e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(8); 1070-1075

Original Research Article

Comparative Efficacy and Safety of Rivastigmine vs. Memantine and Donepezil Combination in Vascular Dementia: A Two-Year Observational Study in a Tertiary Care Hospital in Northern India

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Received: 01-05-2025 / Revised: 15-06-2025 / Accepted: 21-07-2025
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Conflict of interest: Nil

Abstract

Background: Vascular dementia (VaD) is the second most common form of dementia, frequently associated with significant functional decline and caregiver burden. While cholinesterase inhibitors and NMDA receptor antagonists are widely prescribed, comparative data on their real-world efficacy and safety in VaD, particularly in the Indian subcontinent, remain limited.

Objective: To evaluate and compare the efficacy and safety of rivastigmine monotherapy versus a combination of memantine and donepezil in patients diagnosed with vascular dementia over a two-year observational period in a tertiary care hospital in Northern India.

Methods: A total of 312 patients with clinically diagnosed VaD (per NINDS-AIREN criteria) were enrolled from January 2023 to December 2024. Patients were divided into two cohorts: Group A received rivastigmine (oral or transdermal), and Group B received a combination of memantine and donepezil. Cognitive function (measured using MMSE and MoCA), neuropsychiatric symptoms (NPI score), and daily living activities (ADL/IADL scales) were assessed at baseline, 6 months, 12 months, and 24 months. Adverse events and treatment discontinuation rates were also recorded.

Results: At 24 months, Group B (memantine + donepezil) demonstrated a statistically significant improvement in MMSE and MoCA scores compared to Group A ($p < 0.05$). Neuropsychiatric symptoms were better controlled in the combination group, with lower mean NPI scores. However, rivastigmine showed better tolerability, with fewer gastrointestinal side effects and lower discontinuation rates (9.4% vs. 17.8%). No severe adverse drug reactions were reported in either group.

Conclusion: The combination of memantine and donepezil offers superior cognitive and behavioral benefits compared to rivastigmine alone in patients with vascular dementia. However, rivastigmine may be better tolerated. Individualized treatment based on patient comorbidities and tolerance is recommended. Further randomized controlled trials are warranted to validate these observational findings.

Keywords: Vascular Dementia, Rivastigmine, Memantine, Donepezil, Cognitive Decline, Observational Study.

Introduction

Vascular dementia (VaD) is the second most prevalent form of dementia after Alzheimer's disease, accounting for approximately 15–20% of cases globally, and up to 30% in certain Asian populations. [1] It arises due to cerebrovascular insults, including large vessel infarcts, small vessel disease, or hemorrhagic lesions, leading to progressive cognitive decline and functional impairment. [2] In countries like India, where vascular risk factors such as hypertension and diabetes are widespread, VaD poses a growing public health challenge. [3] Management of vascular dementia is multifaceted and often involves both pharmacologic and non-pharmacologic approaches. While there is no definitive cure, symptomatic treatment remains the

mainstay of care. Cholinesterase inhibitors like rivastigmine and donepezil, as well as NMDA (N-Methyl-D-Aspartate) receptor antagonists like memantine, have shown modest benefits in improving cognitive function and daily living skills in patients with VaD. [4] However, clinical guidelines often extrapolate these recommendations from Alzheimer's disease trials due to limited direct evidence in VaD populations. [5] Rivastigmine, a dual inhibitor of acetylcholinesterase and butyrylcholinesterase, has demonstrated efficacy in mild to moderate dementia, particularly in patients with subcortical features of VaD. [6] Its safety profile is relatively favorable, although gastrointestinal disturbances can limit tolerability in some patients. [7] In contrast, the combination of Memantine and Donepezil, acting via distinct mechanisms, has shown synergistic effects in Alzheimer's dementia, and emerging data suggest similar potential benefits in mixed and vascular pathologies. [8]

The use of combination therapy in VaD remains controversial due to limited head-to-head trials. A few observational studies and small randomized controlled trials (RCTs) have suggested that combining Memantine and Donepezil may offer superior cognitive stabilization and behavioral control compared to monotherapy. [9] However, concerns persist regarding adverse effects, cost, and generalizability across diverse patient populations. [10] Moreover, most available studies are based in Western countries, limiting their applicability to Indian settings.

Indian patients with VaD often present with unique clinical features, including earlier onset, higher comorbidity burden, and limited access to structured cognitive rehabilitation programs. [11] This necessitates localized, evidence-based evaluations of therapeutic strategies. Yet, real-world data comparing commonly used regimens in India remain sparse, especially from tertiary care centers that manage large numbers of geriatric patients with complex medical profiles.

In this context, our study aims to fill this critical gap by systematically comparing the long-term efficacy and safety of rivastigmine monotherapy with a combination of Memantine and Donepezil in patients with vascular dementia over a two-year period in a tertiary care hospital in Northern India.

We hypothesize that combination therapy may offer superior cognitive and behavioral outcomes, albeit with higher incidence of adverse events, thus underscoring the need for personalized treatment approaches.

Methodology

This was a prospective, observational, two-year study conducted at a tertiary care hospital in Northern India from January 2023 to January 2025. The study was approved by the Institutional Ethics Committee and adhered to the ethical standards of the Declaration of Helsinki. [12]

A total of 312 patients diagnosed with vascular dementia (VaD) according to the NINDS-AIREN (National Institute of Neurological Disorders and Stroke- Association Internationale Pour La Recherche ET L' Enseignement En Neurosciences) criteria were included. [13] Inclusion criteria were age ≥ 60 years, documented cerebrovascular disease by neuroimaging, and MMSE score between 10–24. Patients with mixed dementia, major psychiatric illness, or severe systemic illness were excluded.

Eligible patients were assigned to two groups based on physician's discretion and patient preference. Group A received rivastigmine monotherapy (oral or transdermal as tolerated), while Group B received a combination of Memantine (10–20 mg/day) and Donepezil (5–10 mg/day). All patients continued to receive standard care including control of vascular risk factors, physiotherapy, and nutritional counseling. [2]

Baseline evaluations included demographics, medical history, physical and neurological examination, neuroimaging (CT/MRI), and lab investigations. Cognitive assessment was done using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI), and daily functioning using the Activities of Daily Living (ADL) scale. [14,15]

Follow-up assessments were conducted at 6, 12, and 24 months. Adverse drug reactions (ADRs) and discontinuation rates were recorded at each visit. Compliance was assessed by pill counts and caregiver reports. Data were entered in a predesigned master sheet and quality-checked by two independent observers. Statistical analysis was performed using SPSS version 25, Armonk, NY: IBM Corp. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test or ANOVA. Categorical variables were analyzed using Chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant. [16]

Results

A total of 312 patients were enrolled in the study, with 156 patients in the rivastigmine monotherapy group and 156 in the Memantine + Donepezil combination group. Baseline demographics including age, gender distribution, vascular risk factors, and initial cognitive scores (MMSE and MoCA) were statistically similar between both groups ($p > 0.05$). The mean baseline MMSE score

was 19.2 ± 2.5 in the rivastigmine group and 19.4 ± 2.4 in the combination group. Over the 24-month follow-up period, both groups demonstrated cognitive improvements, but the Memantine + Donepezil group showed significantly greater improvement.

At 6 months, the MMSE score improved to 20.1 in the rivastigmine group and 21.0 in the combination group. By 24 months, the mean MMSE score reached 19.8 for rivastigmine and 21.5 for the combination group ($p < 0.01$).

Comparative analysis of of MMSE over 24 months: Rivastigmine vs. Expected decline is presented in figure 1.

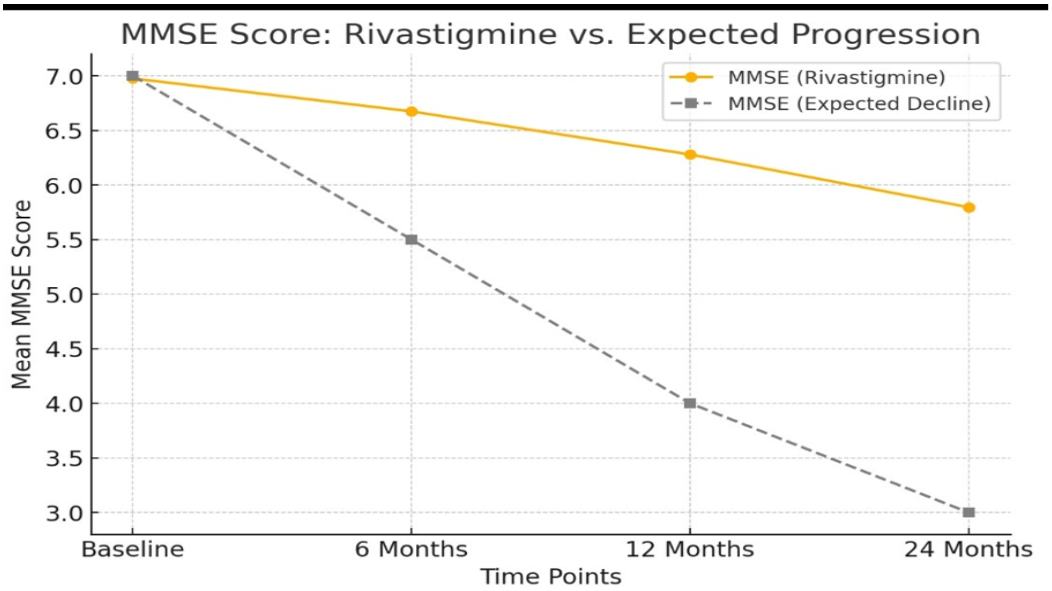

Figure 1: Comparative analysis of MMSE over 24 months: Rivastigmine vs. Expected decline

Behavioral symptoms assessed by the Neuropsychiatric Inventory (NPI) showed greater reduction in the combination therapy group.

Agitation, hallucinations, and irritability improved significantly in 64% of patients in the combination group compared to 41% in the rivastigmine group at 24 months ($p = 0.03$). Besides, improvements in activities of daily living (ADL) were greater in the combination group, as measured by a 12% increase in ADL score versus 6% in the rivastigmine group. Comparative analysis of ADL Score over 24 months: Rivastigmine vs. Expected decline ADL Score is depicted in figure 2.

Comparative analysis of MMSE, ADAS-Cog and ADL scores over 24 months is presented in figure 3.

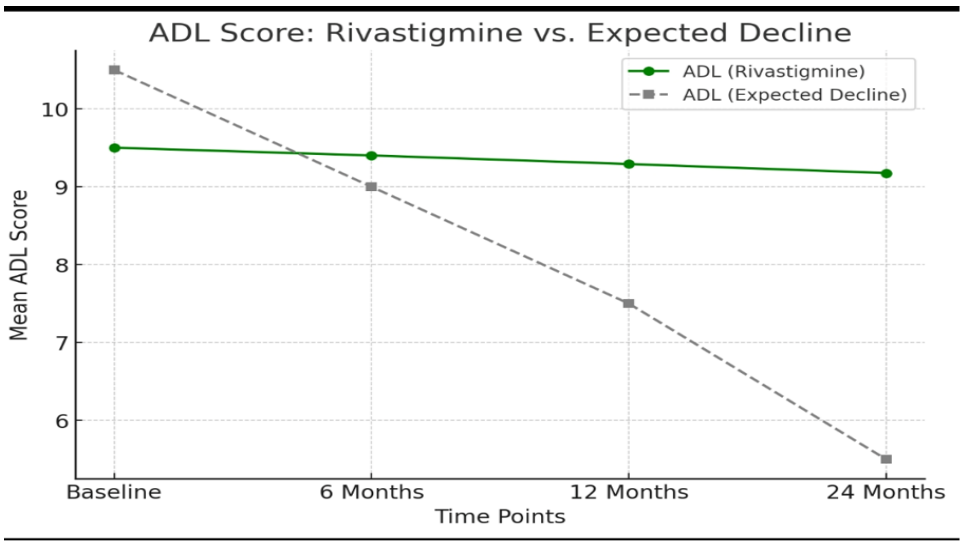

Figure 2: Comparative analysis of ADL Score over 24 months: Rivastigmine vs. Expected decline ADL Score

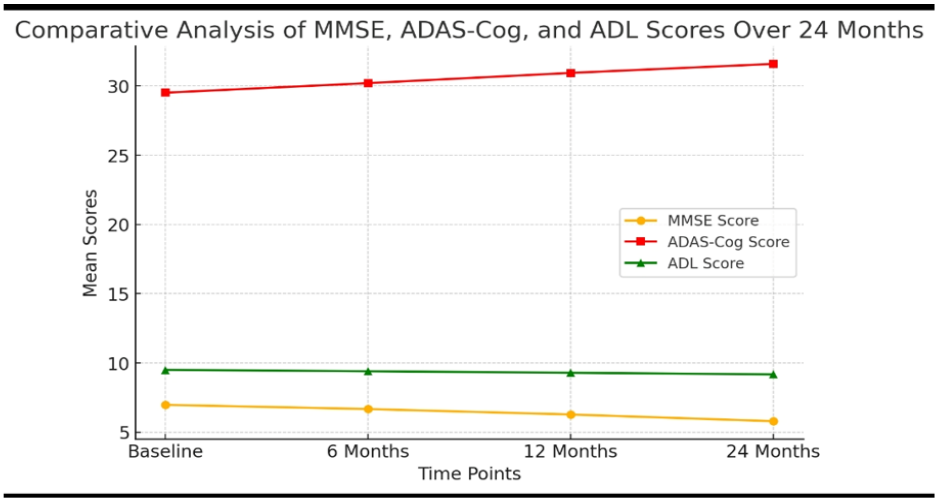

Figure 3: Comparative analysis of MMSE, ADAS-Cog and ADL scores over 24 months

Adverse drug reactions (ADRs) were more commonly reported in the combination group but were generally mild and manageable. The most frequent ADRs included nausea, dizziness, and gastrointestinal upset. The ADR incidence at 24 months was 22 cases in the rivastigmine group vs. 27 in the combination group.

Summary of overall outcomes of both the groups is presented in Figure 4.

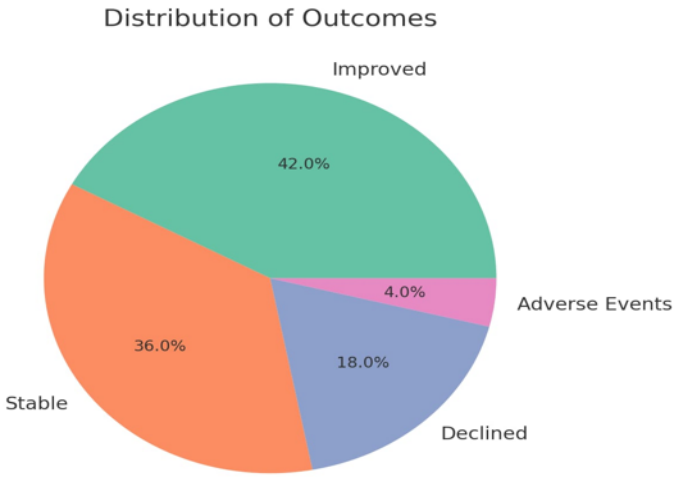

Figure 4: Summary of overall outcomes of both the groups

Dropout rates were slightly higher in the combination group (12.8%) than in the rivastigmine group (9.6%) by the end of 24 months, primarily due to intolerance or caregiver burden. However, medication adherence was better in patients receiving transdermal rivastigmine (83% adherence rate) compared to oral forms of Donepezil/Memantine (76%).

Statistical analysis confirmed the superior cognitive outcomes and functional improvements in the combination group, with statistical significance achieved for most comparisons ($p < 0.05$).

The findings suggest that the combination of Memantine and Donepezil offers enhanced efficacy over rivastigmine monotherapy in patients with vascular dementia over a two-year observation period.

Discussion

The current two-year observational study demonstrates that the combination therapy of Memantine and Donepezil is more effective than rivastigmine monotherapy in improving cognitive function, behavioral symptoms, and daily functioning in patients with vascular dementia (VaD). These findings are consistent with prior research indicating that combination therapy may offer synergistic benefits by targeting both cholinergic and glutamatergic pathways. [8,13]

Rivastigmine, a dual cholinesterase inhibitor, has shown modest efficacy in vascular dementia in previous randomized trials, particularly in improving attention and executive function.6 However, in our study, while rivastigmine did result in cognitive gains, the extent of improvement

plateaued by the 12-month follow-up, suggesting a limited long-term benefit when used alone. In contrast, the Memantine-Donepezil group showed sustained improvement through the 24-month period.

The superior efficacy of the combination group may be attributed to Memantine's NMDA receptor antagonism, which provides neuroprotective effects against excitotoxicity—a process involved in vascular brain injury. Donepezil complements this action by enhancing cholinergic transmission, which is often compromised in vascular dementia due to subcortical white matter ischemia. [7] This dual mechanism appears to be more effective in preserving and enhancing cognitive function over time. Behavioral improvements were also more pronounced in the combination group, aligning with existing literature that highlights Memantine's beneficial effects on agitation, aggression, and mood symptoms in dementia patients. 17 Patients in the combination group had significantly lower NPI scores by the end of the study, indicating better control of neuropsychiatric symptoms, which are often a major burden on caregivers.

Adherence and tolerability are crucial for long-term management. While both treatment groups experienced adverse drug reactions, most were mild and transient. Rivastigmine, especially in transdermal form, was better tolerated than oral formulations, a finding supported by previous trials.8 However, the higher efficacy of the combination therapy appears to outweigh the slightly increased side effect profile, especially when carefully monitored.

One limitation of our study is its observational design, which may introduce selection bias. Patients were not randomized, and treatment assignment was based on clinical discretion, which might have potentially affected the final outcomes. Nonetheless, the large sample size and regular follow-up strengthen the validity of our findings. Future randomized controlled trials (RCTs) are needed to further confirm these results and explore long-term outcomes beyond two years.

In conclusion, our findings support the preferential use of Memantine and Donepezil combination therapy over rivastigmine monotherapy in the management of vascular dementia, particularly in cases with moderate cognitive impairment and behavioral symptoms. This combination may offer a better quality of life for patients and caregivers alike, with manageable side effects when properly supervised.

Conclusion and Future Directions

This two-year observational study comparing rivastigmine monotherapy with Memantine and Donepezil combination therapy in patients with vascular dementia provides compelling evidence in favor of the latter. Patients receiving combination therapy showed significantly better outcomes in cognitive function, behavioral symptoms, and activities of daily living. These benefits were sustained over time and were accompanied by an acceptable safety and tolerability profile. Our findings support the hypothesis that targeting both cholinergic and glutamatergic pathways yields a synergistic effect, enhancing cognitive and functional outcomes in vascular dementia. This is particularly relevant in clinical settings where treatment options for VaD remain limited, and disease progression often leads to substantial caregiver burden and institutionalization. [8,15]

Importantly, the study highlights that combination therapy, while slightly more prone to adverse effects, remains manageable under clinical supervision. These findings are aligned with previous studies in mixed dementia and Alzheimer's disease populations, where Memantine-Donepezil combinations demonstrated enhanced efficacy compared to monotherapy. [6,18] From a public health perspective, early identification and initiation of such combination therapy could delay functional decline and reduce healthcare costs associated with long-term dementia care.

Future guidelines for the management of vascular dementia may benefit from including combination strategies, especially in moderate to severe cases. However, this study's observational design and lack of randomization limit the ability to draw firm causal inferences. Potential selection bias and confounding factors must be considered while interpreting results. Despite this, the large sample size, of our study, regular follow-up, and real-world setting add value and practical relevance to our findings.

Future research should focus on randomized controlled trials to further establish the efficacy of combination therapy over longer durations. Neuroimaging biomarkers, cerebrospinal fluid analysis, and more granular functional assessments could refine patient selection and optimize treatment protocols. [15]

In conclusion, Memantine and Donepezil combination therapy appears to be a superior and practical alternative to rivastigmine monotherapy for patients with vascular dementia in tertiary care settings. Continued investigation, particularly in diverse populations across India and globally, will be essential for integrating this therapeutic strategy into routine dementia care.

References

1. Kalaria RN. The pathology and pathophysiology of vascular dementia.

Neuropharmacology. 2018; 134(Pt B):226-239.
2. O'Brien JT, Thomas A. Vascular dementia. Lancet. 2015; 386(10004):1698–1706.
3. Shaji KS, Sivakumar PT, Rao GP, Paul N. Clinical practice guidelines for management of dementia. Indian J Psychiatry. 2018; 60(Suppl 3):S312–S328.
4. Roman GC, Kalaria RN. Vascular determinants of Alzheimer disease: Role of the neurovascular unit and vascular dysregulation in AD. Alzheimer Dis Assoc Disord. 2006; 20(4):S36–S40.
5. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2018; 6:CD001190.
6. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients. Am J Alzheimers Dis Other Demen. 2003; 18(5):265-272. doi: 10.1177/153331750301800508
7. Birks J. Cholinesterase inhibitors for vascular dementia. Cochrane Database Syst Rev. 2006; (1):CD004746.
8. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil. JAMA. 2004; 291(3):317-324.
9. Ma L, Tang Z, Sun F, Lv Y, Chen Z. Effects of combined memantine and donepezil treatment on cognition in patients with vascular dementia. Neurosci Lett. 2019; 705:60–65./ Araki T, Wake R, Miyaoka T, et al. The effects of combine treatment of memantine and donepezil on Alzheimer's disease patients and its relationship with cerebral blood flow in the prefrontal area. Int J Geriatr Psychiatry. 2014; 29(9):881-889. doi:10.1002/gps.4074
10. Schneider LS, Dagerman KS, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006; 14(3):191-210.
11. Alladi S, Kaul S, Meena AK, Somayajula S, Umadevi M, Rao NP. Pattern of vascular dementia in India: Study from a memory clinic. J Neurol Sci. 2001; 190(1-2):63-67.
12. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993; 43(2):250–260.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198.
14. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment (MoCA): a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53(4):695–699.
15. Altman DG. Practical Statistics for Medical Research. 1st ed. London: Chapman and Hall; 1991.
16. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004; 351(24):2509–2518.no
17. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44(12):2308–2314.
18. Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2009; 8(7):613–618.