Original Article

Comparative effects of telmisartan and lisinopril on cognitive function in metabolic syndrome patients

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Abstract

Background and Aim: Metabolic syndrome has been reported to increase the risks of dementia. Antihypertensives has been reported to improve cognition. Therefore, in the present study, comparative effects of telmisartan, an angiotensin receptor blocker and lisinopril, an angiotensin-converting enzyme inhibitor, on cognitive function in metabolic syndrome patients were studied.

Methods: A prospective, randomized, parallel, open-label clinical trial was carried out on 62 patients of metabolic syndrome. There were two groups: Group A: Telmisartan (31 patients) and Group B: Lisinopril (31 patients) receiving telmisartan 40 mg and lisinopril 5 mg orally once a day respectively for 12 weeks. Assessment of cognitive function was performed by mini-mental state examination (MMSE) and clock drawing test (CDT) at initial stage and repeated after 6 weeks and 12 weeks of treatment in these patients.

Results: It was observed that telmisartan treatment for 12 weeks leads to statistically significant ($P < 0.05$) increase in MMSE score and decrease in CDT score at 12 weeks when compared with baseline. But lisinopril therapy did not show significant improvement in both MMSE and CDT scores when compared with baseline.

Conclusion: Telmisartan is associated with an improvement in cognitive functions, whereas lisinopril could not provide any potential benefits to cognitive improvements in these subjects.

Key words: Cognitive function, lisinopril, metabolic syndrome, telmisartan

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INTRODUCTION

Metabolic syndrome is a medical condition characterized by a cluster of health-related findings, and its clinical identification and management are important to begin efforts to adequately implement treatments to reduce their risk of subsequent disease.[1] Cognitive function refers to the acquisition, processing, integration, storage and retrieval of information. It is divided into perception, attention, memory and executive function, which include higher order planning and decision-making. These distinctions reflect distinct neuroanatomical circuits that subsume different aspects of memory and cognition more generally. Specific pathologies included in metabolic syndrome induced dementia are deposition of amyloid, acceleration of vascular pathology, accelerated production of neurofibrillary tangles, enhanced inflammatory response, or a combination of all the above.[2] Few studies suggest that antihypertensive drug therapy could reduce cognitive impairments.[3-5] Therefore, in the present study use of antihypertensives such as telmisartan, an angiotensin receptor blocker (ARB) and lisinopril, an angiotensin-converting enzyme (ACE) inhibitor on cognitive protection in patients with metabolic syndrome was studied.

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MATERIALS AND METHODS

The present study was approved by the institutional ethics committee. A prospective, randomized, parallel, open-label clinical trial was carried out on 62 patients of metabolic syndrome from December 2010 to October

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2012. Patients were recruited from medicine out-patient department (OPD) of Indira Gandhi Government Medical College and Hospital Nagpur, Maharashtra.

Inclusion criteria

- Patients satisfying 3 or more of the following National Cholesterol Education Program (NCEP): Third Adult Treatment Panel (ATPIII) 2001 criterion[6]
  a. Central obesity: Waist circumference > 102 cm in males, >88 cm in females
  b. Hypertriglyceridemia: Triglycerides ≥ 150 mg/dL
  c. High-density lipoprotein (HDL) cholesterol: <40 mg/dL in males and <50 mg/dL in females respectively
  d. Hypertension: Blood pressure ≥ 140 mmHg systolic or ≥90 mmHg diastolic
  e. Fasting plasma glucose ≥ 100 mg/dL.
- Nondiabetic hypertensive patients
- Patients between 18 and 60 years of age, of either sex
- Patients able to read, write, calculate and understand the clock
- Patients willing to participate in the study and give informed, written consent.

Exclusion criteria

- Patient with history of angina, congestive heart failure, ischemic heart disease, myocardial infarction or co-morbid heart condition
- Pregnant females (excluded by urine pregnancy test)
- Female patient in reproductive age group, not willing to use any contraceptive method to prevent pregnancy during the trial
- Hypersensitivity or allergy to either of drugs (telmisartan or lisinopril)
- Patient with history of chronic diseases or on medication, wherein interruption in therapy is not recommended
- Chronic smokers or alcoholics
- Patients having liver or kidney disease, abnormal liver or kidney function tests
- Patients with obstructive sleep apnea
- Those patients who did not respond to monotherapy of either of the drugs were excluded from the study.

Newly diagnosed hypertensive patients were selected and screened for other criterias, and those satisfying 3 out of 5 of the above mentioned criteria were selected for the study. Only patients with hypertension and satisfying other criteria of metabolic syndrome, but not requiring medication other than antihypertensives were included in the study. Patients on previous medications were not included in the study. Patients with very high blood sugar level or lipid levels and those in need of concomitant therapy with other drugs were also excluded. Monotherapy was given only till the study period of 12 weeks, thereafter, patients were either continued or managed accordingly to their disease condition by the physician. All the patients meeting the inclusion criteria, were briefed about the trial and those willing to give written consent were enrolled in the study. Patient information sheet was given to all participants, and written informed consent was obtained. The treating physician decided the eligibility of the patients for the treatment before random allocation of these subjects in their respective groups.

Sample size was calculated as 54 (27 in each group) using a level of significance a = 5% and power 80%. The study sample size was rounded to 66 (33 patients in each group) considering future rate of drop outs. Open Epi software Version 2.3 (Open Source Epidemiologic Statistics for Public Health), was used for calculation of sample size and statistician of the institute assisted in the calculations.

Drug administration

Drugs were purchased by the investigator and distributed to the patients free of cost. The study drugs were already marketed as standard antihypertensive drugs. All investigations were done by the investigator, and there was no financial burden on the patients. Drugs were purchased from the market and were of the same company and of the same batch within the expiry date well beyond the due date of completion of the study.

Drug	Dose	Remarks
Telmisartan	40 mg single tablet once daily orally	To be taken every morning
Lisinopril	5 mg single tablet once daily orally	To be taken every morning

Study procedure

Patients attending medicine OPD were screened by a physician. The diagnosis of metabolic syndrome was made on the basis of The 2001 NCEP, ATPIII definition (NCEP: ATPIII 2001) criterion.[6] The patients fulfilling the inclusion criteria were briefed about the nature of the study, its purpose, study procedures and follow-ups.

There were two groups, Group A: Telmisartan (31 patients) and Group B: Lisinopril (31 patients). Block randomization procedure was used for random allocation of subjects to study drugs and to ensure uniform allocation ratio. The randomized treatment allocation sequence was generated by random allocation software.[5] Study subjects received drugs accordingly either telmisartan or lisinopril as per group of allocation.

After initial screening, the data regarding age, sex, past medical history, family history, physical and clinical examination was recorded in the case report form. Other laboratory investigations such as fasting blood sugar, fasting lipid profile (triglyceride, very low density lipoprotein, low

density lipoprotein, HDL and total cholesterol), renal function test (blood urea, serum creatinine, serum sodium and serum potassium), liver function test (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase and serum bilirubin) were carried out for screening the patients in the Department of Biochemistry of the Institute.

Five ml venous blood sample from anticubital vein was withdrawn from each patient by using 5 ml sterile plastic disposable syringe with 21 gauge hypodermic needle undertaking all aseptic precautions. Tourniquet was tied over the mid-arm and was held till the blood sample was collected. Blood samples were then carried to the department of biochemistry for further analysis.

Patients received tablets in a plastic container labeled with information such as initial of the patient, group of the drug study, patient code number, date of next follow-up and instruction regarding administration of the tablet. Assessment of cognitive function was done at initial stage and repeated after 6 weeks and 12 weeks of treatment

Assessment of cognitive function

Mini mental state examination

The Folstein Mini Mental State Examination (MMSE) is a standardized screening examination of cognitive function that is extremely easy to administer and takes <10 min to complete.[7,8] When there is sufficient time available, the MMSE is one of the best methods for documenting the current mental status of the patient, and this is especially useful as a baseline assessment to which future scores of the MMSE can be compared. Individual elements of the mental status examination can be subdivided into level of consciousness, orientation, speech and language, memory, fund of information, insight and judgment, abstract thought, and calculations. The calculation of MMSE score is based upon orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), language and praxis (9 points).

Procedure and evaluation of mini-mental state examination scores

The patients were made comfortable and briefed with procedure and they were given a sheet of paper with the following details namely patients ID number, patients initials, about the date, and series of MMSE questionnaire. The MMSE test score were calculated and recorded based on the performance of the patient.

Clock drawing test

The Clock Drawing Test (CDT) is a simple and rapidly administered test of cognitive function.[9] It has been proposed as a screening test for the early signs of dementia and characterizes deficits in visuospatial abilities and abstract thinking.

Procedure for clock drawing test

- Step 1: Patients were given a sheet of paper with a large predrawn circle on it. Patients ID number, patients initials and date were mentioned at the top of the page.
- Step 2: Patients were then instructed to draw numbers in the circle to make the circle look like the face of a clock and then draw the hands of the clock to read 10 min after 11.

Evaluation of clock drawing test

Scoring was followed by the Watson method. The circle is divided into four equal quadrants by drawing one line through the centre of the circle and the number 12, and a second line perpendicular to and bisecting the first. The clock number in each quadrant is counted in a clockwise direction beginning with number 12. Each clock number is counted only once and if a clock number crosses one of the reference lines it is included in the adjacent quadrant in a clock-wise direction. Three clock numbers in a quadrant were considered correct.

Errors in the first to third quadrants were assigned a score of one and errors in the fourth quadrant were assigned a score of four, for a maximum total score of seven. Normal range of the scores was 0-3, and abnormal range of the scores the was 4-7. The scoring system was developed by evaluating the errors in the positioning of the clock numbers.[9]

Statistical analysis of data

The statistical analysis was performed using Graphpad prism software version 5.00 (California, United States). Comparison between groups was made with one-way analysis of variance followed by Tukeys *Post-hoc* test.

RESULTS

The diagnosis of the metabolic syndrome was carried out on the basis of patients satisfying the criteria listed in NCEP: ATPIII using tools at the bedside and in the laboratory.[6] Initially, 66 patients with metabolic syndrome were recruited for the study, out of which 62 patients completed the study, and 4 patients were lost in follow-up. A total of 62 patients completed this study in two groups, Group A: Telmisartan 40 mg (31 patients) and Group B: Lisinopril 5 mg (31 patients). There was no statistically significant difference in the age, sex and baseline study parameters between the two groups [Table 1].

Table 2 depicts the data of mean scores of cognitive functions (MMSE and CDT). In Group A, there was

statistically significant ($P < 0.05$) improvement (increase in MMSE and decrease in CDT) at 12 weeks when compared with baseline and there was no statistically significant difference between baseline-6 weeks and 6-12 weeks comparison. In Group B, there was no statistically significant difference between baseline-6 weeks, baseline -12 weeks and 6-12 weeks comparison.

Table 3 shows the difference between the means of MMSE and CDT of study groups at baseline, 6 and 12 weeks. It was observed that difference between the means of study groups was not statistically significant in both MMSE and CDT at baseline, 6 and 12 weeks.

DISCUSSION

Previous studies suggest that the renin-angiotensin system (RAS) and antihypertensives play a role in the cognitive, central vascular and endothelial function, in addition to their role in preventing cardiovascular disease, stroke, and hypertension. RAS is also a risk factor for cognitive impairment.[3] The overall data suggests that antihypertensive drug therapy can reduce cognitive impairment, although some studies have shown no significant change in the cognitive function with treatment.[4] Most of the observational and experimental studies, although not universally consistent, have shown that use of antihypertensives may provide cognitive protection in the elderly population.[5] However, its not known whether they provide this effect solely by lowering blood pressure or via an additional class specific effect. Antihypertensives inhibit the activity of RAS and the cognitive risk beyond just lowering the blood pressure. They also further protect cognitive functions by restoring endothelial function and cerebral blood flow regulation.[10]

Table 1: Demographic characteristics of metabolic syndrome patients

Baseline parameters	Group A (*n*=31)	Group B (*n*=31)
Age (years)	47.74±1.134	48.83±1.178
Male/female	14/17	12/19
BMI	32.37±0.2175	32.22±0.1989
SBP in mm Hg	148.90±0.8742	147.80±0.8314
DBP in mm Hg	93.55±0.5055	93.68±0.5172

Values are expressed as mean±SEM. $P<0.05$ was considered significant using unpaired *t*-test. SEM: Standard error of the mean, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index

Table 2: Effect of drugs on cognitive functions at 6 and 12 weeks

Parameters	Baseline	6 weeks	12 weeks
Group A (*n*=31)			
MMSE score	28.45±0.2013	28.90±0.1418	29.09±0.1073*
CDT score	1.71±0.1464	1.51±0.0912	1.25±0.1133*
Group B (*n*=31)			
MMSE score	28.22±0.2110	28.61±0.1715	28.81±0.1497
CDT score	1.80±0.1567	1.45±0.0908	1.41±0.1013

Values are expressed as mean±SEM. Mean differing by *$P<0.05$ was considered significant by using one-way ANOVA test followed by Tukeys *Post-hoc* test. SEM: Standard error of the mean, MMSE: Mini-mental state examination, CDT: Clock drawing test, ANOVA: Analysis of variance

Table 3: Comparison of change in cognitive functions between Group A and B

Parameters	Changes at		
	Baseline	6 weeks	12 weeks
MMSE score	0.2258±0.2916	0.2903±0.2226	0.2903±0.1842
CDT score	−0.0645±0.2145	0.0645±0.1288	−0.1613±0.1520

Values are expressed as means±SEM. $P<0.05$ was considered significant using unpaired *t*-test. SEM: Standard error of mean, MMSE: Mini-mental state examination, CDT: Clock drawing test

We investigated the effect of study drugs in cognitive function. It was observed that telmisartan treatment for 12 weeks leads to statistically significant ($P < 0.05$) increase in MMSE score and decrease in CDT score at 12 weeks when compared with baseline [Table 2]. But lisinopril therapy did not show statistically significant improvement in both MMSE and CDT when compared with baseline. Comparison between telmisartan and lisinopril treatment failed to show any statistically significant effect [Table 3].

Telmisartan is proved as peroxisome proliferator-activated receptor gamma (PPAR γ) partial agonist, and these kind of agonists have been reported to effectively attenuate oxidative stress, inflammation and apoptosis in the central nervous system (CNS).[11] Several studies have documented that PPAR γ activation can also prevent or attenuate neurodegeneration.[12] Potential superior effects of ARBs on cognition may be related to restoring proper central endothelial function, decreasing inflammation, and preventing neuronal degeneration through the selective noninhibition of the AT2 angiotensin receptors in the brain.[13] Therefore, telmisartan may be effective in cognitive function. Furthermore, studies have observed that ARBs decreased the infiltration of CNS and peripheral organs by inflammatory cells. However, some conflicting results have also been reported. In accordance with their inhibitory effect on inflammation in the brain, beneficial effects of PPAR γ agonists or AT1 inhibition have been observed in a number of processes mediated by microglial activation and neuroinflammation, including animal models of Alzheimer's disease, brain ischemia, multiple sclerosis, traumatic brain injury and aging.[14]

There is conflicting evidence regarding the potential benefits of ACE inhibitors on cognitive protection, used either in the treatment of heart failure, or other chronic health conditions such as diabetes, stroke, parkinson's

disease and alzheimer's disease.[15,16] The results from our study confirm the same evidence that lisinopril may not have any potential benefit on cognitive protection. However, in the treatment with ARBs or ACE inhibitors, the probability of improving cognitive performance might be higher for higher dosages and may increase with duration of the treatment.

Limitations of the study

As metabolic syndrome is constellation of common diseases which are very common in our set up, sample size of 62 patients may not generate a proper conclusive data. Multicentric studies with longer duration and larger sample size will provide more appropriate information.

CONCLUSION

The present study contributes to growing evidences that telmisartan therapy is associated with improvement in cognitive function, and supports the evidence that ARBs may provide potential benefits in general by delaying the onset or progression of various forms of cognitive decline or dementia.

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