Comparative Study of Telmisartan Alone And With Atorvastatin On Cognitive Functions In Mild To Moderate Hypertensive Patients

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ABSTRACT In this study we evaluated the effects of ARB, Telmisartan alone and with Atorvastatin on cognitive functions in hypertensives. **Material and Methods** : A Prospective, comparative, randomized, before-after, open-label study was conducted at a tertiary care hospital of Ajmer. Memory functions were evaluated with PGI Memory Scale, while psychomotor functions were evaluated with Six Letter Cancellation test and Digit Letter Substitution test. Patients (with SBP≥ 140 mm hg; DBP ≥ 90 mm Hg) devided into two groups, group I (n=52) received Telmisartan 40 mg OD and group II (n=51) received Telmisartan 40 mg OD with Atorvastatin 10 mg OD for 16 weeks. Wilcoxon Signed Rank test and Mann Whitney U test were used. Statistical significance was considered at P<0.05. **Results** : A improvement in scores of memory and psychomotor functions were observed in both the groups. A statistically significant difference (p<0.05) in both groups was shown in 2 subtests out of 10 subtests of memory functions. Both the groups showed significant improvement in psychomotor function tests (p<0.05). **Conclusion** :Telmisartan shows improvement in cognitive functions in both groups. Atorvastatin did not affect memory and psychomotor functions adversely.

Introduction:

Studies have shown that hypertension is a risk factor for cognitive decline and dementia [1]. Angiotensin receptor blockers and Statins are frequently prescribed for cardiovascular diseases. Previous clinical studies have suggested that blockade of the RAS could prevent cognitive impairment associated with hypertension [2].Recent studies shows that angiotensin II inhibitors help to preserve cognitive functions in patients with Alzheimer's disease through a mechanism that is independent of the blood-pressure-lowering effect[3]. Relative stimulation of AT2 signaling during ARB treatment has been highlighted in terms of protection against brain damage[4]. Some ARBs like Telmisartan and Irbesartan have PPAR-γ agonistic activity[5],which is involved in prevention of brain damage by interrupting inflammatory process of brain cells[6].

Statins can also improve cognitive ability by inhibition of cholesterol synthesis[7], suppression of neurogenesis[8], increased cellular proliferation and differentiation in the dentate gyrus, also improved spatial learning[9]. But in 2014 FDA[10] released an alert that Atorvastatin can lead to cognitive impairment. The status of statins for cognitive function is still controvercial.

So, we planned to compare ARB Telmisartan alone and Telmisartan with Atorvastatin on memory and psychomotor function tests in mild to moderate hypertension.

Material and Methods:
Patient selection

Patients of 20 to 70 years with both sexes male and female who were newly diagnosed as per JNC VIII[11](SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) or were not on any antihypertensive for at least one month, having ability to understand, read, write, and communicate in Hindi with primary knowledge of English.

Exclusion criteria for the cases were patients age less than 20 and more than 70, patients known to have psycho-logical and behavioural disorders or any other CNS disorder that could interfere with the memory and psychomotor functions and patients on any other medications (e.g. sedatives, antipsychotics, antidepressants, antihistaminic) that are known to affect memory and psychomotor functions, patients who were unwilling and did not have ability to understand, read, write, and communicate in Hindi with primary knowledge of English, Patients who have history of significant hepatic, renal, gastrointestinal, pulmonary, musculoskeletal, endocrine, neuropsychiatric, hematologic cardiovascular disease other than hypertension, Pregnant women, lactating women and any adverse drug reaction came during the study period due to drug therapy then patients supposed to be excluded from the study .

Methodology: After institutional ethical approval, a prospective, non-randomized, Observational, before-after, open label study was conducted. After sample size calculation 45 patients in each group provided 80% power, considering withdrawal during study, we enrolled 52 patients in each group. Those who met with the inclusion and exclusion criteria were enrolled in the study. Written informed consent was obtained from the patient. One patient was failed to come for follow up so, group I (n=52) received Telmisartan 40 mg OD , group II (n=51) received Telmisartan 40 mg OD with Atorvastatin 10 mg OD for 16 weeks. Patient selection, treatment or drug, dose and route were solely decided by physicians from Dept. of medicine, J.L.N. Medical College and associated hospitals. The baseline information was collected on the day zero i.e. before starting of the drug treatment. The patients were then evaluated with the help of PGI memory scale and psychomotor function tests on day zero and after 4 months. The systolic and diastolic blood pressure was recorded by the auscultatory method with the help of sphygmomanometer every fortnightly. All the cognitive functions tests were conducted in Hindi and English language. They were conducted in particular sequence and this sequence was maintained for every subject.

Tests for memory

The PGI memory scale (PGIMS)[12] was employed to assess memory function of patients. PGI memory scale consists of ten sub-tests. The subjects were explained about the test and were relaxed. The tests were done as per the instructions of PGI memory scale and scoring according to scale was done simultaneously in the following order:

Remote memory, Recent memory, Mental Balance, Attention and concentration, Delayed Recall, Immediate Recall, Verbal retention for similar pair, Verbal retention for dissimilar pairs ,Visual retention, Recognition

Psychomotor function tests: [13,14]

Six Letter Cancellation Test (SLCT) and Digit Letter Substitution Test (DLST)

Statistical analysis G*Power 3.0.10 was used to calculate the sample size. Statistical significance was set at $P < 0.05$.Data obtained in the various tests were analyzed using Graph Pad Prism 5 software. Analysis of distribution of data was done using the Komolgorov--Smirnov test and Wilcoxan signed rank test was used to compare cognitive and psychomotor functions at baseline and after 4 months in each group. Mann whitney U test was used to compare the pre- and post-treatment scores of memory and psychomotor functions in between groups.

Table 1: Age and sex distribution of patients:

	Male	Female
0-20	0	0
21-30	0	0
31-40	4	6
41-50	7	22
51-60	13	24
>60	14	13
Total	38(36.08%)	65(63.1%)

TABLE:2 Effect of Telmisartan on Cognitive and Psychomotor Functions

Parameter	Pre- treatment values	Post-treatment values	Mean of Differences	P-value	
Remote memory	5.58±0.572	5.59±0.63	0.019±0.64	>0.05	NS
Recent memory	4.52±0.58	4.56±0.50	0.038±0.59	>0.05	NS
Mental Balance	5.96±0.86	7.52±1.11	1.56±1.14	<0.05	S
Attention and concentration	8.58±1.39	10.08±1.94	1.5±1.83	<0.05	S
Delayed Recall	6±1.29	6.48±1.11	0.48±1.12	<0.05	S
Immediate Recall	6.52±0.88	6.75±1.15	0.23±0.96	>0.05	NS
Verbal Retention for Similar Pairs	4.38±0.63	4.59±0.49	0.21±0.82	>0.05	NS
Verbal Retention for Dissimilar Pairs	6.88±1.54	7.12±1.35	0.23±1.14	>0.05	NS
Visual Retention	8±1.26	8.31±1.26	0.31±1.39	>0.05	NS
Recognition	6.52±0.91	7.56±1.13	1.04±1.31	<0.05	S
SLCT	34.77±5.85	36.37±5.06	1.59±3.94	<0.05	S
DLST	41.12±7.83	44.28±5.84	3.17±4.41	<0.05	S

SLCT = Six Letter Cancellation Test

DLST = Digit Letter Substitution Test

S= Significant

NS= Not significant

TABLE:3 Effect of Telmisartan with Atorvastatin on Cognitive and Psychomotor Functions

Parameter	Pre- treatment values	Post-treatment values	Mean of Differences	t-value	P-value	
Remote Memory	5.53±0.73	5.74±0.72	0.22±0.78	1.899	>0.05	NS
Recent memory	4.43±0.54	4.65±0.522	0.21±0.73	2.047	<0.05	S
Mental Balance	5.96±1.02	7.35±1.23	1.39±1.15	5.429	< 0.05	S
Attention and concentration	8.82±1.60	10.25±2.31	1.43±2.17	4.098	< 0.05	S
Delayed Recall	5.98±1.25	7.20±1.61	1.22±1.53	4.539	< 0.05	S
Immediate Recall	6.62±0.96	6.86±1.13	0.24±1.08	1.440	>0.05	NS
Verbal Retention for Similar Pairs	4.49±0.50	4.67±0.48	0.17±0.65	1.877	>0.05	NS
Verbal Retention for Dissimilar Pairs	7.45±1.71	7.76±1.80	0.31±1.71	1.363	>0.05	NS
Visual Retention	8.35±1.39	8.71±1.48	0.35±1.60	1.694	>0.05	NS
Recognition	6.76±1.32	7.25±1.57	0.49±1.53	2.206	< 0.05	S
SLCT	33.71±5.74	37.14±5.13	3.43±6.83	3.052	< 0.05	S
DLST	42.29±6.74	45.39±5.32	3.10±7.10	2.827	< 0.05	S

Table 4: Comparative study of Telmisartan and Telmisartan with Atorvastatin on cognitive and psychomotor functions

Parameter	Telmisartan	Telmisartan with Atorvastatin	p-value	
Remote memory	0.019±0.64	0.22±0.78	> 0.05	NS
Recent memory	0.038±0.59	0.21±0.73	> 0.05	NS
Mental Balance	1.56±1.14	1.39±1.15	>0.05	NS
Attention and concentration	1.5±1.83	1.43±2.17	>0.05	NS
Delayed Recall	0.48±1.12	1.22±1.53	<0.05	S

Immediate Recall	0.23±0.96	0.24±1.08	>0.05	NS
Verbal Retention for Similar Pairs	0.21±0.82	0.17±0.65	>0.05	NS
Verbal Retention for Dissimilar Pairs	0.23±1.14	0.31±1.71	>0.05	NS
Visual Retention	0.31±1.39	0.35±1.60	>0.05	NS
Recognition	1.04±1.31	0.49±1.53	<0.05	S
SLCT	1.59±3.94	3.43±6.83	>0.05	NS
DLST	3.17±4.41	3.10±7.10	>0.05	NS

RESULTS:

Table-1 shows the age and sex wise distribution of hypertensives , 63.1% were female. Table-2 shows 4 out 10 subtests were improved significantly (p<0.05) after Telmisartan administration and 5 out of 10 subtests were improved by Telmisartan with Atorvastatin (p<0.05;table-3). Comparative results revealed that improvement in Delayed recall was more with Telmisartan with Atorvastatin while subtest Recognition wasimproved more in Telmisartan alone group. Both SLCT and DLST were improved significantly in group I and II. But Interdrug comparison for groups was statistically not significant (p>0.05; table 4).

Discussion:

In present study 4 out of 10 subtests were improved after Telmisartan administration. After Telmisartan with Atorvastatin administration, 5 subtests were improved statistically. Interdrug comparison shows significant (p<0.05) difference in 2 subtests out of 10 memory function tests. Comparative analysis of psychomotor function tests reveals no statistical significant (p<0.05) differences between groups. Angiotensin receptor blockers (ARB) improve cognitive functions by several mechanism like, increased cerebral blood flow which was decreased by activation of renin angiotensin system activation[15].prevention of accumulation of amyloid β[16].increase release of acetylcholine for neurocommunication [17].Telmisartan is also reported to improve memory impairment of mice that had been intracerebroventricularly injected with Aβ[18].

Wincewicz D & Braszko JJ,[19] found that Telmisartan diminishes deleterious effects of chronic restraint stress on memory in a statistically significant manner (p < 0.01) in both, PA(Passive avoidance) situation and ORT (object recognition test). So, Telmisartan may constitute a new therapeutic option in a stress-related cognitive impairment. Other researcher[20] stated that Telmisartan provides effective neuroprotection against dopaminergic cell death through PPAR-γ activation. Telmisartan protects against cognitive decline via up-regulation of BDNF/TrkB (tropomyosin related kinase B) in the hippocampus of hypertensive rat , partly because of PPAR-gamma activation independent of blood pressure-lowering effect[21].

Statins also improves memory functions by several way apart from cholesterol lowering effect,statins have shown promise in enhancing neurogenesis. Both simvastatin and atorvastatin have been shown to enhance neurogenesis in the dentate gyrus following traumatic brain injury in rats which was associated with increased vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) expression , increased cellular proliferation and differentiation in the dentate gyrus and improved spatial learning[9] , reduced delayed neuronal death in the hippocampus [22].

Zhao L et al,[23] found that administration of Atorvastatin ameliorated the cognitive deficits, depressed the inflammatory responses, improved the (long term potentiation) LTP impairment. It also prevents Aβ25-35-induced neurotoxicity in cultured hippocampal neurons. In contrast, another study[24] found that statins use has been associated with more cognitive impairment. So the status of statins in cognitive function is still controvercial.

Conclusion:

Improvement in cognitive functions was observed throughout the study period. Telmisartan improves cognitive functions probably due to PPARγ activity, it significantly improved (p < 0.05) 4 out of 10 subtests and with Atorvastatin improvement was seen in 5 out of 10 subtests of PGI memory scale which were statistically significant (p < 0.05). Comparative analysis shows, both the treatment groups had almost similar effect on cognitive functions. Atorvastatin does not affect memory and psychomotor functions adversely.

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