

Comparative Study of two ARBs on Memory and Psychomotor Functions in Mild to Moderate Hypertension



Medical Science

KEYWORDS : Telmisartan, Olmesartan, cognitive functions, psychomotor functions

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ABSTRACT

In this study we evaluated the effects of two ARBs, Telmisartan and Olmesartan on memory and psychomotor functions in Indian population. 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. Total 101 patients (SBP \geq 140 mm hg; DBP \geq 90 mm Hg), Group I (n=52) received Telmisartan 40 mg OD and group II (n=49) received Olmesartan 20 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 improvement (p<0.05) was shown in 3 subtests out of 10 subtests of cognitive fuctions in telmisartan as compare to Olmesartan. Both the drugs showed significant improvement in psychomotor function tests (P<0.05). Conclusion : Telmisartan showed more improvement as compare to Olmesartan.

Introduction:

Hypertension is the most important factor that negatively affects the modalities of cerebral aging¹ and is associated with cognitive compromise in aging individuals². Studies have demonstrated that hypertensives exhibit reduced cerebral blood flow and metabolism (utilization of glucose to obtain energy), particularly in certain brain regions³. Neurochemical transmission within the brain and basic cellular functions are also affected by hypertension⁴.

Experimental studies suggest that treatments targeting RAS such as Angiotensin converting enzyme inhibitors(ACEIs) and Angiotensin receptor blockers (ARBs) may have beneficial effect on cognitive decline and dementia⁵. Angiotensin receptor blockers (ARBs) may have greater neuroprotective effect than ACEIs through prevention of vascular damage induced by β -amyloid⁶. They potentially and selectively inhibit effects of angiotensin II , including angiotensin II induced contraction of vascular smooth muscles, rapid and slow pressor response ,vasopressin release, increase in sympathetic tone, enhancement of nor- adrenergic neurotransmission, changes of renal function etc.⁷ In this study to compare the effects of two ARBs, Telmisartan and Olmesartan on memory and Psychomotor functions in mild to moderate hypertensive patients in Indian population.

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(SBP \geq 140 mmHg and/or DBP \geq 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 psychological and behavioral 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. 3 patients were failed to come for followup so, Group I (n=52) received Telmisartan 40 mg OD , group II (n=49) received Olmesartan 20 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 asso. 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)⁹ 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:^{10,11}

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. Power analysis indicated that a sample size of Total 90 patients (45 per group) would give 80% power to detect differences between groups, at an α level of <0.05 and with 95% confidence interval. 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 Wilcoxon 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 distribtution of patients in Telmisartan and Olmesartan group

| | Male | Female |
|--------------|--------|--------|
| 20-29 | 0 | 0 |
| 30-39 | 3 | 2 |
| 40-49 | 4 | 15 |
| 50-59 | 12 | 17 |
| 60 and above | 25 | 23 |
| Total | 44 | 57 |
| | 43.56% | 56.44% |

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 Olmesartan on Cognitive and Psychomotor Functions

| Parameter | Pre- treatment values | Post-treatment values | Mean of Differences | P-value | |
|---------------------------------------|-----------------------|-----------------------|---------------------|---------|----|
| Remote memory | 5.63±0.60 | 5.83±0.66 | 0.20±0.49 | > 0.05 | NS |
| Recent memory | 4.61±0.49 | 4.65±0.48 | 0.04±0.61 | >0.05 | NS |
| Mental Balance | 6.04±1.02 | 6.78±1.17 | 0.73±1.08 | < 0.05 | S |
| Attention and concentration | 8.96±1.65 | 9.26±1.90 | 0.30±1.62 | >0.05 | NS |
| Delayed Recall | 5.78±1.30 | 6.55±1.28 | 0.78±1.36 | <0.05 | S |
| Immediate Recall | 6.65±1.18 | 7.06±1.34 | 0.40±1.31 | >0.05 | NS |
| Verbal Retention for Similar Pairs | 4.42±0.58 | 4.59±0.53 | 0.16±0.87 | >0.05 | NS |
| Verbal Retention for Dissimilar Pairs | 7.10±1.62 | 7.56±1.83 | 0.44±1.64 | > 0.05 | NS |
| Visual Retention | 7.89±1.71 | 8±1.90 | 0.10±1.37 | >0.05 | NS |
| Recognition | 6.51±1.19 | 6.95±1.27 | 0.44±1.31 | < 0.05 | S |
| SLCT | 33.90±5.45 | 35.24±4.77 | 1.35±2.74 | < 0.05 | S |
| DLST | 40.53±7.62 | 41.86±7.44 | 1.32±2.50 | <0.05 | S |

Table 4: Comparative study of Telmisartan and Olmesartan cognitive and psychomotor functions

| Parameter | Telmisartan | Olmesartan | P-value | |
|---------------------------------------|-------------|------------|----------|----|
| Remote memory | 0.019±0.64 | 0.20±0.49 | P > 0.05 | NS |
| Recent memory | 0.038±0.59 | 0.04±0.61 | P >0.05 | NS |
| Mental Balance | 1.56±1.14 | 0.73±1.08 | P < 0.05 | S |
| Attention and concentration | 1.5±1.83 | 0.30±1.62 | P < 0.05 | S |
| Delayed Recall | 0.48±1.12 | 0.78±1.36 | P > 0.05 | NS |
| Immediate Recall | 0.23±0.96 | 0.40±1.31 | P >0.05 | NS |
| Verbal Retention for Similar Pairs | 0.21±0.82 | 0.16±0.87 | P >0.05 | NS |
| Verbal Retention for Dissimilar Pairs | 0.23±1.14 | 0.44±1.64 | P >0.05 | NS |
| Visual Retention | 0.31±1.39 | 0.10±1.37 | P >0.05 | NS |
| Recognition | 1.04±1.31 | 0.44±1.31 | P <0.05 | S |
| SLCT | 1.59±3.94 | 1.35±2.74 | P >0.05 | NS |
| DLST | 3.17±4.41 | 1.32±2.50 | P >0.05 | NS |

Results:

Table 1 shows the age and sex distribution of patients enrolled in Telmisartan and olmesartan group. Out of them 43.56% were male and 56.44% female. As shown in table 2, Telmisartan improved cognitive and psychomotor function tests. Out 10 , 4 sub-tests were improved significantly ($P < 0.05$) in memory function tests and improvement in psychomotor functions (SLCT & DLST) also found significant. Effect of Olmesartan on above mentioned parameters were tabulated in table 3, it shows, 3 out of 10 sub-test were improved after olmesartan administration. SLCT and DLST were also significantly improved. Table 4 shows comparative analysis of two ARBs on memory and psycho-

motor function tests. A significant ($P < 0.05$) change was observed in 3 out of 10 subtests i.e mental balance, attention and concentration and recognition in Telmisartan group as compare to Olmesartan. Both the drugs showed significant improvement in psychomotor function tests ($P < 0.05$) but Telmisartan showed greater improvement as compare to Olmesartan, However, comparative results were not statistically significant.

Discussion:

Age and sex distribution shows (Table 1) that maximum hypertensive patients were of 60 and above in age and female (57) patients. In our study, an improvement in the scores of memory and psychomotor functions was observed in both the groups throughout the study period. Telmisartan significantly improved ($P < 0.05$) 4 out of 10 subtests and in comparison between two drugs, statistically significant improvement ($P < 0.05$) was seen in 3 out of 10 subtests of cognitive functions for telmisartan as compare to Olmesartan. Similarly, In a another study,¹² found that Telmisartan(40 mg) is associated with an improvement in cognitive functions, whereas Lisinopril (5 mg) could not provide any potential benefits to cognitive improvements after 12 weeks in metabolic syndrome patients. Swetha ES et al¹³, also concluded that ARBs Losartan and Olmesartan at higher doses, Telmisartan at both lower and higher doses possess significant anti-anxiety property on elevated plus maze test. However other study, found that Pretreatment with a low dose of Olmesartan completely prevented beta-amyloid induced vascular dysregulation and partially attenuated the impairment of hippocampal synaptic plasticity in young Alzheimer's disease model transgenic mice (APP23 mice) with cerebrovascular dysfunction. Telmisartan is also reported to improve memory impairment of mice that had been intracerebroventricularly injected with Amyloid β ¹⁴ Additionally, Telmisartan partially induce PPAR γ activity¹⁵. The PPAR γ activation in the brain suppresses the inflammatory response in neuronal cells¹⁶, endothelial cells¹⁷, astrocytes, microglia¹⁸ and also increases Amyloid- β clearance¹⁹. While, Olmesartan has low affinity towards PPAR γ receptor²⁰.

Conclusion:

Long stayed hypertension is associated with cognitive decline. ARBs are claimed to have positive effect on cognitive performance. In present study, we observed that improvement in memory and psychomotor function tests was more with Telmisartan as compare to Olmesartan.

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