse reactions in the observation group was lower than that in the control group; although the difference was not statistically significant, it could be observed from the clinical details. The symptoms of nausea and dizziness

in the control group were related to the gastrointestinal stimulation and central regulatory effects of memantine hydrochloride, while only one mild headache in the observation group had spontaneous relief. The traditional Chinese medicine properties of Yinao capsule play a key role in this: Codonopsis and Poria in its formula have the effect of strengthening the spleen and stomach, and can reduce the direct irritation of memantine hydrochloride to the gastrointestinal tract [27–29]. The yin-nourishing and latent yang effects of Ganoderma lucidum and tortoiseshell gum can buffer the regulation fluctuations of memantine hydrochloride on the central nervous system, thereby reducing the risk of adverse reactions such as dizziness [29]. This characteristic of "reducing toxicity and increasing efficiency" provides a guarantee for the safety of long-term treatment and is also in line with the treatment of integrated traditional Chinese and Western medicine, "Increasing efficiency without increasing toxicity" clinical expectations.

There are two limitations of this study: first, the sample size is small, and it is a single-center study, and the results may be geographical or population bias; Second, the observation period was only 3 months, and the long-term efficacy and drug tolerability were not evaluated. In the future, the following directions can be further explored: expand the sample size, carry out multicenter, randomized, double-blind trials, and enhance the universality of the results. The follow-up time was extended to analyze the long-term safety and delay of disease progression of combination therapy. Combined with cerebrospinal fluid biomarkers, imaging examinations, and other objective indicators, the molecular mechanism of drug synergy is deeply analyzed.

5. Conclusion

Yinao capsule combined with memantine hydrochloride in the treatment of elderly AD can significantly improve patients' cognitive function and quality of life through multi-target synergy, and has a good safety profile, making it a treatment plan worthy of clinical promotion.

Disclosure statement

The authors declare no conflict of interest.

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