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Original Article

Pharmacological study of nimodipine plus donepezil in treating senile dementia

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Abstract: Objective: To investigate the pharmacological effects of nimodipine (Nim) plus donepezil (Don) in treating senile dementia (SD). Methods: 125 SD patients were randomly divided into control group (treated with single Nim) and combination group (treated with Nim plus Don). The scores of Mini Mental State Examination (MMSE), Hasegawa Dementia Scale (HDS) and activities of daily living (ADL) were observed before and after treatment. The Clinical Dementia Rating (CDR) and Global Deterioration Scale (GDS) were applied to assess the SD degree before and after treatment. The adverse reactions in two groups were observed. Results: The effective rate in combination group was 90.48%, which significantly higher than 67.74% in control group ($P < 0.05$). Before treatment, there was no significant difference of MMSE, HDS or AD score between two groups ($P > 0.05$), but after treatment the scores of MMSE, HDS and ADL in combination group were significantly higher than control group ($P < 0.05$). Before treatment, there was no significant difference of CDR and GDS score between two groups ($P > 0.05$), but after treatment, the scores of CDR and GDS in two groups were decreased, and those in combination were significantly lower than control group ($P < 0.05$). During the observation period, no serious adverse reaction occurred in both 2 groups. Conclusions: The combination of Nim and Don are safe in treating SD, and the effects are more obvious than single Nim treatment.

Keywords: Nimodipine, donepezil, senile dementia, effect

Introduction

Along with social progress, improvements of life quality and life expectancy, the incidence of senile dementia (SD) is also increased year by year. Vascular dementia and Alzheimer's disease are two common types of SD, which not only seriously affect the life qualities of older persons, but also bring heavy mental and economic burdens to society and patient's family [1-3]. Clinical manifestations of SD are mainly progressive cognitive disorder, disorders in memory, comprehension and calculation, and comprehensive loss of other daily living activities [4, 5]. There is no clinical developed drug that could cure SD currently [6], and the current drugs for SD can only slow disease process [7]. Alzheimer's disease is caused by the significant reduction of choline acetyltransferase and acetylcholine in patients' brain tissues, which thus affects cerebral cortical cholinergic neurotransmitters and causes dysfunctions [8]. Vascular dementia is the persisting advanced neural dysfunction caused by cerebrovascular diseases. Nimodipine (Nim) belongs to the calcium antagonist, with obvious roles of expanding cerebral blood vessels and protecting brain cells. Donepezil (Don) belongs to the acetylcholinesterase inhibitor, and can reversibly inhibit the acetylcholinesterase-caused acid hydrolysis of acetylcholine, thus increasing the content of acetylcholine at the receptor sites [9, 10]. Nim and Don have certain roles in improving brain functions, but the combination of Nim and Don in treating SD still lacks large-scale clinical trial. The objective of this study is to observe the clinical pharmacological effects of Nim plus Don in treating SD, thus providing reference for clinical treatment of SD.

Table 1. General information of patients

Index	Combination group (n = 63)	Control group (n = 62)
Age (year)	73 ± 4.1	73 ± 5.6
Female (n, %)	25, 39.7%	24, 38.7%
Body weight (kg)	68.4 ± 11.5	69.1 ± 13.3
Height (cm)	172 ± 4.9	171 ± 3.1
Systolic pressure (mmHg)	137 ± 21	134 ± 14
Education level (n, %)		
Under junior high school	28, 44.4%	27, 43.5%
Senior high school	23, 36.5%	23, 37.1%
College	12, 19.1%	12, 19.4%
Occupation (n, %)		
Farmer	24, 38.1%	22, 35.5%
Worker	22, 34.9%	23, 37.1%
Intellectual	17, 27.0%	17, 27.4%
Dementia type (n, %)		
Vascular dementia	24, 38.1%	22, 35.5%
Alzheimer's disease	41, 65.1%	38, 61.3%

Materials and methods

General information of patients

125 SD patients admitted into the department of Neurology, the Second Affiliated Hospital of Zhengzhou University from December 2010 to December 2013 were enrolled in this study. There were 77 males and 48 females, aged 65-78 years. Among the patients, 46 patients had vascular dementia, while the other 79 patients had Alzheimer's dementia. The inclusion criteria were as follows: patients met the diagnostic criteria of SD, with Mini Mental State Examination (MMSE) scores between 4.5 to 22 points. The exclusion criteria were as follows: severe liver and kidney dysfunctions, heart failure, severe neurological deficit, could not complete trial-related assessment and determination. The enrolled patients were randomly divided into the combination group (63 cases) and control group (62 cases). The two groups showed no significant difference in age, gender, and disease types ($P > 0.05$) (**Table 1**). This study was approved by the Ethics Committee of Second Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants.

Treatment methods

The combination group was orally administrated with Nim (tablets, Eisai Co., Ltd., Tokyo, Japan; 30 mg daily, divided into three times) plus Don (Aricept tablets; Bayer HealthCare Co., Ltd., Beijing, China; 10 mg daily). The control group was only administrated with Nim tablets, with dosage and administration method the same as combination group. The treatment period was 12 months. Two groups were performed with symptomatic treatment throughout the treatment period, and other appropriate symptomatic treatments using antiplatelet drug, hypoglycemic agent, antihypertensive drug, etc. was administered depending on patient's symptoms. No other nootropic drug was used during the observation period. Before treatment, the blood routine and liver and kidney functions of patients included were tested, and close attentions were paid towards various adverse reactions associated with the observation period.

Outcome measurement

The changes of MMSE, Hasegawa Dementia Scale (HDS) and activities of daily living (ADL) were observed before and after treatment. The Clinical Dementia Rating (CDR) and Global Deterioration Scale (GDS) were applied to assess the SD degree before and after treatment. CDR was used to assess the patient's judgment and problem solving skills. The sum of 6 skills scores was the total score. Based on the assessment results, five levels (0, 0.5, 1, 2 and 3 points) was used to represent normal, questionable, mild, medium and severe SD. GDS was used to assess the SD degree, focusing on patient's social life and personal self-care abilities.

The treatment effects of the 2 groups were evaluated by MMSE score, among which "notable" referred to MMSE score increased by 5 points or more after treatment than before, "improved" referred to MMSE score increased by more than 2 points while less than 5 points after treatment than before, and "invalid" referred to MMSE score increased less than 2 points after treatment than before.

Statistical analysis

The statistical analysis was carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). The numeration data were analyzed using chi-square test. The clinical efficacies with ranking treatment were processed with rank

Table 2. Comparison of clinical efficacy between 2 groups

Group	n	Notable	Improved	Invalid	Effective rate
Combination	63	41 (65.1%)	16 (25.4%)	6 (9.5%)	57 (90.48%)
Control	62	24 (38.7%)	18 (29.0%)	20 (32.3%)	40 (67.74%)
U/X^2		U = 4.205			X^2 = 4.286
P		< 0.05			< 0.05

Table 3. Comparison of MMSE, HDS and ADL between 2 groups

Group		Control (n = 62)	Combination (n = 63)	P
MMSE	Before treatment	15.21 ± 2.51	14.92 ± 1.56	> 0.05
	After treatment	21.11 ± 3.62	26.71 ± 2.63	< 0.05
HDS	Before treatment	14.02 ± 2.53	15.21 ± 2.73	> 0.05
	After treatment	21.52 ± 2.35	26.67 ± 3.54	< 0.05
ADL	Before treatment	36.29 ± 3.88	35.10 ± 4.22	> 0.05
	After treatment	48.92 ± 5.33	74.90 ± 5.24	< 0.05

MMSE: Mini Mental State Examination, HDS: Hasegawa Dementia Scale, ADL: activities of daily living

Table 4. Comparison of CDR and GDS between 2 groups

Group	n	CDR score		GDS score	
		Before treatment	After treatment	Before treatment	After treatment
Combination	63	2.29 ± 0.12	1.85 ± 0.29	5.20 ± 0.15	4.89 ± 0.25
Control	62	2.32 ± 0.42	2.10 ± 0.19	5.19 ± 0.59	5.08 ± 0.49
P		> 0.05	< 0.05	> 0.05	< 0.05

CDR: Clinical Dementia Rating, GDS: Global Deterioration Scale.

sum test, and the data with significance were performed with chi-square test towards clinical total efficiency. The measurement data were analyzed using t test. P < 0.05 was considered as statistically significant.

Results

Comparison of clinical efficacy between 2 groups

As shown in **Table 2**, there were 41 (65.1%) notable cases, 16 (25.4%) improved cases and 6 (9.5%) invalid cases in combination group, and 24 (38.7%) notable cases, 18 (29.0%) improved cases and 20 (32.3%) invalid cases in control group. There was significant difference between two groups (P < 0.05). The effective rate in combination group was 90.48%, which was significantly higher than 67.74% in control group (P < 0.05).

Comparison of MMSE, HDS and ADL between the 2 groups

The cognition, life skills and other living aspects before and treatment in two groups were compared. Before treatment, there was no significant difference in above indexes between 2 groups. After treatment, the scores of MMSE, HDS and ADL in combination group were significantly higher than control group (P < 0.05) (**Table 3**).

Comparison of CDR and GDS between 2 groups

Before treatment, there was no significant difference of CDR and GDS score between two groups (P > 0.05). After treatment, the scores of CDR and GDS in two groups were decreased, and those in combination group were significantly lower than control group (P < 0.05) (**Table 4**).

Adverse reaction

During the observation period, no serious adverse reaction occurred in both 2 groups.

Discussion

As mankind is gradually entering aging society, the incidences of more and more age-related diseases are significantly increased, exhibiting the developing trend towards younger and younger patients. SD is a common disease affecting elderly patients. It not only severely leads to the decreasing of life quality, but also increases mental burdens and life pressures to the family, community and patients themselves, thus severely damaging patients' family happiness [11]. Presently, there is no fundamentally effective drug towards SD, and the clinical treatment mainly uses traditional Chinese medicine, anti-cholinesterase drugs and symptomatic therapy to slow the progression of SD, ensure patients' life quality and delay the degree of SD [12, 13]. Because the etiology and pathogenesis of SD are not fully understood, medication is mainly used in clini-

cal treatment [14]. The more commonly used clinical drugs such as cholinesterase inhibitors can improve the transferring of cholinergic neurotransmitters, thereby improving the cognitive abilities of patients and maintaining their normal behaviors and ADL [15, 16]. On the other hand, these drugs can improve the utilization rate of glucose in brain tissues, thus improving the patients' brain neuron functions and learning, attention and memory abilities [17, 18].

Nim is a calcium channel blocker, and can penetrate blood-brain barrier and enter brain blood vessels and nerve cells, thus dilating the brain blood vessels and playing its effects [19, 20]. Don is a new highly selective reversible inhibitor of acetylcholinesterase. Through inhibiting the hydrolysis of acetylcholine neurotransmitter, it increases the concentration of acetylcholine among synaptic clefts, enhances cholinergic functions, thereby improving cognitive functions in patients [21].

This study assesses the abilities of patients' daily behaviors from many aspects, and observes the combined effects of Nim and Don in treating SD. Several rating scales are used to evaluate the treatment efficacies, among which MMSE is mainly used to assess patients' such abilities as orientation, calculation, attention, memory, language and visual space after treatment. HDS is mainly used to understand the improvements of cognitive functions, and ADL is mainly used to assess the impacts on patients' ADL and associated improvements. The other two indicators, CRG and GDS, are mainly used to assess patients' thinking, judgment, problem-solving skills and the degrees of SD. The results suggest that, Nim plus Don can obtain satisfactory results in treating SD. The effective rate in combination is 90.48%, significantly higher than control group (67.74%). At the same time, after treatment the scores of MMSE, HDS and ADL in combination group are significantly higher than those of the control group. This indicates that, all indicators, cognitive function and ADL in combination group were better improved than control group, and Nim plus Don can better improve patients' ADL. After treatment the scores of CDR and GDS in combination group are significantly decreased, and the declining amplitude is significantly higher than control group, indicating that after treatment the SD degree in combination group is significantly lower than control group, and patients' judgment is significantly better than control group. This confirms that Nim plus Don can obtain satisfactory therapeutic effects in treating SD, and can delay the progression of SD, improve the memory and cognitive ability and life quality for elderly SD patients, thus reducing life and mental burdens of patients' family.

In this study, no serious adverse event occurs in both 2 groups. Combined with most current clinical reports [22, 23], the adverse reactions of Nim are mainly headache, facial flushing and other mild symptoms, while those of Don are mainly gastrointestinal reactions. The combination of Nim and Don are safe in treating SD, and the effects are more obvious than single Nim treatment.

Disclosure of conflict of interest

None.

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References

[1] Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ, Davies P, Del Tredici K, Duyckaerts C, Frosch MP, Haroutunian V, Hof PR, Hulette CM, Hyman BT, Iwatsubo T, Jellinger KA, Jicha GA, Kövari E, Kukull WA, Leverenz JB, Love S, Mackenzie IR, Mann DM, Masliah E, McKee AC, Montine TJ, Morris JC, Schneider JA, Sonnen JA, Thal DR, Trojanowski JQ, Troncoso JC, Wisniewski T, Woltjer RL, Beach TG. Correlation ofalzheimer disease neuropathologic changes with cognitive status: A review of the literature. J Neuropathol Exp Neurol 2012; 71: 362-381.

[2] Christiane R, Carol B, Richard M. Epidemiology ofa alzheimer disease. Nat Rev Neurol 2011; 7: 137-152.

[3] Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vas-

cular contributions to cognitive impairment anddementia: A statement for healthcare professionals from the american heart association/ american stroke association. Stroke 2011; 42: 2672-2713.

[4] Bradley TH, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. National Institute on aging-alzheimer's association guidelines for the neuropathologic assessment of alzheimer's disease. Neurology 2012; 78: 468-476.

[5] Renata TV, Leonardo C, Sergio M, Adriana CS, Antonio EN, Oscar AC, Mauro GC. Epidemiology of early-onsetdementia: a review of the literature. Clin Pract Epidemiol Ment Health 2013; 9: 88-95.

[6] Caramelli P, Laks J, Palmini AL, Nitrini R, Chaves ML, Forlenza OV, Vale Fde A, Barbosa MT, Bottino CM, Machado JC, Charchat-Fichman H, Lawson FL. Effects of galantamine and galantamine combined with nimodipine on cognitive speed and quality of life in mixed dementia: a 24-week, randomized, placebo-controlled exploratory trial (the REMIX study). Arq Neuropsiquiatr 2014; 72: 411-417.

[7] Nimmrich V, Eckert A. Calcium channel blockers and dementia. Br J Pharmacol 2013; 169: 1203-1210.

[8] Vardarajan BN, Faber KM, Bird TD, Bennett DA, Rosenberg R, Boeve BF, Graff-Radford NR, Goate AM, Farlow M, Sweet RA, Lantigua R, Medrano MZ, Ottman R, Schaid DJ, Foroud TM, Mayeux R; NIA-LOAD/NCRAD Family Study Group. Age-specific incidence rates for dementia and Alzheimer disease in NIA-LOAD/NCRAD and EFIGA families: National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease (NIA-LOAD/NCRAD) and Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA). JAMA Neurol 2014; 71: 315-323.

[9] Lee S, Zemianek J, Shea TB. Rapid, reversible impairment of synaptic signaling in cultured cortical neurons by exogenously-applied amyloid-β. J Alzheimers Dis 2013; 35: 395-402.

[10] Sabbagh M, Cummings J, Christensen D, Doody R, Farlow M, Liu L, Mackell J, Fain R. Evaluating the cognitive effects of donepezil 23 mg/d in moderate and severe Alzheimer's disease: analysis of effects of baseline features on treatment response. BMC Geriatr 2013; 13: 56.

[11] Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, Luchsinger JA, Ogunniyi A, Perry EK, Potocnik F, Prince M, Stewart R, Wimo A, Zhang ZX, Antuono P; World Federation of Neurology Dementia Research Group. Alzheimer's disease and vasculardementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008; 7: 812-826.

[12] Daschil N, Humpel C. Nifedipine and nimodipine protect dopaminergic substantia nigra neurons against axotomy-induced cell death in rat vibrosections via modulating inflammatory responses. Brain Res 2014; 1581: 1-11.

[13] Yukiko H, Shuko T, Hansang C, Susanne W, Timothy MS, Kazue T, Daniel I, David RE, Bradley TH, Eloise H. FDA approved asthma therapeutic agent impacts amyloid β in the brain in a transgenic model of Alzheimer's disease. J Biol Chem 2015; 290: 1966-1978.

[14] Health Quality Ontario. Caregiver- and Patient-Directed Interventions for Dementia:An Evidence-Based Analysis. Ont Health Technol Assess Ser 2008; 8: 1-98.

[15] Stephen J, Richard JH, David W. The safety and tolerability ofdonepezilin patients with Alzheimer's disease. Br J Clin Pharmacol 2004; 58: 1-8.

[16] Li DQ, Zhou YP, Yang H. Donepezil Combined with Natural Hirudin Improves the Clinical Symptoms of Patients with Mild-to-Moderate Alzheimer's Disease: A 20-Week Open-Label Pilot Study. Int J Med Sci 2012; 9: 248-255.

[17] Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart association/American stroke association. Stroke 2011; 42: 2672-2713.

[18] Jacqueline OB, John WJ, Francine G. Postmenopausal HormoneTherapyIs Not Associated With Risk of All-CauseDementiaand Alzheimer's Disease. Epidemiol Rev 2014; 36: 83-103.

[19] Deborah AL, Kenneth ML. Vascular Cognitive Impairment: Disease Mechanisms and Therapeutic Implications. Neurotherapeutics 2011; 8: 361-373.

[20] Nimmrich V, Eckert A. Calcium channel blockers anddementia. Br J Pharmacol 2013; 169: 1203-1210.

[21] Gustavo CR, Stephen S, Sandra EB, Donald RR Charles D, Michael WW, Margaret M, Dinesh K, Rachel S, Holly P. Randomized, Placebo-Controlled, Clinical Trial of Donepezilin Vascular Dementia: Differential Effects by Hippocampal Size. Stroke 2010; 41: 1213-1221.

[22] Wang YY, Gao ZY. A study on adverse reactions of Nimodipine. North Pharmaceutical 2011; 8: 8-9.

[23] Shintani EY, Uchida KM. Donepezil: an anticholinesterase inhibitor for Alzheimer's disease. Am J Health Syst Pharm 1997; 54: 2805-2810.