

A systematic review of the efficacy of donepezil hydrochloride combined with nimodipine on treating vascular dementia

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Abstract

Background: Vascular dementia (VaD) is a comprehensive syndrome related to the damage of cognitive function and various cerebral vascular illnesses. VaD is also generally recognized as the second most common type of dementia after Alzheimer disease, contributing to 30% of the dementia population in Asia and developing countries. The ability of donepezil hydrochloride and nimodipine had been respectively proven in improving cognitive function in vascular dementia. However, whether the combined application of both drugs contribute to better efficacy remains as a research hotspot. Studies had shown definite satisfactory result with such combination, however evidence-based evaluation of the efficacy is still lacking. Therefore, meta-analysis is employed in this study to evaluate the efficacy and safety of using donepezil hydrochloride combined with nimodipine in treating VaD to provide references for clinical treatments. The efficacy of donepezil hydrochloride combined with nimodipine on treating vascular dementia is systematically reviewed to provide evidence-based references for clinical applications.

Methods: Both Chinese and English databases were searched from the start till August, 2020 for any RCT regarding the combined use of the 2 drugs in treating vascular dementia. Two investigators would later evaluate and screened out research and data based on an improved Jaded scale. Software Rev Man 5.3.0 was employed to carry out meta-analysis on clinical effificacy, mini-mental state examination (MMSE) ratings, activity of daily living (ADL) ratings, and clinical dementia scale (CDR) ratings.

Results: Donepezil hydrochloride combined with nimodipine had demonstrated satisfactory efficacy on the treatment of vascular dementia. Improvements were namely spotted on MMSE scale, ADL scale, and CDR scale, with the utmost efficacy by 12 weeks after intervention.

Conclusions: Donepezil hydrochloride combined with nimodipine had good efficacy in the treatment of patients with vascular dementia, mainly in terms of improving the Simple MMSE scores, the ability to use daily living scale (ADL) scores and the CDR, and the best results were obtained after 12 weeks of intervention. Such conclusion should be cautiously evaluated.

Abbreviations: ADL = activity of daily living, CDR = clinical dementia scale, MMSE = mini-mental state examination, VaD = vascular dementia.

Keywords: donepezil hydrochloride, efficacy, meta-analysis, nimodipine, vascular dementia

1. Introduction

Vascular dementia (VaD) is a comprehensive syndrome related to the damage of cognitive function and various cerebral vascular illnesses. VaD is also generally recognized as the second most common type of dementia after Alzheimer disease, contributing to 30% of the dementia population in Asia and developing countries.^[1] The ability of donepezil hydrochloride

Data Availability: All data compiled or analyzed during this study are included in this published article.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

^aMinda Hospital of Hubei Minzu University, Enshi, Hubei, China, ^bDongzhimen Hospital, Beijing University of Traditional Chinese Medicine, Beijing, China, ^cThe First Affiliated Hospital of Guangxi University of Chinese Medicine, Guangxi, China, ^dSchool of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, ^eHuangGang Hospital of TCM Affifiliated to Hubei University of Chinese Medicine, Huang Gang, Hubei, China, ^Institute of Geriatrics, Hubei University of Chinese Medicine, Hubei, China. and nimodipine had been respectively proven in improving cognitive function in vascular dementia.^[2,3] However, whether the combined application of both drugs contribute to better efficacy remains as a research hotspot. Studies had shown definite satisfactory result with such combination, however evidence-based evaluation of the efficacy is still lacking. Therefore, meta-analysis is employed in this study to evaluate the efficacy and safety of using donepezil hydrochloride combined with

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nimodipine in treating VaD to provide references for clinical treatments. $^{[4,5]}$

2. Data and Methods

2.1. Inclusion criteria

Studies that employed randomized or quasi-randomized controlled trial, with or without blinding methods. Research object fulfilled the diagnostic criteria of VaD.^[6] Interventions: The observation group should employ a combination usage of donepezil hydrochloride and nimodipine, while the control group should employ a sole usage of either 1 drug. Efficacy indicators: general clinical efficacy; mini-mental state examination (MMSE); activity of daily living (ADL); clinical dementia scale (CDR).

2.2. Exclusion criteria

Combined with other types of dementia apart from VaD; duplicated researches; fundamental laboratory report; literature review; non-RCT researches; interventions incoherent with inclusion criteria; incomplete data; unclear diagnosis.

2.3. Research strategy

Research is conducted based on the following databases: China National Knowledge Infrastructure, Wanfang database, China Science and Technology Journal Database, China Biomedical Database, PubMed Embase, Cochrane Library. Studies were included from the time of start to October 30, 2020. Keywords: vascular dementia, vascular cognitive impairment, donepezil hydrochloride, nimodipine.

2.4. Selection of studies and data extractions

Studies and data were selected and extracted by 2 independent investigators. When the consensus on a certain piece of information cannot be reached, it would be discussed and consulted by a third party. The following components were extracted from the data: name of the first author, time of publish, sample size, ways of intervention, result indicators, and risk of bias related indicators.

2.5. Quality evaluation of studies

Clinical trials within the studies included were evaluated by Cochrane risk of bias tool^[7]: whether it is randomized; whether allocation method was concealed; whether both the participants and investigators were blinded; whether the results were drawn under double blinding; whether the data throughout the process to conclusion was complete; selective reporting of research results; other source of bias. All items evaluated as correct would be considered as low risk of bias. One or more than one item evaluated as unclear would be considered as uncertain. One or more than one item evaluated as incorrect would be considered as high risk of bias.

2.6. Statistical method

Software RevMan5.3 by Cochrane was employed to conduct statistical analysis. Heterogeneity test would indicate studies with higher homogeneity (P > .1) and fixed effect model would be utilized for analysis. The remaining studies would be analyzed by random effect model. Odd ratio and 95% confidence interval of count data was calculated. When P < .05 and 1 was not included within 95% confidence interval, the point estimation differences of OR were considered as statistically significance. Mean difference and 95% confidence interval of count

data were calculated. Funnel plot was drawn to analyze publication bias, the better completion and symmetricity of the plot would demonstrate lower publication bias to ensure the stability of the analytical results.

2.7. Ethical review

This study does not involve a clinical trial and ethical review is not applicable.

3. Results

3.1. Studies inclusion

One hundred thirteen studies were obtained through database searching. Forty nine studies including duplicated studies were than excluded through screening at title and abstract. Full text screening were then carried out to further exclude 46 studies. Eighteen RCTs with a sample size of 1647 patients were ultimately included in our study. See Fig. 1 and Table 1.

3.2. Quality evaluation of included studies

Eighteen studies^[8-25] mentioned the word "randomized," 8 studies^[8,9,17,20,21,23-25] mentioned specific randomization methods. Allocation concealment, blinding, and other risks were not mentioned in all studies. Eighteen studies had given detailed description on the baseline situation of included cases, and the employment of software RevMan5.3 on carrying risk of bias evaluation. Results on Figs. 2 and 3.

3.3. Results of meta-analysis

3.3.1. Results of the meta-analysis on MMSE. Seventeen studies^[8-19,21-25] had compared the MMSE score before and after the combined usage of donepezil hydrochloride and nimodipine in the treatment of vascular dementia. Heterogeneity (P < .000001, $I^2 = 76\%$) were perceived in respective group of study, therefore meta-analysis was carried out by random effect model as shown in Fig. 4.

Results of the meta-analysis showed a statistically significant improvement on MMSE score (OR = 2.50, 95% CI [1.92, 3.09], P < .00001) on the experimental group than on the control group. Sub-group analysis was further conducted base on the duration of treatment (12, 8, 4 weeks). Eleven studies had observed the MMSE score after 12 weeks of intervention, heterogeneity (P < .000001, $I^2 = 74\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on MMSE score (OR = 2.55, 95% CI [1.79, 3.31], P < .00001). Sensitivity analysis was further conducted: As the 11 groups of study regarding improvements of the MMSE score after 12 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, $I^2 = 74\%$), study was therefore individually excluded respectively. The exclusion of the 3 studies conducted by Yangqin Kong, Kui Xiong, Zhiqiang Wang had induced a significant change in the heterogeneity among the remaining 8 studies, indicating absence of heterogeneity (P = .31, $I^2 = 15\%$). Therefore the 3 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Seven studies had observed the MMSE score after 8 weeks of intervention, heterogeneity ($P = .0004, I^2$ = 76%) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on MMSE score (OR = 2.33, 95% CI [1.52, 3.14], P < .00001). Sensitivity analysis was further conducted: as the 7 groups of study regarding improvements of the MMSE score after 8 weeks had demonstrated a relatively higher statistical heterogeneity





 $(P = .0004, I^2 = 76\%)$, study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Xin He, Dandan Zhang had induced a significant change in the heterogeneity among the remaining 5 studies, indicating absence of heterogeneity (P = .84, $I^2 = 0\%$). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Eight studies had observed the MMSE score after 4 weeks of intervention, heterogeneity (P < .000001, $I^2 = 81\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on MMSE score (OR = 0.88, 95% CI [-0.15, 1.91], P < .00001). Sensitivity analysis was further conducted: as the 8 groups of study regarding improvements of the MMSE score after 4 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, $I^2 = 81\%$), study was therefore individually excluded respectively. The exclusion of the 1 study conducted by Dandan Zhang had induced a significant change in the heterogeneity among the remaining 5 studies, indicating absence of heterogeneity (P = .49, $I^2 = 0\%$). Therefore the studies were highly considered as the source of heterogeneity in regard of this specific indicator. While at the same time, MMSE score improvement was considered most satisfactory with 12 weeks of combined usage of donepezil hydrochloride

Table 1 Basic information of the included literatures.

			Numbe	r of cases		Interv	ventions	Random method	
First author	Year of publication	Country	Control group	Treatment group	Basic information	Control group	Treatment group		Observation target
Cuiyun Zhang ^[8]	2016	China	40	40	Similarity	А	A+B	Table of random numbers	
Jinxia Huo ^[9]	2015	China	65	59	Similarity	В	A+B	Table of random numbers	
Haibo Zeng ^[10]	2015	China	34	34	Similarity	А	A+B	Random	
Mahebula ^[11]	2012	China	34	34	Similarity	А	A+B	Random	
Lu Wang ^[12]	2015	China	30	30	Similarity	А	A+B	Random	
Jinsong Yang ^[13]	2014	China	150	150	Similarity	А	A+B	Random	
Zhiqing Wang ^[14]	2014	China	40	40	Similarity	А	A+B	Random	
Yanwei Zhu ^[15]	2018	China	48	48	Similarity	А	A+B	Random	
Erhen Ai ^[16]	2013	China	20	20	Similarity	А	A+B	Random	
Xin He ^[17]	2020	China	43	43	Similarity	A	A+B	Table of random numbers	
Xia Wang ^[18]	2012	China	19	20	Similarity	А	A+B	Random	
Xiaojing Sun ^[19]	2016	China	42	42	Similarity	A	A+B	Random	
Xiaohong	2020	China	30	30	Similarity	А	A+B	Lottery	
Zhang ^[20]					-				
Kui Xiong ^[21]	2020	China	60	60	Similarity	А	A+B	Lotterv	
Yanggin Kong ^[22]	2017	China	25	25	Similarity	А	A+B	Random	
Dandan Zhang ^[23]	2018	China	76	76	Similarity	В	A+B	Random	
Shiving Zhao ^[24]	2019	China	40	40	Similarity	В	A+B	Random envelope method	
Yongwei Zhang ^[25]	2017	China	30	30	Similarity	В	A+B	Random	

and nimodipine in treating VaD through subgroup analysis. Detail as shown in Figs. 5 and 6.

3.3.2. Results of the meta-analysis on activity daily scale. Thirteen studies^[10-18,20,22-24] had compared the CDR score before and after the combined usage of donepezil hydrochloride and nimodipine in the treatment of vascular dementia. Heterogeneity (P < .000001, $I^2 = 99\%$) were perceived in respective group of study, therefore meta-analysis was carried out by random effect model as shown in Fig. 7.

Results of the meta-analysis showed an improvement on ADL score among the experimental group compared with the controlled group but indicates no statistical significance (OR = 0.16, 95% CI [-3.55, 3.87], P = .93). Sub-group analysis was further conducted based on the duration of treatment (12, 8, 4 weeks). Eight studies had observed the ADL score after 12 weeks of intervention, heterogeneity (P < .000001, $I^2 = 99\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated improvement on ADL score among the experimental

group compared with the controlled group but indicates no statistical significance (OR = 0.33, 95% CI [-3.97, 4.63], P = .88). Sensitivity analysis was further conducted: As the 8 groups of study regarding improvements of the ADL score after 12 weeks had demonstrated a relatively higher statistical heterogeneity $(P < .000001, I^2 = 99\%)$, study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Yangqin Kong and Zhiqiang Wang had induced a significant change in the heterogeneity among the remaining 6 studies, indicating absence of heterogeneity (P < .000001, $I^2 = 0\%$). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Six studies had observed the ADL score after 8 weeks of intervention, heterogeneity (P < .000001, $I^2 = 98\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated improvement on ADL score among the experimental group compared with the controlled group but indicates no statistical significance (OR = -2.4, 95% CI [-5.36, 4.87], P = .93). Sensitivity analysis was further conducted: as the 8 groups of study regarding improvements of the ADL score



Figure 2. Risk of bias graph.



Figure 3. Risk of bias summary.

after 12 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, $I^2 = 98\%$), study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Xin He and Xiaotong Zhang had induced a significant change in the heterogeneity among the remaining 4 studies, but significant heterogeneity was still present (P = .04, $I^2 = 63\%$). The improvement on ADL score within the experimental group was significantly higher than the controlled group

(OR = -4.31, 95% CI [-5.90, -2.73], P < .000001). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Five studies had observed the ADL score after 4 weeks of intervention, heterogeneity $(P < .000001, I^2 = 89\%)$ was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated improvement on ADL score among the experimental group compared with the controlled group but indicates no statistical significance (OR = -1.46, 95% CI [-4.91, 2.00], P = .41). Sensitivity analysis was further conducted: As the 5 groups of study regarding improvements of the ADL score after 4 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, $I^2 = 98\%$), study was therefore individually excluded respectively. The exclusion of the study conducted by Dandan Zhang had induced a significant change in the heterogeneity among the remaining 4 studies, indicating an absence of heterogeneity (P = .79, $I^2 = 0\%$). Result from the meta-analysis had shown improvements on ADL score within the experimental group io comparison with the controlled group without statistical significance (OR = -0.16, 95% CI [-1.58, 1.26], P = .83). Therefore this study was highly considered as the source of heterogeneity in regard of this specific indicator. While at the same time, ADL score improvement was considered most satisfactory with 12 weeks of combined usage of donepezil hydrochloride and nimodipine in treating VaD through subgroup analysis. Detail as shown in Figs. 8 and 9.

3.3.3. Results of the meta-analysis on clinical dementia scale. Eight studies^[8,12,13,19-21,23,24] had compared the ADL score before and after the combined usage of donepezil hydrochloride and nimodipine in the treatment of vascular dementia. Heterogeneity (P < .000001, $I^2 = 84\%$) were perceived in respective group of study, therefore meta-analysis was carried out by random effect model as shown in Fig. 10.

Results of the meta-analysis showed a statistically significant improvement on CDR score (OR = -0.28, 95% CI [-0.40, -0.17], P < .000001) on the experimental group than on the control group. Sub-group analysis was further conducted based on the duration of treatment (12, 8, 4 weeks). Two studies had observed the CDR score after 12 weeks of intervention, heterogeneity (P = .06, $I^2 = 72\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on CDR score (OR = -0.32, 95% CI [-0.52, -0.11], P = .002) within the experimental group in comparison with the controlled group. Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Five studies had observed the CDR score after 8 weeks of intervention, heterogeneity (P < $.000001, I^2 = 90\%$) was detected in respective group of study, meta-analysis was than conducted through random effect model. Result had indicated statistically significant improvement on CDR score (OR = -0.24, 95% CI [-0.42, -0.07], P = .006) within the experimental group in comparison with the controlled group. Sensitivity analysis was further conducted: as the 5 groups of study regarding improvements of the CDR score after 8 weeks had demonstrated a relatively higher statistical heterogeneity (P < .000001, $I^2 = 90\%$), study was therefore individually excluded respectively. The exclusion of the 2 studies conducted by Dandan Zhang, Xiaohong Zhang had induced a significant change in the heterogeneity among the remaining 3 studies, but significant heterogeneity was still present (P = .27, $I^2 = 24\%$). The improvement on CDR score was statistically significant within the experimental group in comparison with the controlled group (OR = -0.12, 95% CI [-0.21, -0.03], P = .001). Therefore the 2 studies were highly considered as the source of heterogeneity in regard of this specific indicator. Four studies had observed the CDR score after 4 weeks of intervention, heterogeneity ($P = .01, I^2 = 73\%$) was detected in respective group of study, meta-analysis was

	Experimental			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cuiyun Zhang2016	15.34	2.81	40	13.88	2.52	40	6.2%	1.46 [0.29, 2.63]	
Dandan Zhang2018	25.89	2.75	76	22.35	2.13	76	7.3%	3.54 [2.76, 4.32]	-
Erken Ai2013	23.1	2.2	20	22	1.4	20	6.3%	1.10 [-0.04, 2.24]	
Haibo Zhang2015	20.39	3.27	34	18.75	3.05	34	5.4%	1.64 [0.14, 3.14]	<u>⊢</u>
Jingsong Yang2016	15.26	2.97	150	13.73	2.42	150	7.6%	1.53 [0.92, 2.14]	-
Jinxia Huo2015	24.4	3.6	65	21.9	3.8	59	5.9%	2.50 [1.19, 3.81]	
Kui Xiong2020	22.01	4.18	60	18.29	3.54	60	5.7%	3.72 [2.33, 5.11]	
Lu Wang2015	15.27	2.98	30	13.74	2.43	30	5.7%	1.53 (0.15, 2.91)	
Mahebula2012	20.39	3.27	34	18.75	3.05	34	5.4%	1.64 (0.14, 3.14)	<u>⊢</u>
Shiying Zhao2019	15.5	3	40	13.8	2.4	40	6.2%	1.70 (0.51, 2.89)	
Xia Wang2012	24.2	3.2	19	23.1	1.5	20	5.2%	1.10 [-0.48, 2.68]	+
Xiaojing Sun2016	22.37	5.67	42	19.74	5.12	42	3.6%	2.63 [0.32, 4.94]	
Xin He2020	26.62	2.92	43	22.81	2.92	43	6.1%	3.81 [2.58, 5.04]	
Yangqin Kong2017	25.2	1.8	25	21.6	1.1	25	7.1%	3.60 [2.77, 4.43]	-
Yanwei Zhu2018	22.37	4.61	48	19.57	4.34	38	4.4%	2.80 (0.90, 4.70)	
Yongwei Zhang2017	26.23	3.74	30	22.69	3.09	30	4.8%	3.54 [1.80, 5.28]	
Zhiqiang Wang2014	24.4	2.4	40	20.1	1.3	40	7.1%	4.30 [3.45, 5.15]	-
Total (95% CI)			796			781	100.0%	2.50 [1.92, 3.09]	•
Heterogeneity: Tau ² = 1	.07; Chi	² = 67.	10, df=	:16 (P <	< 0.000	101); I ^z :	= 76%		
Test for overall effect: Z	= 8.38 (P < 0.0	-10 -5 U 5 10						
			/						Favours (experimental) Favours (control)

Figure 4. The forest plot of MMSE. MMSE = mini-mental state examination.

	Exp∉	erimen	ıtal	С	ontrol			Mean Difference	Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.1 MMSEscore (1	2w)								
rken Ai2013	23.1	2.2	20	22	1.4	20	4.1%	1.10 [-0.04, 2.24]	<u>├</u>
aibo Zhang2015	20.39	3.27	34	18.75	3.05	34	3.6%	1.64 [0.14, 3.14]	
nxia Huo2015	24.4	3.6	65	21.9	3.8	59	3.9%	2.50 [1.19, 3.81]	
ui Xiong2020	22.01	4.18	60	18.29	3.54	60	3.7%	3.72 [2.33, 5.11]	
ahebula2012	20.39	3.27	34	18.75	3.05	34	3.6%	1.64 [0.14, 3.14]	
hiying Zhao2019	15.5	3	40	13.8	2.4	40	4.0%	1.70 [0.51, 2.89]	
a Wang2012	24.2	3.2	19	23.1	1.5	20	3.5%	1.10 [-0.48, 2.68]	
angqin Kong2017	25.2	1.8	25	21.6	1.1	25	4.5%	3.60 [2.77, 4.43]	
anwei Zhu2018	22.37	4.61	48	19.57	4.34	38	3.0%	2.80 [0.90, 4.70]	
ongwei Zhang2017	26.23	3.74	30	22.69	3.09	30	3.3%	3.54 [1.80, 5.28]	
hiqiang Wang2014	24.4	2.4	40	20.1	1.3	40	4.5%	4.30 [3.45, 5.15]	
ubtotal (95% CI)			415			400	41.7%	2.55 [1.79, 3.31]	•
eterogeneity: Tau ² =	1.17; Chi	i ² = 39.	.06. df=	= 10 (P <	< 0.000	01); I ² =	74%		
est for overall effect:	Z= 6.59 ((P < 0.0	00001)						
1.2 MMSEscore (8	w)								
uiyun Zhang2016	15.34	2.81	40	13.88	2.52	40	4.1%	1.46 [0.29, 2.63]	
andan Zhang2018	25.89	2.75	76	22.35	2.13	76	4.6%	3.54 [2.76, 4.32]	
nasona Yana2016	15.26	2.97	150	13.73	2.42	150	4.8%	1.53 (0.92, 2.14)	
nxia Huo2015	22.2	3.5	65	20	3.1	59	4.1%	2.20 [1.04, 3.36]	
u Wang2015	15.27	2.98	30	13.74	2.43	30	3.8%	1.53 (0.15, 2.91)	
in He2020	26.62	2.92	43	22.81	2.92	43	4.0%	3.81 [2.58, 5.04]	
anwei Zhu2018	18.27	4.17	48	16.15	4.25	48	3.3%	2 12 [0 44 3 80]	
ubtotal (95% CI)	10.21		452			446	28.6%	2.33 [1.52, 3.14]	•
eterogeneity: Tau ² =	0.85: Ch ⁱ	i ² = 24.	70. df=	= 6 (P =	0.0004	4): $ ^2 = 7$	76%		
est for overall effect:	Z= 5.64 ((P < 0.1	00001)	- (.,,			
1.3 MMSEscore (4	w)								
uiyun Zhang2016	12.72	3.19	40	12.69	2.61	40	3.9%	0.03 [-1.25, 1.31]	
andan Zhang2018	21.76	2.06	76	18.98	1.89	76	4.8%	2.78 [2.15, 3.41]	
rken Ai2013	19.7	2.3	20	19.8	1.8	20	3.9%	-0.10 [-1.38, 1.18]	
nxia Huo2015	18.5	2.7	65	18	2.9	59	4.3%	0.50 [-0.49, 1.49]	-+
u Wang2015	12.78	3.21	30	12.41	2.62	30	3.6%	0.37 [-1.11, 1.85]	
a Wang2012	20.8	3.4	19	20.9	1.9	20	3.2%	-0.10 [-1.84, 1.64]	
-	22.37	5.67	42	19.74	5.12	42	2.5%	2.63 [0.32, 4.94]	
aojing Sun2016	15.68	4.21	48	14.67	3.82	48	3.4%	1.01 [-0.60, 2.62]	
aojing Sun2016 anwei Zhu2018			340			335	29.7%	0.88 [-0.15, 1.91]	
aojing Sun2016 anwei Zhu2018 ubtotal (95% CI)				= 7 (P <	0.0000	01); I ² =	81%		
aojing Sun2016 anwei Zhu2018 ubtotal (95% Cl) eterogeneity: Tau² =	1.68: Chi	² = 37.	41. dt =			/ 1 -			1
aojing Sun2016 anwei Zhu2018 ubtotal (95% CI) eterogeneity: Tau ² = est for overall effect:	1.68; Chi Z = 1.68 (i² = 37. (P = 0.)	.41, ατ: D9)						
aojing Sun2016 anwei Zhu2018 ubtotal (95% Cl) eterogeneity: Tau ² = est for overall effect: otal (95% Cl)	1.68; Chi Z = 1.68 (i² = 37. (P = 0.1	.41, af: 09) 1207			1181	100.0%	1.99 [1.47, 2.51]	•
aojing Sun2016 anwei Zhu2018 ubtotal (95% Cl) eterogeneity: Tau ² = est for overall effect: otal (95% Cl) eterogeneity: Tau ² =	1.68; Chi Z = 1.68 (1.36; Chi	i² = 37. (P = 0.0 i² = 12)	.41, df: 09) 1207 7.11, df	i = 25 (P	< 0.01	1181	100.0 % ² = 80%	1.99 [1.47, 2.51]	· · · · · · · · · · · · · · · · · · ·
aojing Sun2016 anwei Zhu2018 ubtotal (95% CI) eterogeneity: Tau ² = est for overall effect: otal (95% CI) eterogeneity: Tau ² = est for overall effect	1.68; Chi Z = 1.68 (1.36; Chi Z = 7.52 (i² = 37. (P = 0.) i² = 12; 'P < 0.)	.41, df= 09) 1207 7.11, df 10001)	í = 25 (P	< 0.0(1181 0001); I	100.0 % ² = 80%	1.99 [1.47, 2.51]	

Figure 5. The forest plot of MMSE (subgroup analysis by duration of treatment: 12, 8, and 4 weeks). MMSE = mini-mental state examination.

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl			
1.1.1 MMSEscore (12	(w)											
Erken Ai2013	23.1	2.2	20	22	1.4	20	6.1%	1.10 [-0.04, 2.24]				
Haibo Zhang2015	20.39	3.27	34	18.75	3.05	34	4.4%	1.64 [0.14, 3.14]				
Jinxia Huo2015	24.4	3.6	65	21.9	3.8	59	5.3%	2.50 [1.19, 3.81]				
Kui Xiong2020	22.01	4.18	60	18.29	3.54	60	0.0%	3.72 [2.33, 5.11]				
Mahebula2012	20.39	3.27	34	18.75	3.05	34	4.4%	1.64 [0.14, 3.14]				
Shiying Zhao2019	15.5	3	40	13.8	2.4	40	5.9%	1.70 [0.51, 2.89]				
Xia Wang2012	24.2	3.2	19	23.1	1.5	20	4.2%	1.10 [-0.48, 2.68]				
Yangqin Kong2017	25.2	1.8	25	21.6	1.1	25	0.0%	3.60 [2.77, 4.43]				
Yanwei Zhu2018	22.37	4.61	48	19.57	4.34	38	3.2%	2.80 [0.90, 4.70]				
Yongwei Zhang2017	26.23	3.74	30	22.69	3.09	30	3.6%	3.54 [1.80, 5.28]				
Zhiqiang Wang2014	24.4	2.4	40	20.1	1.3	40	0.0%	4.30 [3.45, 5.15]				
Subtotal (95% CI)			290			275	37.1%	1.88 [1.33, 2.43]	•			
Heterogeneity: Tau ² = 0.10; Chi ² = 8.28, df = 7 (P = 0.31); l ² = 15%												
Test for overall effect: Z	(= 6.68	(P < 0.0	00001)									
1.1.2 MMSEscore (8v	(v											
Cuivun Zhang2016	15.34	2.81	40	13.88	2.52	40	6.0%	1.46 [0.29, 2.63]				
Dandan Zhang2018	25.89	2.75	76	22.35	2.13	76	0.0%	3.54 [2.76, 4.32]				
Jingsong Yang2016	15.26	2.97	150	13.73	2.42	150	9.7%	1.53 [0.92, 2.14]				
Jinxia Huo2015	22.2	3.5	65	20	3.1	59	6.0%	2.20 [1.04, 3.36]				
Lu Wang2015	15.27	2.98	30	13.74	2.43	30	5.0%	1.53 [0.15, 2.91]				
Xin He2020	26.62	2.92	43	22.81	2.92	43	0.0%	3.81 [2.58, 5.04]				
Yanwei Zhu2018	18 27	417	48	1615	4 25	48	3.8%	2 12 [0 44 3 80]				
Subtotal (95% CI)			333			327	30.4%	1.66 [1.21, 2.11]	◆			
Heterogeneity: Tau ² = ().00: Chi	² =1.4	4. df =	4 (P = 0	.84): I ^z	= 0%						
Test for overall effect: Z	= 7.29 ((P < 0.0	00001)									
1.1.3 MMSEscore (4v	()											
Cuivun Zhang2016	12 72	3 1 9	40	12.69	2 61	40	5.4%	0.037-1.25.1.311				
Dandan Zhang2010	21.76	2.06	76	18.98	1.89	76	0.4%	2 78 [2 15 3 41]				
Erken Ai2013	197	2.00	20	19.8	1.00	20	5.4%	-0.10[-1.38_1.18]				
Jinxia Hun2015	18.5	2.0	65	18	2.9	59	7.0%	0.50 [-0.49 1.49]	_ 			
Lu Wang2015	12 78	3 21	30	12 41	2 62	30	4.5%	0.37 [-1.11.1.85]				
Xia Wang2010	20.8	3.4	19	20.9	19	20	3.6%	-0.10[-1.84_1.64]				
Xianiing Sun2016	22.37	5.67	42	1974	5.12	42	24%	2 63 [0 32 4 94]				
Yanwei 7hu2018	15.68	4 21	48	14.67	3.82	48	41%	1 01 (-0 60 2 62)				
Subtotal (95% CI)	10.00	4.21	264	14.01	0.02	259	32.4%	0.41 [-0.11, 0.94]	◆			
Heterogeneity: Tau ² = (0.00; Chi	² = 5.4	0, df =	6 (P = 0	.49); I²	= 0%						
Test for overall effect. 2	.= 1.54 ((P = 0.1	12)									
Total (95% CI)			887			861	100.0%	1.38 [0.99, 1.77]	◆			
Heterogeneity: Tau² = ().32; Chi	i ^z = 33.	07, df=	= 19 (P =	= 0.02)	; I ² = 43	3%	-	-4 -2 0 2 4			
Test for overall effect: Z	(= 6.88	(P < 0.0	00001)						Favours (experimental) Favours (control)			
Test for subaroup diffe	rences:	Chi² =	17.57.	df = 2 (F	P = 0.0	002). I ^z	= 88.6%		r arears texperimental in around foundel			
igure 6. Sensitivity analysi	e 6. Sensitivity analysis of MMSE. MMSE = mini-mental state examination.											

	Experimental			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Dandan Zhang2018	40.17	3.23	76	45.19	3.91	76	7.9%	-5.02 [-6.16, -3.88]	+
Erken Ai2013	40	5.7	20	42	4.7	20	7.5%	-2.00 [-5.24, 1.24]	
Haibo Zhang2015	25.57	4.01	34	28.01	3.59	34	7.8%	-2.44 [-4.25, -0.63]	-
Jingsong Yang2016	40.55	7.38	150	46.43	6.81	150	7.8%	-5.88 [-7.49, -4.27]	-
Lu Wang2015	40.56	7.39	30	41.62	6.81	30	7.4%	-1.06 [-4.66, 2.54]	
Mahebula2012	25.57	4.01	34	28.01	3.59	34	7.8%	-2.44 [-4.25, -0.63]	-
Shiying Zhao2019	40.1	6	40	43.1	7	40	7.6%	-3.00 [-5.86, -0.14]	
Xia Wang2012	41	6.2	19	43.1	5.8	20	7.3%	-2.10 [-5.87, 1.67]	
Xiaohong Zhang2020	73.56	3.27	30	65.87	3.31	30	7.8%	7.69 [6.03, 9.35]	-
Xin He2020	26.62	2.92	43	22.81	2.92	43	7.8%	3.81 [2.58, 5.04]	-
Yangqin Kong2017	75.7	1.5	25	68.8	1.6	25	7.9%	6.90 [6.04, 7.76]	-
Yanwei Zhu2018	36.15	5.29	48	39.17	5.27	48	7.7%	-3.02 [-5.13, -0.91]	
Zhiqiang Wang2014	76.2	1.3	40	66.2	1	40	7.9%	10.00 [9.49, 10.51]	•
Total (95% CI)			589			590	100.0%	0.16 [-3.55, 3.87]	+
Heterogeneity: Tau ² = 4	5.22; Ch	i² = 11	34.07,	df = 12 ((P < 0.)	00001);	, I² = 99%	-	
Test for overall effect: Z:	= 0.08 (F	P = 0.9	3)						-20 -10 0 10 20
									Favours (experimental) Favours (control)

Figure 7. The forest plot of ADL. ADL = activity of daily living.

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl			
3.1.1 ADLscore (12w)												
Erken Ai2013	40	5.7	20	42	4.7	20	5.1%	-2.00 [-5.24, 1.24]				
Haibo Zhang2015	25.57	4.01	34	28.01	3.59	34	5.3%	-2.44 [-4.25, -0.63]				
Mahebula2012	25.57	4.01	34	28.01	3.59	34	5.3%	-2.44 [-4.25, -0.63]				
Shiying Zhao2019	40.1	6	40	43.1	7	40	5.2%	-3.00 [-5.86, -0.14]				
Xia Wang2012	41	6.2	19	43.1	5.8	20	5.0%	-2.10 [-5.87, 1.67]				
Yangqin Kong2017	75.7	1.5	25	68.8	1.6	25	5.4%	6.90 [6.04, 7.76]				
Yanwei Zhu2018	36.15	5.29	48	39.17	5.27	48	5.3%	-3.02 [-5.13, -0.91]				
Zhiqiang Wang2014	76.2	1.3	40	66.2	1	40	5.4%	10.00 [9.49, 10.51]				
Subtotal (95% CI)			260			261	42.1%	0.33 [-3.97, 4.63]				
Heterogeneity: Tau ² = 37.11; Chi ² = 528.26, df = 7 (P < 0.00001); I ² = 99%												
Test for overall effect: Z = 0.15 (P = 0.88)												
312 ADI score (8w)												
Dandan Zhang2018	40 17	3 22	76	1510	2 01	76	5.4%	-5 02 66 16 -3 88				
Jingeong Vang2016	40.17	7 39	150	45.15	6.91	150	5 2%	-5.82 [-7.49 -4.27]				
Lu Wang2015	40.55	7 20	20	40.45	6.91	20	5 1 96	-1.06 [.4.66 2.54]				
Vischong 7hang2020	72.66	2.33	20	66.07	2.21	20	5 204	7 60 (6 02 0 25)				
Xiaohong Zhang2020 Xin Ho2020	76.11	3.74	43	70.27	3.61	43	5.4%	5 94 [4 20 7 20]				
Vanwai 7hu2019	40.14	5.74	40	12 22	5.70	40	6 206	2 09 (6 29 , 0 79)				
Subtotal (95% CI)	40.14	3.11	377	43.22	5.70	377	31.9%	0 24 [5 36 4 87]				
Hotorogonoity Tou2 - 20	0 60. Ch	2- 20	102 4		- 0 00	0011	- 000%	-0.24 [-5.50, 4.07]				
Test for overall effect: Z =	= 0.09 (F	P = 0.9	4.02, ui 3)	1 – 0 (F	~ 0.00	001),1	- 30%					
		07.042	-,									
3.1.3 ADLscore (4w)												
Dandan Zhang2018	43.17	4.69	76	49.86	5.12	76	5.4%	-6.69 [-8.25, -5.13]				
Erken Ai2013	45	4.2	20	45.2	4.1	20	5.2%	-0.20 [-2.77, 2.37]				
Lu Wang2015	46.98	6.49	30	45.62	7.18	30	5.1%	1.36 [-2.10, 4.82]				
Xia Wang2012	46.1	5.3	19	46.3	5.2	20	5.1%	-0.20 [-3.50, 3.10]				
Yanwei Zhu2018	46.28	6.12	48	47.12	6.04	48	5.3%	-0.84 [-3.27, 1.59]				
Subtotal (95% CI)			193			194	26.1%	-1.46 [-4.91, 2.00]				
Heterogeneity: Tau ² = 13	3.64; Ch	i² = 37	.86, df=	= 4 (P <	0.000	01); I² =	89%					
Test for overall effect: Z =	= 0.83 (F	° = 0.4	1)									
Total (95% CI)			830			832	100.0%	-0.30 [-3.50, 2.89]	-			
Heterogeneity: Tau ² = 48	Heterogeneity: Tau ² = 48.97; Chi ² = 1429.58, df = 18 (P < 0.00001); l ² = 99%											
Test for overall effect: Z =	= 0.19 (F	P = 0.8	5)						-10 -5 0 5 10			
Test for subaroup differe	ences: C	chi² = C).43. df	= 2 (P =	0.81)	l² = 09	6		ravours texpennientalij ravours (control)			

Figure 8. The forest plot of ADL (subgroup analysis by duration of treatment: 12, 8, and 4 weeks). ADL = activity of daily living.

than conducted through random effect model. Result had indicated statistically significant improvement on CDR score (OR = -0.24, 95% CI [-0.39, -0.08], P = .004) within the experimental group in comparison with the controlled group. Sensitivity analysis was further conducted: as the 4 groups of study regarding improvements of the CDR score after 4 weeks had demonstrated a relatively higher statistical heterogeneity $(P < .000001, I^2 = 90\%)$, study was therefore individually excluded respectively. The exclusion of the study conducted by Cuiyun Zhang had induced a statistically significant decrease $(P = .14, I^2 = 50\%)$ in the heterogeneity among the remaining 3 studies. Meta-analysis shown improvement in CDR score within experimental group in comparison with controlled group without statistical significance (OR = -0.31, 95% CI [-0.43, -0.18], P < .000001). This study is highly considered as the source of heterogeneity in regard of this specific indicator. CDR score improvement was considered most satisfactory with 12 weeks of combined usage of donepezil hydrochloride and nimodipine in treating VaD through subgroup analysis. Detail as shown in Figs. 11 and 12.

3.3.4. Results on the meta-analysis of clinical efficacy Seven studies^[8-11,15,16,18] (n = 524) had compared the clinical efficacy of the combined usage of donepezil hydrochloride and nimodipine in VaD treatment, there were no heterogeneity among respective group of study (P = 81, $I^2 = 0\%$). Therefore, meta-analysis was conducted through fixed effect model as shown in Fig. 13. The result indicates the efficacy of the experimental group was

significantly higher than the controlled group (OR = 1.21, 95% CI [1.13, 1.29], *P* < .000001).

3.4. Publication bias

Funnel plot and result analysis: Funnel plot analysis is carried based on the MMSE score before and after the combined usage of donepezil hydrochloride and nimodipine in VaD treatment. The funnel plot was drawn based on using MD as the *x*-axis and standard error SE(MD) as the *y*-axis. Result has indicates a mostly symmetric funnel with true value as its symmetry, therefore the publication bias of studies included was considered relatively small. Funnel plot and result analysis as shown in Fig. 14.

4. Discussion

Vascular dementia (VaD) is an illness which specify in cerebral dysfunction after cerebral vascular disease. Blood flow of the brain decreased with the nutritional substances and oxygen which was originally carried into the brain cells. Therefore lowering the patient's cognitive function. Pathogenesis of VaD is considered in close relation with the hypothesis of calcium overload and cholinergic nerve damage.^[26,27] Donepezil is 2nd generation cholinesterase suppressant; its curative effects is demonstrated through a reversible suppression of acetylcholinesterase. Acetylcholinesterase would induce the hydrolysis

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl			
3.1.1 ADLscore (12w)												
Erken Ai2013	40	5.7	20	42	4.7	20	5.8%	-2.00 [-5.24, 1.24]				
Haibo Zhang2015	25.57	4.01	34	28.01	3.59	34	8.7%	-2.44 [-4.25, -0.63]	<u> </u>			
Mahebula2012	25.57	4.01	34	28.01	3.59	34	8.7%	-2.44 [-4.25, -0.63]	(
Shiying Zhao2019	40.1	6	40	43.1	7	40	6.5%	-3.00 [-5.86, -0.14]				
Xia Wang2012	41	6.2	19	43.1	5.8	20	4.9%	-2.10 [-5.87, 1.67]				
Yangqin Kong2017	75.7	1.5	25	68.8	1.6	25	0.0%	6.90 [6.04, 7.76]				
Yanwei Zhu2018	36.15	5.29	48	39.17	5.27	48	8.0%	-3.02 [-5.13, -0.91]	[
Zhiqiang Wang2014	76.2	1.3	40	66.2	1	40	0.0%	10.00 [9.49, 10.51]				
Subtotal (95% CI)			195			196	42.6%	-2.56 [-3.50, -1.61]	◆			
Heterogeneity: Tau ² = 0.00; Chi ² = 0.48, df = 5 (P = 0.99); I ² = 0%												
Test for overall effect: Z = 5.31 (P < 0.00001)												
3.1.2 ADLscore (8w)												
Dandan Zhang2018	40.17	3.23	76	45.19	3.91	76	10.1%	-5.02 [-6.16, -3.88]	—			
Jingsong Yang2016	40.55	7.38	150	46.43	6.81	150	9.1%	-5.88 [-7.49, -4.27]				
Lu Wang2015	40.56	7.39	30	41.62	6.81	30	5.2%	-1.06 [-4.66, 2.54]				
Xiaohong Zhang2020	73.56	3.27	30	65.87	3.31	30	0.0%	7.69 [6.03, 9.35]				
Xin He2020	76.11	3.74	43	70.27	3.61	43	0.0%	5.84 [4.29, 7.39]				
Yanwei Zhu2018	40.14	5.71	48	43.22	5.78	48	7.6%	-3.08 [-5.38, -0.78]				
Subtotal (95% CI)			304			304	32.0%	-4.31 [-5.90, -2.73]	◆			
Heterogeneity: Tau ² = 1.	55; Chi ^z	= 8.18), df = 3	(P = 0.0)	04); l² =	= 63%						
Test for overall effect: Z :	= 5.33 (F	• < 0.0	0001)									
3.1.3 ADLscore (4w)												
Dandan Zhang2018	43.17	4.69	76	49.86	5.12	76	0.0%	-6.69 [-8.25, -5.13]				
Erken Ai2013	45	4.2	20	45.2	4.1	20	7.0%	-0.20 [-2.77, 2.37]				
Lu Wang2015	46.98	6.49	30	45.62	7.18	30	5.4%	1.36 [-2.10, 4.82]				
Xia Wang2012	46.1	5.3	19	46.3	5.2	20	5.7%	-0.20 [-3.50, 3.10]				
Yanwei Zhu2018	46.28	6.12	48	47.12	6.04	48	7.3%	-0.84 [-3.27, 1.59]				
Subtotal (95% CI)			117			118	25.5%	-0.16 [-1.58, 1.26]	•			
Heterogeneity: Tau ² = 0.	00; Chi ^z	= 1.04	, df = 3	(P = 0.1)	79); l² =	= 0%						
Test for overall effect: Z:	= 0.21 (F	° = 0.8	3)	-								
Total (95% CI)			616			618	100.0%	-2.42 [-3.54, -1.30]	◆			
Heterogeneity: Tau ² = 2.	90; Chi ²	= 42.7	'8, df =	13 (P <	0.000	1); l² = 3	70%					
Test for overall effect: Z :	Test for overall effect: Z = 4.25 (P < 0.0001)											
Test for subaroup differe	Test for subaroup differences: Chi ² = 15.21. df = 2 (P = 0.0005). I ² = 86.9%											
Figure 9. Sensitivity analy	Figure 9. Sensitivity analysis of ADL. ADL = activity of daily living.											

of cholinergic neuron while increasing the amount of cholinesterase within receptor. Nimodipine can change the functions of neurons, and perceived both neuroactive and psychoactive pharmacological property.^[28] Nimodipine has high lipid solubility and demonstrates selective effects on cerebral vascular smooth muscle. This could ease the calcium overloaded within cell by preventing the inflow of calcium ions. The mechanism of the combined usage of both drugs on treating VaD is reasonable. Several clinical studies have confirmed the therapeutic efficacy of donepezil in combination with nimodipine in VaD, but as the results of these studies were derived from small single-center studies, there has been no systematic evaluation of donepezil in combination with nimodipine in the treatment of VaD. Therefore, we designed this study to provide a higher level of evidence-based clinical use of donepezil hydrochloride in combination with nimodipine for the treatment of VaD through systematic evaluation.

The results of this study show that donepezil combined with nimodipine can better improve the MMSE score, ADL score, and CDR score of patients with vascular dementia. Sensitivity

	Experimental			C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cuiyun Zhang2016	2.03	0.22	40	2.21	0.28	40	14.2%	-0.18 [-0.29, -0.07]	*
Dandan Zhang2018	1.24	0.15	76	1.65	0.19	76	15.7%	-0.41 [-0.46, -0.36]	•
Jingsong Yang2016	2.01	0.5	150	2.06	0.52	150	14.0%	-0.05 [-0.17, 0.07]	4
Kui Xiong2020	1.17	0.32	60	1.58	0.35	60	13.9%	-0.41 [-0.53, -0.29]	+
Lu Wang2015	2.01	0.51	30	2.17	0.53	30	8.9%	-0.16 [-0.42, 0.10]	
Shiying Zhao2019	1.9	0.3	40	2.1	0.5	40	11.7%	-0.20 [-0.38, -0.02]	-
Xiaohong Zhang2020	1.96	0.57	30	2.37	0.33	30	9.7%	-0.41 [-0.65, -0.17]	
Xiaojing Sun2016	1.54	0.38	42	1.97	0.42	42	12.0%	-0.43 [-0.60, -0.26]	-
Total (95% Cl)			468			468	100.0%	-0.28 [-0.40, -0.17]	•
Heterogeneity: Tau ² = 0.	.02; Chi²	= 45.0	11, df =	7 (P < 0	.0000	1); l² = (34%	-	
Test for overall effect: Z	= 4.78 (F	° < 0.0	Favours [experimental] Favours [control]						

Figure 10. The forest plot of CDR. CDR = clinical dementia scale.

	Experimental			C	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
4.1.1 CDRscore (12w)										
Shiying Zhao2019	1.9	0.3	40	2.1	0.5	40	8.5%	-0.20 [-0.38, -0.02]	_ _	
Kui Xiong2020	1.17	0.32	60	1.58	0.35	60	10.4%	-0.41 [-0.53, -0.29]		
Subtotal (95% CI)			100			100	18.9%	-0.32 [-0.52, -0.11]		
Heterogeneity: Tau ² = 0.	02; Chi ^z	= 3.60), df = 1	(P = 0.0	06); I ^z :	= 72%				
Test for overall effect: Z	= 3.03 (F	° = 0.0	02)							
4.1.2 CDRscore (8w)										
Xiaohong Zhang2020	1.96	0.57	30	2.37	0.33	30	6.9%	-0.41 [-0.65, -0.17]		
Lu Wang2015	2.01	0.51	30	2.17	0.53	30	6.2%	-0.16 [-0.42, 0.10]		
Jingsong Yang2016	2.01	0.5	150	2.06	0.52	150	10.6%	-0.05 [-0.17, 0.07]		
Dandan Zhang2018	1.24	0.15	76	1.65	0.19	76	12.2%	-0.41 [-0.46, -0.36]	+	
Cuiyun Zhang2016	2.03	0.22	40	2.21	0.28	40	10.7%	-0.18 [-0.29, -0.07]		
Subtotal (95% CI)			326			326	46.6%	-0.24 [-0.42, -0.07]	-	
Heterogeneity: Tau² = 0.	03; Chi²	= 39.6	i5, df =	4 (P < 0	.0000	1); l² = 9	30%			
Test for overall effect: Z :	= 2.72 (F	° = 0.0	06)							
4.4.3 CDPccoro (4w)										
4.1.3 CDRScore (4w)	1 5 4	0.20	40	1.07	0 4 2	40	0.00	190.0.090		
Alaojing Sunzoro	1.04	0.30	42	1.97	0.42	42	0.0%	-0.43 [-0.60, -0.26]		
Lu Wang2015 Dondon Zhong2019	2.20	0.01	20	2.4	0.52	30 76	0.270	-0.12 [-0.30, 0.14]	+	
Cuivup Zhong2016	1.70	0.21	40	2.00	0.24	10	7 7 94	-0.30 [-0.37, -0.23]		
Subtotal (95% CI)	2.30	0.40	40	2.39	0.49	40	34.5%	-0.01 [-0.22, 0.20]	•	
Hotorogonoity: Tou ² – 0	02: Chiž	- 11 1	5 df-	2/0-0	01\-	- 72%	54.570	-0.24 [-0.33, -0.00]	•	
Teet for overall effect: 7	- 2 00 /9		04)	3 (F = 0	.01),1	-73%				
Testion overall ellect. Z.	- 2.50 (r	- 0.0	04)							
Total (95% CI)			614			614	100.0%	-0.25 [-0.35, -0.16]	◆	
Heterogeneity: Tau ² = 0.	02; Chi ^z	= 55.7	'8, df =	10 (P <	0.000	01); I ^z =	82%	-		
Test for overall effect: Z :	= 5.46 (F	° < 0.0	0001)				-1 -0.5 0 0.5 1 Eavours (experimental) Eavours (control)			
Test for subaroup differe	ences: C	hi² = 0	1.43. df	= 2 (P =	0.81)	l² = 0%	5		Favours (experimental) Favours (control)	
Figure 11. The forest plot of CDR (subgroup analysis by duration of treatment 12, 8, and 4 weeks). CDR = clinical dementia scale.										

	Experimental		Control				Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl				
4.1.1 CDRscore (12w)													
Shiying Zhao2019	1.9	0.3	40	2.1	0.5	40	11.3%	-0.20 [-0.38, -0.02]					
Kui Xiong2020	1.17	0.32	60	1.58	0.35	60	14.5%	-0.41 [-0.53, -0.29]					
Subtotal (95% CI)			100			100	25.8%	-0.32 [-0.52, -0.11]					
Heterogeneity: Tau ² = 0.	02; Chi²	= 3.60), df = 1	(P = 0.0	06); l² :	= 72%							
Test for overall effect: Z =	: 3.03 (F	° = 0.0	02)										
4.1.2 CDRscore (8w)													
Xiaohong Zhang2020	1.96	0.57	30	2.37	0.33	30	0.0%	-0.41 [-0.65, -0.17]					
Lu Wang2015	2.01	0.51	30	2.17	0.53	30	7.9%	-0.16 [-0.42, 0.10]					
Jingsong Yang2016	2.01	0.5	150	2.06	0.52	150	14.7%	-0.05 [-0.17, 0.07]					
Dandan Zhang2018	1.24	0.15	76	1.65	0.19	76	0.0%	-0.41 [-0.46, -0.36]					
Cuiyun Zhang2016	2.03	0.22	40	2.21	0.28	40	15.0%	-0.18 [-0.29, -0.07]					
Subtotal (95% Cl)			220			220	37.6%	-0.12 [-0.21, -0.03]	\bullet				
Heterogeneity: Tau ² = 0.00; Chi ² = 2.64, df = 2 (P = 0.27); I ² = 24%													
Test for overall effect: Z =	: 2.59 (F	° = 0.0	10)										
4.1.3 CDRscore (4w)													
Xiaojing Sun2016	1.54	0.38	42	1.97	0.42	42	11.8%	-0.43 [-0.60, -0.26]					
Lu Wang2015	2.28	0.51	30	2.4	0.52	30	8.0%	-0.12 [-0.38, 0.14]					
Dandan Zhang2018	1.76	0.21	76	2.06	0.24	76	16.8%	-0.30 [-0.37, -0.23]					
Cuiyun Zhang2016	2.38	0.46	40	2.39	0.49	40	0.0%	-0.01 [-0.22, 0.20]					
Subtotal (95% CI)			148			148	36.6%	-0.31 [-0.43, -0.18]	◆				
Heterogeneity: Tau ² = 0.	01; Chi²	= 3.99	8, df = 2	(P = 0.1	14); I² :	= 50%							
Test for overall effect: Z =	= 4.80 (F	° < 0.0	0001)										
Total (95% CI)			468			468	100.0%	0 24 [-0 34 -0 14]	•				
Hotorogonoity: Tou ² = 01	01 · Chiz	- 27 7	-100 -11-01	7 /0 - 0	0002	12 - 76	50%	-0.24 [-0.34, -0.14]					
Tect for overall effect: 7 -	- 1 02 /0	- 21.1	0, ui = 0001\	r (F - 0		n = n	0.0		-1 -0.5 0 0.5 1				
Test for subgroup differe	• 4.02 (F ancae: C	` - 0.0 `hi≅ - 0	Favours [experimental] Favours [control]										
Figure 10 Constitute and	unio of (וסו. עו		100000	tio oost	.070						
Figure 12. Sensitivity anal	ysis or ($_{\rm JDH.}$ (JUH = 0	cimical c	Jernen	ua scal	e.						

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Cuiyun Zhang2016	37	40	30	40	12.6%	1.23 [1.01, 1.51]	
Haibo Zhang2015	32	34	24	34	10.1%	1.33 [1.06, 1.68]	
Jinxia Huo2015	61	65	49	59	21.6%	1.13 (0.99, 1.29)	-
Mahebula2012	32	34	24	34	10.1%	1.33 [1.06, 1.68]	
Xiaojing Sun2016	41	42	35	42	14.7%	1.17 [1.02, 1.35]	
Xin He2020	40	43	33	43	13.9%	1.21 [1.01, 1.46]	
Yanwei Zhu2018	46	48	40	48	16.9%	1.15 [1.00, 1.32]	-
Total (95% CI)		306		300	100.0%	1.21 [1.13, 1.29]	•
Total events	289		235				
Heterogeneity: Chi ² =	3.02, df = 6	6 (P = 0	.81); I ² = (0%			
Test for overall effect:	Z=5.61 (F	° < 0.00	001)				Favours [experimental] Favours [control]

Figure 13. The forest plot of curative effect.



analysis had proven efficacy is considered most satisfactory after 12 weeks of intervention. The possibility of publication bias perceived in this study is relatively lower.

Certain limitations are pertained to this meta-analysis: the quality of research methodologies included were relatively low, certain heterogeneity remained beyond explanations, the lack of strong evidence. The result should be clinically evaluated with cautiousness. The sample size of the respective studies is generally small, this may affect the authenticity of the research. Methodology of certain studies included was not explained in detail, this may contribute to a certain risk of bias. Therefore the above results should be perceived with cautious.

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Author contributions

All the authors have contributed to the topic selection, design, data retrieval, extraction, analysis, interpretation and drafting.

Ai-hua Tan and Qiang Yang conceived the study. Si-miao Ran, Jia Liu, and Kai-lin Huang were responsible for the screening and data extraction and analysis of the literature; Jia Liu and Miyuan Wang drafted the draft; Guang-yao Wang interpreted and edited the analysis results; Ai-hua Tan and Si-miao Ran were responsible for writing the manuscript. All authors agree to the publication of this manuscript and agree to be responsible for it. Qiang Yang, Jia Liu and Kai-lin Huang are contribute equally to the article.

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