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Original Research Article

Effect of telmisartan on hypertensive dementia patients: an observational study

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ABSTRACT

Background: This was a prospective observational study done to observe the effects of telmisartan on cognitive function in hypertensive dementia patients.

Methods: The study included new diagnosed hypertensive and normotensive dementia patients. Patients comprised of four groups; hypertensive dementia patients taking telmisartan (group 1), hypertensive dementia patients taking donepezil and telmisartan (group 2), normotensive dementia patients taking donepezil (group 3) and normotensive dementia patients taking drugs which does not affect memory (group 4). Cognitive function of four groups were compared to each other at 4, 8 and 12 weeks.

Results: In group 1, 2 and 3 mini-mental state examination (MMSE) scores has increased by 1.69, 16.81, and 13.28 percent and in group 4 there is decrease in MMSE score by 6.03 percent in 12 weeks.

Conclusions: In this study we can conclude that telmisartan has dementia preventing propensity which is better than placebo but not as good as donepezil.

Keywords: Telmisartan, Hypertensive dementia, Mini-mental state examination score

INTRODUCTION

Dementia is a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities. It is marked by progressive cognitive impairment in clear consciousness. The cognitive function declines from previous level of functioning. It involves multiple cognitive domains including memory thus causing a significant impairment in social or occupational functioning compared to mild cognitive impairment (MCI) which is similar but does not cause significant impairment in functioning.¹ Dementia is a complex and multifactorial disease.

Risk factors of dementia have been classified into modifiable and non-modifiable risk factors. Modifiable risk factors are vascular disease, hypertension, diabetes, dyslipidemia, depression, alcohol, smoking, obesity etc. Non-modifiable risk factors are age, family history, Apo E4 allele, female sex, head trauma, Down's syndrome, mutation of 1,4 and 21 chromosomes. Prevalence of all types of dementia increases with increasing age. In some other recent study, it was found that users of ARBs had superior memory performance over time compared with other antihypertensive drug users.

Hypertension is one of the important risk factors for dementia.² Telmisartan, an angiotensin-receptor blocker (ARB) is commonly used for treatment of

hypertension. Two well characterized receptors are angiotensin type 1 receptor (AT₁ receptor) and type 2 receptor (AT₂ receptor). AT₁ inhibition reduces cardiac and vascular oxidative stress, inflammation and remodeling, thus improving endothelial dysfunction, increased angiotensin II activity on AT₂ receptors, leading to vasodilation and natriuresis through bradykinin, nitric oxide, prostaglandin and cyclic guanosine monophosphate (GMP) pathways, generally showing an opposite effect to the action of AT₁ receptors. Recently renin-angiotensin-aldosterone system (RAAS) has been found to have an important role in cognitive function.

ARB blocks AT₁ receptors also resulting in AT₂ activation and contributes to some protective effects of ARBs. In the brain, the activation of AT₂ reduces inflammation, superoxide production and axon degeneration, promotes neuronal cell differentiation and leads to activation of the repair systems. Several animal studies suggest the benefits of ARBs on cognitive function.³

Clinical study had been done on effect of telmisartan and ACE inhibitors on different aspect of dementia. The result is not very conclusive.

METHODS

It was an observational, prospective, open-label, non-interventional study. This was conducted in the Department of Pharmacology and Therapeutics, Rajendra Institute of Medical Sciences (RIMS), Ranchi amongst the patients attending outpatient and indoor Departments of Medicine and Psychiatry of Rajendra Institute of Medical Sciences (RIMS), Ranchi; Central Institute of Psychiatry, Kanke, Ranchi and Ranchi Institute of Neuro Psychiatry and Allied Sciences (RINPAS), Kanke, Ranchi.

Ethical considerations

Prior approval from Institutional ethics committee was taken before study and consent was taken from all patients on separate consent form for each patient.

Study duration

The study was conducted from March 2018 till October 2019. Every participant was followed up for 12 weeks in totality.

Inclusion criteria

Inclusion criteria were newly diagnosed hypertensive (systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg) and normotensive (systolic blood pressure < 140 mmHg and/or a diastolic blood pressure < 90 mmHg) dementia patients (MMSE score

range 11-25) of age 55 years and above of both sexes suffering from mild to moderate dementia.

Exclusion criteria

Exclusion criteria were patients who were suffering from critical diseases and required emergency management or with co-morbidities other than hypertension (cardiac, renal, hepatic disorders and other psychiatric illness), HIV infected patients, patients taking drugs which affects memory like antidepressants, antipsychotic, beta-blockers, antihistaminics, benzodiazepines, antiepileptics, narcotics, antiparkinsonian drugs; patients with hypersensitivity to telmisartan and/or donepezil.

The patients were divided into four groups comprising thirty patients in each group; first two groups were hypertensive patients and last two groups were non hypertensive patients. The groups are as follows.

Group 1: Dementia patients taking telmisartan (dose 40 mg per day).

Group 2: Dementia patients taking telmisartan and donepezil (dose of telmisartan 40 mg per day and donepezil 5 mg per day).

Group 3: Dementia patients taking donepezil (dose 5 mg per day).

Group 4: Dementia patients not taking drugs which affects memory but taking some other drugs, this group will be known as placebo group.

In this group those patients were included who came to OPD for various problems and found suffering from dementia and not had willingness for the treatment of this condition.

The mini-mental state examination (MMSE) scores were used as parameter for memory test at baseline and at intervals of 4th, 8th and 12th weeks. It is a 30 points questionnaire used extensively in clinical and research settings to measure cognitive impairment and also as a screening test for dementia. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time. Increase in MMSE score is indicative of cognitive improvement.^{4,5}

Blood pressure was also measured with the help of mercury sphygmomanometer at baseline and same follow-up intervals of all patients.

Statistical analysis

Statistical analysis was done using the software statistical package for the social sciences (SPSS) version 17. Anova and Tukey's post hoc test was done.

RESULTS

Demographic data of patients is presented group wise in (Table 1). Overall, there were total 45 females and 75 males in all four groups and low education level (illiterate

and primary level of education) was found in 76% of cases. In group 1, 2 and 3 MMSE score has increased by 1.69, 16.81, and 13.28 percent and in group 4 there is decrease in MMSE score by 6.03 percent in 12 weeks.

Table 1: Demographic data of the patients.

Characteristics	Group 1	Group 2	Group 3	Group 4	P value
Age in years (mean±SD)	65.80±7.09	68.73±6.62	66.60±6.63	64.63±6.60	0.116
Gender					
Male	10	11	15	9	0.399
Female	20	19	15	21	
Education level					
Illiterate	8	8	8	8	0.523
Primary	18	11	15	16	
Higher secondary	4	6	3	2	
Graduate		4	4	4	
Postgraduate		1			
Economic status					
Lower	19	13	20	13	0.212
Middle	11	17	10	16	
Higher				1	
Habitat					
Rural	20	21	21	18	0.825
Urban	10	9	9	12	

Table 2: Mean mini-mental state examination scores group-wise at 4, 8 and 12 weeks.

MMSE	Group 1	Group 2	Group 3	Group 4	P value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Baseline	19.50±4.14	19.03±3.87	19.13±4.38	19.40±3.69	0.966
4week	19.63±4.24	21.53±3.73	21.40±4.49	19.50±3.84	0.095
8week	19.67±4.25	21.83±3.77	21.60±4.42	18.63±3.86	0.007
12week	19.83±4.14	22.23±3.79	21.67±4.51	18.23±3.88	0.001

DISCUSSION

Our study found that there is no significant difference in mean MMSE score of telmisartan treated hypertensive dementia group (group 1) as compared to other three groups (2, 3 and 4) at 4, 8 and 12th week (significance 0.11, 0.31 and 0.432 respectively).

Statistically the effect of telmisartan on hypertensive dementia patients is not significant in comparison to placebo in enhancing cognitive function but clinically it prevented decline in cognitive function. In the placebo group memory has declined by 6.03% (as evaluated by MMSE score) but there is no decline in memory in hypertensive dementia patients who were taking telmisartan. Instead in hypertensive dementia patients taking telmisartan there was little gain of 1.69% in cognitive function.

Donepezil is an effective drug for dementia and it was found better when compared with telmisartan. When donepezil and telmisartan were used simultaneously telmisartan showed the potentiating effect in dementia prevention.

Several mechanisms have been proposed to account for the apparent protective effect of ARBs, including their role in remodeling of cerebral microvasculature, inducing neural differentiation and DNA repair, reversing oxidative stress and inflammation, and preventing ischemic brain injury.^{6,7,8} It is supportive of our study because hypertensive dementia group (group 1) taking telmisartan (an ARB) had no decline in mean cognitive score when compared to the normotensive dementia patients taking no telmisartan or no donepezil (group 4).

Telmisartan along with donepezil (group 2) and donepezil alone (group 3) both enhanced cognitive effects compared to group 1 and group 4, group 2 having significant effect because of additional effect of telmisartan which has different mechanisms of action which results in cognitive improvement.

Donepezil is a standard dementia drug approved by FDA.⁹ It has role of reference drug in this study.¹⁰ It acts by inhibiting acetylcholinesterase enzyme increasing the amount of acetylcholine in brain which increase cognition and memory. Accordingly, MMSE score in group-3 are significantly better at 8th and 12th weeks in comparison to group 4 (p values 0.029 and 0.008 respectively).

Cutuli et al showed that donepezil pre-treatment had beneficial effects on behavioral deficits induced by cholinergic depletion in rats.

Cholinergic depletion increased hippocampal and neocortical caspase-3 activity and impaired working memory, spatial discrimination, social interactions and behavior in rats.¹¹

In a study patient with probable Alzheimer's disease (AD) and essential hypertension were randomly assigned to the telmisartan group or the amlodipine group (daily) for 6 months. The groups had a similar significant reduction in systolic and diastolic blood pressure after treatment. The telmisartan group did not show any changes in cognitive function test scores, while the amlodipine group showed significant decline on the AD assessment scale cognitive subscale.¹² This indicates that telmisartan may have additional benefits and be useful for the treatment of elderly hypertensive patients with dementia.

One brain autopsy series study showed that ARB use was associated with significantly lower AD pathology, while no alteration of vascular pathology was observed when compared to other or no antihypertensive medication users.¹³

In animal study it has been found that low dose of telmisartan has a protective effect on the cognitive decline via up-regulation of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (BDNF/TrkB) in the hippocampus of stroke-prone spontaneously hypertensive rats (SHRSPs) without hypotensive effect.¹⁴

Telmisartan has a unique binding mode to the AT1 receptor due to its distal benzimidazole portion. This portion could explain the highest lipophilicity, the greatest volume distribution and the strongest binding affinity of telmisartan to AT1 receptor. Furthermore, telmisartan was found to firmly bind to the AT1 receptor through the unique "delta lock" structure. A study suggests that due to its "delta lock" structure, telmisartan

may be superior to other ARBs in halting cardiovascular disease in patients with hypertension. Cardiovascular disorders are one of the important risk factors of dementia and its progression.¹⁵

In the study on cognition and prognosis in the elderly (SCOPE) to assess whether candesartan-based ARB antihypertensive treatment in elderly patients with mildly to moderately elevated blood confers a reduction in cardiovascular events, cognitive decline and dementia, it was found that cognitive function was well maintained in both treatment groups in the presence of substantial blood pressure reductions.¹⁶ It correlates with our study.

Users of ARBs or ACEIs (blood brain barrier crossing medications) showed better memory performance over time than all other groups, including normotensives, and had less white matter hyper intensity volume over time than users of non- blood brain barrier crossing medications.¹⁷

In a recent longitudinal analysis of cerebrospinal fluid biomarker data from Alzheimer's disease neuroimaging initiative, attenuation of cerebral amyloid retention and progression to dementia among older adults taking ARBs were reported.¹⁸

ACEIs reduce the amount of free angiotensin II and decrease damaging AT1 receptor activity, they also reduce beneficial AT2 receptor activity. ARBs block AT1 receptors and not the production of angiotensin II, they promote AT2 receptor activity and are "angiotensin-converting enzyme-sparing," allowing ACE to continue its suggested A β -degrading function, unlike ACEIs.^{19,20}

Researchers in a nested case-control study of adults aged 60 years or older, who had either Alzheimer's disease, vascular dementia, or unspecified/other dementia, reported that patients taking ARBs and ACEIs had 53% and 24% lower risks of Alzheimer's disease, respectively, than those taking other antihypertensive medications.²¹

However, large clinical intervention trials such as ON TARGET (ongoing telmisartan alone and in combination with ramipril global endpoint trial) and TRANSCEND (telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease) have not found significant differences in the incidence of dementia (which was one of its secondary outcome) between groups taking ARBs, ACEIs, or placebo.²²

The PROGRESS (perindopril protection against recurrent stroke) study did not find a clear effect of hypertensive treatment on dementia, but reduced the risk of cognitive decline by approximately 20% and reduced the risk of "cognitive decline with recurrent stroke" by approximately 50%.²³

Recently, telmisartan, an ARB, was found to act as a partial agonist of peroxisome proliferator-activated

receptor-gamma (PPAR-gamma).²⁴ PPAR-gamma influences the gene expression involved in carbohydrate metabolism, and pioglitazone and rosiglitazone, ligands for PPAR-gamma, improve insulin resistance in diabetic patients. Activators of PPAR-gamma exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus decreasing the risks for atherosclerosis. It has also been hypothesized here that due to its unique PPAR-gamma-modulating activity, telmisartan will become a promising cardiometabolic sartin, that targets both diabetes and CVD in hypertensive patients.²⁵

Recently, a Phase-I trial is going on to determine if telmisartan affects cognition and biomarkers of Alzheimer's in African Americans who is hypertensive and at risk of dementia and their parent or biological family member with Alzheimer's disease. Another trial of losartan (phase-2) to test the efficacy of reducing pathology in Alzheimer's Disease through angiotensin targeting (RADAR) is going on in mild to moderate Alzheimer's disease cases.²⁶ These clinical studies will be helpful in revealing the role of telmisartan and ACE inhibitors in dementia prevention.

CONCLUSION

In this study we can conclude that telmisartan has dementia preventing propensity which is better than placebo but not as good as donepezil. The effect on cognition was better in the hypertensive dementia patients who were taking donepezil and telmisartan than the normotensive dementia patients who were taking only donepezil. This also shows potentiating effect of telmisartan on cognition.

There is need of clinical study with more specific tools and sensitive methods in a big sample size for longer period to establish telmisartan as dementia preventing drug in hypertensive dementia patients.

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