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Efficacy of Sodium Oligomannate Capsules Combined with Memantine Hydrochloride and Donepezil Hydrochloride in Treating Moderate Alzheimer's Disease

Qi Wang[1], Wenqi Wu[1], Yue He[1], Qiuyue Zheng[1], Ming Yu[1]*

Department of Neurology, Affiliated Hospital of Jiangsu University, Zhenjiang 212000, Jiangsu Province, China

***Corresponding author:** Ming Yu, yuming72251@163.com

Abstract: *Objective:* To explore the clinical efficacy of sodium oligomannate capsules combined with memantine hydrochloride and donepezil hydrochloride in the treatment of moderate Alzheimer's disease (AD) and analyze its impact on cognitive function. *Methods:* Eighty patients with moderate AD admitted to the neurology outpatient clinic of our hospital from June 2021 to December 2022 were selected as the study subjects and randomly divided into a study group and a control group, each with 40 patients. The control group was treated with oral memantine hydrochloride and donepezil hydrochloride, while the study group was additionally treated with oral sodium oligomannate capsules for 24 weeks. The scores of neuropsychological scales [Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE)], and Activities of Daily Living (ADL) scale were compared before and after treatment. Additionally, the levels of homocysteine (Hcy), central nervous system-specific protein (S100-β), interleukin (IL)-6, and tumor necrosis factor (TNF)-α were measured in both groups, and the treatment effects and adverse reactions were compared. *Results:* After 24 weeks of treatment, the MMSE, MoCA, and ADL scores of both groups were significantly higher than those before treatment ($P < 0.05$). Compared with the control group after 24 weeks of treatment, the study group had significantly higher MMSE, MoCA, and ADL scores ($P < 0.05$), and significantly lower levels of Hcy, IL-6, and TNF-α ($P < 0.05$). Both the study group and the control group showed reduced levels of Hcy, IL-6, and TNF-α after 24 weeks of treatment compared to before ($P < 0.05$), but there was no significant change in S100-β levels ($P > 0.05$). *Conclusion:* The combination of sodium oligomannate capsules, memantine hydrochloride, and donepezil hydrochloride is effective in the treatment of moderate AD. It can improve the cognitive function and daily living abilities of patients with dementia, enhancing their quality of life.

Keywords: Sodium oligomannate capsules; Alzheimer's disease; Memantine hydrochloride; Donepezil hydrochloride

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1. Introduction

Alzheimer's disease (AD), the most common neurodegenerative disease in clinical practice, is primarily characterized by progressive cognitive dysfunction, behavioral changes, and emotional disturbances. These higher nervous function impairments manifest as memory decline, compromised calculation abilities, aphasia, agnosia, apraxia, and visuospatial disorders. In severe cases, patients may exhibit psychiatric and behavioral abnormalities and lose their ability to perform daily activities. Previous studies have linked the pathogenesis of AD to the deposition of β-amyloid protein (Aβ) and tau protein in the brain [1-3]. Recent research has highlighted the critical role of persistent and excessive inflammatory responses in the pathogenesis of degenerative diseases such as AD [4]. Memantine hydrochloride, an N-methyl-D-aspartate receptor antagonist (NMDAR-A), regulates excitatory neurotransmitters by reducing the "noise" generated by excessive NMDA activation. It inhibits the formation of Aβ, delays neurodegeneration, and improves cognitive function [5]. Donepezil hydrochloride, a second-generation cholinesterase inhibitor, treats mild to moderate AD by inhibiting the hydrolysis of acetylcholine and increasing its synaptic levels. However, monotherapy with donepezil often fails to achieve ideal therapeutic effects [6]. There is a relationship between AD and gut microbiota. Dysbiosis can affect intestinal permeability and inflammation levels, which in turn can impact the central nervous system, leading to cognitive dysfunction. Studies have indicated that sodium oligomannate capsules (GV-971), a novel drug developed in China, significantly improve cognitive function in AD patients by reshaping gut microbiota balance and targeting the brain-gut axis [7]. This article compares the clinical efficacy and safety of GV-971 combined with memantine hydrochloride and donepezil hydrochloride versus dual therapy of memantine hydrochloride and donepezil hydrochloride in the treatment of AD patients.

2. General information and methods

2.1. General information

Eighty patients with moderate AD who visited the neurology outpatient clinic of the Affiliated Hospital of Jiangsu University from June 2021 to December 2022 were selected as study subjects. They were randomly divided into a study group and a control group, with 40 patients in each group. This study was approved by the ethics committee of our hospital. The control group received oral treatment with memantine hydrochloride and donepezil hydrochloride. The study group, on this basis, received additional oral treatment with sodium oligomannate capsules. The treatment was continuous for 24 weeks. Neuropsychological scale scores, including the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), were compared before and after treatment in both groups. Simultaneously, levels of homocysteine (Hcy), central nervous system-specific protein (S100-β), interleukin (IL)-6, and tumor necrosis factor (TNF)-α were measured in both groups. The treatment efficacy and adverse reactions were also compared between the two groups. The general information of the two groups was comparable ($P > 0.05$).

2.2. Inclusion and exclusion criteria

The diagnosis of AD follows the criteria established by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* in 1999. The diagnosis is primarily based on clinical symptoms, medical history, neurological examination, and neuropsychological assessment using the MMSE scale. Among the patients with dementia, 80 were identified as having moderate symptoms. Inclusion

criteria are as follows: (1) Meet the DSM-5 criteria for dementia diagnosis; (2) Age greater than 65 years; (3) MMSE scores are graded according to severity using the guidelines from the first edition of the "Operational Guidelines for Neuropsychological Cognitive Scales" in 2015: scores of 21–26 are defined as mild dementia and scores of 10–20 are defined as moderate dementia. Cognitive impairment is also defined based on education level, with scores less than 17 for illiteracy, less than 20 for primary school education, and less than 24 for middle school education and above; (4) Normal laboratory test results for blood routine, liver and kidney function, urine routine, thyroid function, and vitamin levels; (5) Presence of bilateral temporal lobe and hippocampal atrophy on magnetic resonance imaging (MRI) of the brain; (6) Negative for syphilis and HIV infection. Exclusion criteria are as follows: (1) Cognitive decline due to other causes such as mental retardation, bipolar disorder, hypothyroidism, schizophrenia, etc.; (2) Comorbidities including malignant tumors, active tuberculosis, severe respiratory, circulatory, or digestive system diseases, or other internal medical conditions or severe organ failure; (3) History of drug abuse, alcohol abuse, or allergies; (4) Use of medications that may improve cognition within the past month; (5) Simultaneous participation in other drug clinical trials; (6) Absence of multiple or widespread cerebral infarction lesions, or severe white matter lesions on MRI of the brain.

2.3. Drugs

Donepezil hydrochloride tablets: Produced by Jiangsu Hansoh Pharmaceutical Group Co., Ltd., specifications: 150 mg, 14 tablets/plate, batch number: National Medical Approval Number H20030472, expiration date: from September 30, 2020 to September 29, 2023; Memantine hydrochloride tablets: Produced by CSPC Ouyi Pharmaceutical Co., Ltd., specifications: 10 mg, 60 tablets/bottle, batch number: National Medical Approval Number H20203319, expiration date: from May 16, 2020 to May 15, 2024; Sodium oligomannate capsules: Produced by Shanghai Green Valley Pharmaceutical Co., Ltd., specifications: 150 mg, 14 capsules/plate, batch number: National Medical Approval Number H20190031, expiration date: from April 01, 2021 to March 31, 2023.

2.4. Grouping and drug administration

Using the random number table method, 80 patients with moderate dementia were divided into a control group and a study group, with 40 patients in each group. Patients in the control group were orally administered 5 mg of donepezil hydrochloride once daily, which was increased to 10 mg after one month. Additionally, they received memantine hydrochloride once daily, starting with 5 mg in the first week, increasing to 10 mg in the second week, 15 mg in the third week, and 20 mg in the fourth week, maintained at 20 mg thereafter. Patients in the treatment group received the same treatment as the control group, but with the addition of 450 mg of sodium oligomannate capsules, taken twice daily (morning and evening). Both groups were treated continuously for 24 weeks.

2.5. Observation indicators and efficacy evaluation

The cognitive function and activities of daily living (ADL) of patients in both groups were evaluated before treatment and after 24 weeks of treatment using the MMSE score, MoCA score, and ADL score. The levels of Hcy, S100-β, IL-6, and TNF-α were measured in both groups before treatment and after 24 weeks of treatment using enzyme-linked immunosorbent assay (ELISA).

2.6. Adverse reactions

Patients in both groups were observed for adverse reactions, including dizziness, fatigue, lethargy, gastrointestinal

reactions (vomiting, diarrhea, abdominal distension), weight gain, increased muscle tone, akathisia, and obstructive sleep apnea-hypopnea syndrome. Additionally, safety evaluations of the two treatment regimens were conducted based on the results of electrocardiograms, blood and urine routine tests, and renal and liver function tests.

2.7. Statistical analysis

Statistical analysis was performed using SPSS25.0 software. Measurement data were expressed as mean ± standard deviation (SD). If the data met the assumptions of normality and homogeneity of variance, an independent samples *t*-test was used. A paired samples *t*-test was applied to compare pre- and post-treatment data. If the assumptions were not met, the Mann–Whitney *U* test was employed. Count data were expressed as percentages (%) and analyzed using the chi-square test. A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical data analysis

In the control group, there were 22 males and 18 females, with an average age of 73.20 ± 5.86 years and an average disease duration of 22.88 ± 2.87 months. In the study group, there were 24 males and 16 females, with an average age of 75.35 ± 6.46 years and the same average disease duration of 22.88 ± 2.87 months. There were no statistically significant differences between the two groups in terms of age, gender, education level, MMSE score, MoCA score, ADL score, underlying diseases, nutritional and immunological indicators, and average disease duration (all $P > 0.05$). **Table 1** shows the details.

Table 1. Demographic information and basic clinical characteristics of subjects (mean ± SD

	Study group (*n* = 40)	**Control group (*n* = 40)**	***P* value**
Age (years)	75.35 ± 6.46	73.20 ± 5.86	0.123
Gender (male/female)	16/12	24/16	0.821
Education (years)	8.50 ± 2.11	9.18 ± 2.14	0.159
Duration of illness (months)	22.25 ± 2.84	22.88 ± 2.87	0.330
MMSE score	15.58 ± 2.43	15.83 ± 2.50	0.651
ADL score	62.38 ± 5.66	63.00 ± 6.39	0.644
MoCA score	13.65 ± 2.41	13.95 ± 2.45	0.583
Underlying diseases			
Hypertension	11	13	0.808
Diabetes	10	8	0.790
Nutrition and immune indicators			
Hcy (μmol/L)	8.34 ± 1.31	8.85 ± 1.77	0.147
S100 (ng/ml）	0.064 ± 0.044	0.064 ± 0.043	0.959
IL-6 (pg/ml)	58.45 ± 10.51	57.48 ± 9.03	0.658
TNF-α (pg/ml)	7.52 ± 2.02	8.85 ± 1.77	0.089

3.2. Improvement in cognitive abilities and daily living abilities in two groups

After 24 weeks of treatment, both groups showed varying degrees of improvement in cognitive function and daily living abilities compared to before treatment, with statistically significant differences ($P < 0.05$). Before treatment, there were no statistically significant differences in MMSE scores, MoCA scores, and ADL scores between the two groups ($P > 0.05$). However, after treatment, the study group had significantly higher MMSE scores, MoCA scores, and ADL scores compared to the control group ($P < 0.05$). This indicates that the combination therapy of sodium oligomannate, memantine hydrochloride, and donepezil hydrochloride is more effective in improving cognitive function and daily living abilities of patients with moderate AD than the combination therapy of memantine hydrochloride and donepezil hydrochloride ($P < 0.05$). **Table 2** presents the details.

Table 2. Comparison of MMSE, MoCA, and ADL scores between two groups (mean ± SD, points)

Group	*n*	MMSE		MoCA		ADL	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Study group	40	15.58 ± 2.43	17.98 ± 2.41*	13.65 ± 2.41	16.28 ± 2.59*	62.38 ± 5.66	71.67 ± 6.82*
Control group	40	15.83 ± 2.50	16.63 ± 2.60*	13.95 ± 2.45	15.08 ± 2.54*	63.00 ± 6.39	65.75 ± 6.66*
t	-	0.173	2.408	0.552	0.583	0.211	3.903
P	-	0.863	0.018	2.093	0.040	0.833	＜ 0.001

Note: Compared with before treatment, *$P < 0.05$.

3.3. Comparison of inflammatory factor levels before and after treatment in the two groups

Before treatment, there were no statistically significant differences in the levels of Hcy, S100-β, IL-6, and TNF-α between the two groups ($P > 0.05$). After 24 weeks of treatment, the levels of Hcy, IL-6, and TNF-α decreased in both the study group and the control group ($P < 0.05$), but there was no significant change in the level of S100-β ($P > 0.05$). The levels of Hcy, IL-6, and TNF-α in the study group were significantly lower than those in the control group after 24 weeks of treatment ($P < 0.05$), as shown in **Table 3**.

Table 3. Comparison of serological indicators between the two groups (mean ± SD)

Group	*n*	Hcy (μmol/L)		S100-β (ng/ml)		IL-6 (pg/ml)		TNF-α (pg/ml)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Study group	40	8.34 ± 1.31	6.56 ± 1.71*	0.064 ± 0.044	0.063 ± 0.037	58.45 ± 10.51	38.88 ± 11.92*	119.18 ± 15.16	84.23 ± 16.53*
Control group	40	8.85 ± 1.77	8.47 ± 1.59*	0.064 ± 0.043	0.065 ± 0.043	57.48 ± 9.03	56.40 ± 9.59*	119.45 ± 21.71	101.73 ± 19.03*
t	-	1.466	5.178	0.052	0.280	0.445	7.245	0.066	4.391
P	-	0.147	< 0.001	0.959	0.780	0.658	< 0.001	0.948	< 0.001

Note: Compared with before treatment, *$P < 0.05$.

3.4. Occurrence of adverse reactions in both groups

During treatment, no significant changes were observed in liver and kidney function or electrocardiogram in both groups. In the observation group, there was one case of diarrhea, one case of dry mouth, and one case of nausea

and vomiting, with an adverse reaction rate of 7.5%. In the control group, there was one case of diarrhea, two cases of dizziness, and one case of nausea and vomiting, with an adverse reaction rate of 10%. The adverse reactions were mild and resolved spontaneously in later stages. There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$).

4. Discussion

Alzheimer's disease, as the world's leading degenerative neurological disease, has a very high disability rate, severely affecting patients' daily lives and imposing a huge economic and caregiving burden on their families. Research shows that the number of AD patients in China is expected to exceed 30 million by 2050, and the annual medical cost for AD patients will reach up to $1,887.18 billion [8,9]. The pathogenesis of AD is complex, and although its etiology and pathogenesis have not been fully elucidated, many scholars and hypotheses suggest that the occurrence of AD is related to the deposition of Aβ, neuroinflammation caused by hyperphosphorylation of tau protein, neuronal degeneration, and neurofibrillary tangles. Additionally, the loss or dysfunction of cholinergic neurons is also an important factor that induces AD, mainly manifested by a decrease in acetylcholine (ACh) levels and an increase in acetylcholine esterase (AChE) activity [10]. So far, no drug can reverse the progression of the disease, including the seven drugs approved by the US Food and Drug Administration for the treatment of AD. These include three acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine), NMDAR-A (memantine, memantine-donepezil combination), and two anti-Aβ monoclonal antibodies approved in January 2021 and January 2023—aducanumab and lecanemab. Memantine hydrochloride mainly non-competitively blocks MDAR in a functionally dependent manner, inhibits the formation of Aβ deposition and its adverse reactions, readjusts the balance between inhibition and excitation, delays neurodegeneration, and improves cognitive function [5]. Donepezil hydrochloride, as a typical cholinesterase inhibitor, can effectively regulate the level of ACh in the brain. However, as the number of intact cholinergic neurons decreases, its clinical effect gradually weakens, and it has no significant inhibitory effect on the progression of AD [11]. Although memantine hydrochloride and donepezil hydrochloride are first-line drugs for the treatment of AD, some patients have insufficient understanding of the disease and their cognitive impairment has reached moderate dementia when seeking medical attention. In such cases, the combined use of these two drugs still cannot achieve good results, which requires continuous exploration and research to develop new drugs. Sodium oligomannate (GV-971) is a novel AD therapeutic drug originally developed in China and is the world's first drug targeting the brain-gut axis. It has a disease-modifying effect by adjusting intestinal flora imbalance and inhibiting neuroinflammation. It was conditionally approved by the China National Medical Products Administration in November 2019 for the treatment of mild to moderate AD, making it the first drug with independent intellectual property rights in China for the treatment of AD. Clinical study results show that sodium oligomannate can continuously improve the cognitive function and daily self-care ability of AD patients, while also improving patient symptoms and delaying the progression of AD, with good tolerability [12,13].

Alzheimer's disease mostly affects elderly patients and is often accompanied by issues such as reduced digestive enzyme secretion, periodontitis, taste bud degeneration, intestinal flora imbalance, and weakened gastrointestinal motility. These patients are also highly susceptible to metabolic disorders of the three major nutrients: carbohydrates, proteins, and fats. Among these, lipid metabolism defects have a significant impact on cognitive function. Imbalances in intestinal flora can simultaneously cause lipid metabolism disorders and

increased levels of inflammatory factors in dementia patients, leading to immune system dysfunction and affecting higher nervous system functions through the brain-gut axis mechanism [14,15]. Sodium oligomannate capsule is a mixture of oligosaccharides with a polymerization degree of 2–10 extracted from marine brown algae. It can directly bind to multiple subdomains of Aβ, inhibiting the formation of Aβ fibers and stabilizing preformed fibers into non-toxic monomers. After oral administration, most of the ingested sodium oligomannate remains in the intestine, where it can rebuild the gut microbiota, reduce the peripheral infiltration of immune cells driven by bacterial metabolites into the brain, and inhibit neuroinflammation in the brain through the brain-gut axis. Studies have shown that sodium oligomannate improves patients' nutritional status, metabolic capacity, and immunity by enhancing the diversity and richness of gut microbiota, thus delaying the aging process of neuromotor functions in AD patients. In recent years, it has been widely used to treat patients with mild and moderate AD [16,17]. MMSE, MoCA, and ADL are commonly used scales for the clinical evaluation of patients' cognitive function and daily living abilities. The results of this study indicate that the combination therapy of sodium oligomannate with memantine hydrochloride and donepezil hydrochloride is more effective than the dual therapy of memantine hydrochloride and donepezil hydrochloride in improving neurological function and daily living abilities of AD patients. Additionally, Hcy, S100, IL-6, and TNF-α are important inflammatory factors, and the study results suggest that sodium oligomannate can lower the serum levels of Hcy, IL-6, and TNF-α in AD patients, improving inflammatory cell infiltration in neuronal cells. The study also demonstrates the good safety and compatibility of sodium oligomannate combined with memantine hydrochloride and donepezil hydrochloride, making it a suitable treatment option for moderate AD.

5. Conclusion

In summary, the combination therapy of sodium oligomannate capsules with memantine hydrochloride and donepezil hydrochloride has proven efficacy in the treatment of moderate AD. It can improve the cognitive function and daily living abilities of these patients, leading to an enhanced quality of life.

Disclosure statement

The authors declare no conflict of interest.

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