Journal of Kerman University of Medical Sciences

JKMU

Journal of Kerman University of Medical Sciences, 2020; 27 (2): 113-119

The Effects of Donepezil, Galantamine, Rivastigmine and Memantine on Mini-Mental State Examination and Mean Flow Velocity in Patients with Vascular Dementia: A Double-Blinded Randomized Clinical Trial

Farhad Iranmanesh, M.D.[1], Kaveh Shafiee, M.D.[2], Ali Farzan, M.D.[3]

1- Professor of Neurology, Stroke fellowship, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran (Corresponding author; E-mail: fpp_farhad@yahoo.com)

2- Assistant Professor of Neurology, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran

3- Neurologist, Neurology Research Center, Kerman University of Medical sciences, Kerman, Iran

Received: 31 December, 2019 Accepted: 20 February, 2020

ARTICLE INFO

Article type:
Original Article

Keywords:
Donepezil
Galantamine
Rivastigmine
Memantine
Vascular dementia

Abstract

Background: Vascular dementia is one of the most common forms of dementia. At now, there is no treatment available to cure vascular dementia or to alter its clinical course. Some studies suggest that some drugs may be useful in controlling symptoms. The aim of this study was to evaluate the effects of donepezil, memantine, rivastigmine and galantamine on mean flow velocity and Mini-Mental State Examination of patients with vascular dementia in a three- month follow-up period.

Methods: This double-blind clinical trial was conducted on 44 patients with vascular dementia. Vascular dementia was diagnosed based on the DSM-V criteria. According to the order of entry into the study, the participants were treated with one of the selected drugs [donepezil (10 mg/d), memantine (10 mg/d), galantamine (8 mg/d) and rivastigmine (6 mg/d)]. The sampling finished whenever 11 patients in each group completed the three-month trial. The MMSE and color Doppler ultrasound was performed for all participants before and three months after the intervention.

Results: According to the findings, there was no significant difference among the groups in the frequency of variables and the mean scores of Mini-Mental State Examination before the intervention, but the administration of memantine and donepezil significantly increased Mini-Mental State Examination score (P = 0.009 and P = 0.001 respectively). Moreover, rivastigmine, galantamin and donepezil significantly increased mean flow velocity in some arteries.

Discussion: Memantine and donepazil improve cognitive function in patients with vascular dementia. Rivastigmine, galantamin and donepezil have some effects on cerebral blood flow.

Citation: Iranmanesh F, Shafiee K, Farzan A. The Effects of Donepezil, Galantamine, Rivastigmine and Memantine on Mini-Mental State Examination and Mean Flow Velocity in Patients with Vascular Dementia: A Double-Blinded Randomized Clinical Trial. *Journal of Kerman University of Medical Sciences*, 2020; 27 (2): 113-119.

Introduction

The prevalence of dementia among people over 60 is about 5-7% (1). Vascular dementia is the second leading cause of dementia in many countries (2, 3). In this type of dementia, clinical symptoms develop after a stroke and cause functional impairment in the patient that eventually, affects the patient's family and community (4). Currently, there is no approved treatment to control clinical signs of post stoke dementia (2, 5).

Rivastigmine, donepezil, memantine, and galantamine are approved drugs that their therapeutic effects have been proven in the treatment of dementia caused by Alzheimer's disease (6-9). However, literature review indicates that there is no consensus on their therapeutic effects in vascular dementia (5, 7,10, 11). According to a review study conducted by Farooq et al. in 2017, donepezil has had somewhat beneficial cognitive effects on patients with vascular dementia, galantamine has showed some beneficial effects on patients afflicted with both vascular dementia and AD, and the benefits of rivastigmine and memantine in the treatment of vascular dementia were not clear (5). Servello et al. (2014) studied the effects of rivastigmine on the Mini-Mental State Examination (MMSE) score of patients with vascular dementia and reported that the MMSE score remained the same after 6 months in patients who received rivastigmine and aspirin, whereas it decreased significantly in those who were treated with only aspirin (7). Ghorbani et al. (2009) investigated the effects of donepezil on mean blood flow velocity (MFV) in cerebral arteries of patients with AD and found that donepezil, especially at a dosage of 10 mg/d, can increase the cerebral blood flow and the MMSE score of these patients (11). As an alternative to invasive techniques such as angiography, Doppler ultrasound is a safe technique for studying cerebral blood flow (12, 13). Given that hemodynamic abnormality is the main cause of vascular dementia, the present study compared the clinical effects of the above-mentioned drugs on MFV.

Methods

This double-blind clinical trial was conducted on 44 patients with vascular dementia in Shafa Hospital, Kerman/ Iran in 2018-2019. Vascular dementia was diagnosed based on the DSM-V criteria (14).The range of disease duration was 3-12 months. Patients with any underlying disease other than hypertension (HTN), diabetes (DM), hyperlipidemia (HLP) and ischemic heart disease (IHD), and patients that took any drug such as sedatives and opiates other than those for controlling HTN, DM, HLP, and IHD, were excluded from the study. The participants were selected through convenience sampling. The MMSE scores of the patients before the study ranged between 10 and 27 (15). The patients showed no difference in terms of the level of education. After ensuring that all participants and one of their family members were fully aware of the research method, an informed consent was taken. The dosages of donepezil, rivastigmine, and memantine were gradually increased from 5 mg/d to 10 mg/d over 10 days, from 1.5 mg twice a day to 3 mg twice a day over one week, and from 5 mg/d to 10 mg/d over one week, respectively; while, galantamine was administered at the stable dosage of 8 mg/d. The trial lasted three months. Considering the possibility of attrition and poor window in ultrasound, a greater number of patients were selected for the study. The sampling was stopped whenever 11 patients in each group completed the three-month trial. The MMSE was done in the morning under the same environmental conditions for all patients, and color Doppler ultrasound was performed for all participants before the intervention and three months after the intervention. For all cases, ultrasonography was performed with a Multi-Dop X Digital-DWL ultrasound instrument. Posterior cerebral arteries (PCAs), middle cerebral arteries (MCAs), anterior cerebral arteries (ACAs), vertebral arteries (VAs), and the basilar artery (BA) were investigated using a 2-MHz probe and the internal carotid artery (ICA) was investigated using a 4-MHz probe. The mean flow velocity of each cerebral artery was measured

at the standard depth (16). In this study, diabetes was defined as having a fasting blood sugar level of 126 or greater or being under the treatment, hypertension was defined as having a systolic blood pressure of greater than 160 mm Hg or a diastolic blood pressure of greater than 90 mm Hg or being under the treatment, and ischemic heart disease was defined as the history of angina, myocardial infarction or congestive heart failure diagnosed by a cardiologist (17). This research was approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1397.093), and was registered on the Iranian Registry of Clinical Trial (IRCT20181210041912N1). Personal information of patients, including age, gender and the history of underlying diseases, medications, and the MMSE score, and MFV of cerebral arteries were recorded on a special checklist. The level of significance was determined to be $p<0.05$ and the data were analyzed using Chi-square test, independent t-test and paired t-test.

Results

Twenty three (52.27%) of the patients were male and the rest were female. Table 1 shows demographic information and vascular risk factors of the different groups. None of the patients were smoker after stroke. There was no significant difference between the groups on the baseline variables (Table 1). Table 2 shows the mean MMSE scores in the groups before and after the intervention. As it is seen, there was no significant difference among the groups on the baseline variables and the mean MMSE scores before the intervention, but the administration of memantine (p=0.009) and donepezil (p=0.01) increased the MMSE scores significantly. The findings also demonstrated that all studied drugs, except memantine, improved the MFV in some arteries (Table 3). Rivastigmine increased the MFV in PCAs (p=0.003) and ACAs (p=0.045) and galantamine (p=0.001) and donepezil (p=0.001) improved the MFV in PCAs.

Table 1. The comparison of baseline variables among the studied groups

	Memantine	Rivastigmine	Galantamine	Donepezil	p.value
Sex					
Female	5 (45.5)	6 (54.5)	4 (36.4)	6 (54.5)	0.801
Male	6 (54.5)	5 (45.5)	7 (63.6)	5 (45.5)	
IHD					
Yes	4 (36.4)	4 (36.4)	4 (36.4)	5 (45.5)	0.962
No	7 (63.6)	7 (63.6)	7 (63.6)	6 (54.5)	
HLP					
Yes	4 (36.4)	5 (45.5)	5 (45.5)	4 (36.4)	0.945
No	7 (63.6)	6 (54.5)	6 (54.5)	7 (63.6)	
DM					
Yes	5 (45.5)	6 (54.5)	5 (45.5)	5 (45.5)	0.965
No	6 (54.5)	5 (45.5)	6 (54.5)	6 (54.5)	
HTN					
Yes	7 (63.6)	6 (54.5)	5 (45.5)	7 (63.6)	0.797
No	4 (36. 4)	5 (45.5)	6 (54.5)	4 (36.4)	
Mean age (year)	63.36±9.63	64.27±9.38	67.36±8.96	66.36±10.80	0.757

Table 2. Comparison of MMSE mean scores before and after the intervention in the studied groups

Group / MMSE score	Memantine	Rivastigmine	Galantamine	Donepezil
Before the intervention	16.18±3.37	15.81±3.34	16.09±3.08	17.09±4.01
After the intervention	17.63±3.82	15.18±3.45	16.72±3.90	18.90±3.64
p.value	0.009	0.11	0.451	0.001

Table 3. Comparison of MFV before and after the intervention in the studied groups

	Memantine	Rivastigmine	Galantamine	Donepezil	p.value*
BA Before	59.72±18.02	52.54±14.92	55.09±24.05	55.18±15.01	0.541
After	60.6±15.92	59±16.51	65±15.69	62.54±17.96	0.609
p.value&	0.903	0.319	0.212	0.340	
VA Before	61.31±14.56	63.22±11.73	59.18±10.08	60±14.62	0.638
After	64±12.95	65.54±9.52	61.18±14.47	61.04±12.23	0.932
p.value&	0.618	0.538	0.642	0.845	
PCA Before	59.68±9.07	58.59±12.63	56.27±8.10	56.63±6.68	0.806
After	73.90±11.29	83.36±11.55	74.18±10.82	83.31±16.17	0.240
p.value&	0.056	0.003	0.001	0.001	
ACA Before	61.54±19.34	62.95±12.33	68.54±14.83	63.45±15	0.738
After	74.50±12.51	77.45±14.86	74.18±17.31	72.13±14.91	0.872
p.value&	0.058	0.045	0.457	0.223	
MCA Before	65.50±13.08	60.09±9.55	60.45±16.41	64.77±10.81	0.656
After	68.31±16.49	58.95±15.08	57.63±11.64	67.31±11.41	0.170
p.value&	0.639	0.804	0.641	0.359	
ICA Before	60.90±13.02	64.59±18.62	64.95±11.75	66.18±10.05	0.666
After	63.50±11.85	65.90±9.51	69.31±11.97	78.18±16.71	0.058
p.value&	0.664	0.852	0.462	0.094	

Discussion

The present study investigated the effects of rivastigmine, donepezil, memantine, and galantamine on cognition and MFV of patients with vascular dementia. Memantine and donepezil significantly increased the MMSE scores in the studied groups. Since there was not any significant difference between the studied groups in terms of demographic factors, cerebrovascular risk factors, and MMSE before the intervention, it can be concluded that the administration of memantine and donepezil improved cognitive function of patients with vascular dementia. Similar studies corroborate this finding regarding donepezil. In their clinical trial, Wilkinson et al. noticed that donepezil at 5 mg and 10 mg doses increased the MMSE scores compared to the control group

(17). Roman et al. conducted a double-blind clinical trial and reported that the administration of donepezil had beneficial effects on daily living activities (18). In Román et al. study, donepezil improved cognitive function of patients with vascular dementia but had no effect on their global function (19). Contrary to our findings and the above-mentioned studies, Dichgans reported that donepezil had no effect on Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) in patients with CADASIL (15). Consistent with the present study, Wilcock et al. showed that memantine has positive mental effects based on ADAS-cog (20). Orgogozo conducted a clinical trial on patients with vascular dementia and concluded that memantine affected ADAS-Cog but did not change global function (21). The findings of the present study did not prove any therapeutic effects for rivastigmine and galantamine. However, a few studies have reported the effects of galantamine (22, 23) and the positive effects (24) and negative effects (25, 26) of rivastigmine. In the present study, the administration of rivastigmine, donepezil, and galantamine increased blood flow in some arteries, especially in PCAs, but these effects seem to be limited and there was no similar study for comparison of the results. However, it is interesting that this effect was more pronounced on PCAs for all the studied drugs, although this may be a coincidental finding. Because the effects of these drugs on MFV were limited, it appears that the therapeutic effects of these drugs are primarily due to their mechanisms such as depletion of acetylcholine in the cerebral cortex and hippocampus. In the latest meta-analysis published in 2019, Jin et al. compared the effects of rivastigmine, donepezil, memantine, and galantamine on cognition, behavior, function, and global status in patients with vascular cognitive impairment. They evaluated clinical trials based on various criteria such as the MMSE score. General results indicated that all four drugs, expect for rivastigmine, had improved cognitive function and only memantine had positively affected the global status (27). The present study was a pilot study and had some limitations that should be considered in future studies. Therefore, we recommend further studies with a longer follow-up period, higher doses of drugs and a larger sample size in order to increase the accuracy, and also use of Duplex ultrasound. In conclusion, our findings show that Memantine and donepazil can improve cognitive function in patients with vascular dementia. Rivastigmine, galantamin and donepezil increase MFV in some arteries aalthough this effect seems to be limited.

Acknowledgments: The authors thank Kerman Neurology Research Center for supporting this project.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013; 9(1):63-75.e2.
2. Birks J, McGuinness B, Craig D. Rivastigmine for vascular cognitive impairment. Cochrane Database Syst Rev 2013; 5:CD004744.
3. Farooq MU, Min J, Goshgarian C, Gorelick PB. Pharmacotherapy for vascular cognitive impairment. CNS Drugs 2017; 31(9):759-76.
4. Malouf R, Birks J. Donepezil for vascular cognitive impairment. Cochrane Database Syst Rev 2004; (1):CD004395.

5. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: an open 22-month study. J Neurol Sci 2002; 203-204:141-6.

6. Liu Q, Wang XJ, Zhang ZC, Xue R, Li P, Li B. Neuroprotection against vascular dementia after acupuncture combined with donepezil hydrochloride: P300 event related potential. Neural Regen Res 2016; 11(3):460-4.

7. Servello A, Andreozzi P, Bechini F, De Angelis R, Pontecorvo ML, Vulcano A, et al. Effect of AChE and BuChE inhibition by rivastigmin in a group of old-old elderly patients with cerebrovascular impairment (SIVD type). Minerva Med 2014; 105(2):167-74. [In Italian].

8. Kandiah N, Pai MC, Senanarong V, Looi I, Ampil E, Park KW, et al. Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. Clin Interv Aging 2017; 12:697-707.

9. Chen YD, Zhang J, Wang Y, Yuan JL, Hu WL. Efficacy of cholinesterase inhibitors in vascular dementia: an updated meta-analysis. Eur Neurol 2016; 75(3-4):132-41.

10. Wang F, Zou Z, Gong Y, Yuan D, Chen X, Sun T. Regulation of human brain microvascular endothelial cell adhesion and barrier functions by memantine. J Mol Neurosci 2017; 62(1):123-29.

11. Ghorbani A, Chitsaz A, Shishegar M, Akbari M. Evaluation the effect of donepezil on cerebral blood flow velocity in alzheimer's disease. Neurosciences (Riyadh) 2010; 15(3):172-6.

12. D'Andrea A, Conte M, Scarafile R, Riegler L, Cocchia R, Pezzullo E, et al. Transcranial doppler ultrasound: physical principles and principal applications in neurocritical care unit. J Cardiovasc Echogr 2016; 26(2):28-41.

13. Purkayastha S, Sorond F. Transcranial doppler ultrasound: technique and application. Semin Neurol 2012; 32(4):411-20.

14. Sinha P, Bharath S, Chandra SR. DSM-5 in Vascular Dementia- Comparison with other diagnostic criteria in a retrospective study. *EC Neurology* 2015; 2(3):135-43.

15. Seifaddini R, Hamze Moghadam A, Iranmanesh F, Arvan H, Naghibzadeh-Tahami A. The effects of citicoline on cerebrovascular hemodynamic status in ischemic stroke patients. Journal of Kerman University of Medical Sciences 2017; 24(6):480-6.

16. Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, et al. Donepezil in vascular dementia: a randomized, placebo-controlled study. Neurology 2003; 61(4):479-86.

17. Black S, Román GC, Geldmacher DS, Salloway S, Hecker J, Burns A, et al. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke 2003; 34(10):2323-30.

18. Román GC, Salloway S, Black SE, Royall DR, Decarli C, Weiner MW, et al. Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. Stroke 2010; 41(6):1213-21.

19. Dichgans M, Markus HS, Salloway S, Verkkoniemi A, Moline M, Wang Q, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. Lancet Neurol 2008; 7(4):310-8.

20. Wilcock G, Möbius HJ, Stöffler A, MMM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol 2002; 17(6):297-305.

21. Orgogozo JM, Rigaud AS, Stöffler A, Möbius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002; 33(7):1834-9.

22. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002; 359(9314):1283-90.

23. Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP, Gassmann-Mayer C, et al. Galantamine treatment of vascular dementia: a randomized trial. Neurology 2007; 69(5):448-58.

24. Ballard C, Sauter M, Scheltens P, He Y, Barkhof F, van Straaten EC, et al. Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: the VantagE study. Curr Med Res Opin 2008; 24(9):2561-74.

25. Mok V, Wong A, Ho S, Leung T, Lam WW, Wong KS. Rivastigmine in Chinese patients with subcortical vascular dementia. Neuropsychiatr Dis Treat 2007; 3(6):943-8.

26. Narasimhalu K, Effendy S, Sim CH, Lee JM, Chen I, Hia SB, et al. A randomized controlled trial of rivastigmine in patients with cognitive impairment no dementia because of cerebrovascular disease. Acta Neurol Scand 2010; 121(4):217-24.

27. Jin BR, Liu HY. Comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment: systematic review and Bayesian network meta-analysis. Neural Regen Res 2019; 14(5):805-16.