Effect of antihypertensive therapy on some cognitive functions of patients of hypertension.

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Abstract

Aim- Hypertension associated with the decline in cognitive functions. There are certain studies which revealed that antihypertensive therapy improves the cognitive functions in patients of hypertension. Some other studies do not support this conclusion. So this study was done to see the effect of antihypertensive therapy on cognitive functions in patients of hypertension in our setting.Material and methods: Cases of hypertensions were recruited from the OPD of private physician. Baseline cognitive function tests were administered before starting the antihypertensive therapy and after three months of treatment. To see the effect of hypertension on cognitive functions baseline cognitive functions of cases were compared with healthy volunteers.Results: During comparison of cases and controls, it was found that there is decline in cognitive functions as indicated by Immediate recall test, Mental balance test, Forward digit span test, Word list memory test, Recognition test and Six letter cancellation test. Out of these tests, Immediate recall test, Word list memory test, Recognition and Six letter cancellation test showed improvement after three months of antihypertensive therapy. Some tests like Remote memory test, Recent memory test, Backward digit span test, Paired associate test, Ray's figure test, Line test, Delayed recall test showed no decline. Out of these, only Delayed recall test showed improvement after three months of antihypertensive therapy.Conclusion: hypertension associated with the decline in cognitive functions and antihypertensive therapy improves the cognitive functions in these patients.

INTRODUCTION

Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with age. Elevated arterial pressure is associated with progressive pathological changes which leads to various cardiovascular and central nervous system related complications like stroke, [1] vascular dementia [2] and probably Alzheimer's disease. [3] Uncontrolled hypertension may lead to the cognitive decline. [4] Hypertension brings certain pathophysiological changes in brain like vascular remodeling, impaired cerebral auto regulation, small lacunar infarct, white matter lesion, microbleed and amyloid angiopathy etc which may result into deterioration of the cognitive functions. [5]

Many studies revealed that control of hypertension with antihypertensive therapy controls the cognitive decline associated with hypertension. [6] Nevertheless, there are reports which suggest that antihypertensive drugs do not provide protection from cognitive decline. [7]

The present study is designed to evaluate cognitive status of patients recently diagnosed as hypertensive and compare it with suitable controls to see the effect of antihypertensive treatment on cognitive functions of patients of hypertension.

MATERIALS AND METHOD

Study Design: Case Control study.

Study period: Three months, May 2008 to July 2008.

SELECTION OF CASES AND CONTROLS:

Cases: Patients who were recently diagnosed as hypertensive and were prescribed antihypertensive therapy by their treating physician.

INCLUSION CRITERIA

Patients recently diagnosed as hypertensive: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Age: Between 20-60 years.

Sex: Both males as well as females.

Literacy level: Ability to understand, read, write and communicate in Gujarati with primary knowledge of English.

EXCLUSION CRITERIA:

Patients with pre hypertension (SBP 120-139 mmHg and DBP 80- 89).

Age less than 20 and more than 60.

Patients having psychological and behavioral disorders or any other CNS disorder that could interfere with the memory and psychomotor functions.

Patients on any other medications (e.g sedatives, antipsychotics, antidepressants, antihistaminic) that are known to affect memory and psychomotor functions.

CONTROLS: PERSONS WHO MET WITH THE FOLLOWING CRITERIA:
INCLUSION CRITERIA:

Blood pressure within normal and pre hypertension range.

Sex- Both males as well as females.

Age- Between 20 to 60 years.

Literacy level- Ability to understand, read, write and communicate in Gujarati with primary knowledge of English.

EXCLUSION CRITERIA:

Persons diagnosed as Hypertensive (SBP≥ 140 mmHg, DBP≥ 90 mmHg).

Persons with psychological and behavioral disorders or any other CNS disorder that could interfere with the memory and psychomotor functions.

Patients on any other medications (e.g. sedatives, antipsychotics, antidepressants, antihistaminic) that are known to affect memory and psychomotor functions.

Study tool: Predesigned pretested questionnaire was used to collect the information. The PGI memory scale (PGIMS) [10, 11] was employed to assess memory function of patients.

Methodology: Between May to July 2005, the investigator visited the OPD of private physician, each day in the morning from 9:00 A.M to 1:00 P.M for screening the patients. Those who met with the inclusion and exclusion

criteria were enrolled in the study group. The aim and procedure of the study and the tests were explained to the subjects. Written informed consent was obtained from the patient. 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 PGI memory scale after 3 months. Control group subjects were recruited from the faculty and staff of Govt. medical college, Surat. They were evaluated only once i.e. on the day of recruitment. Before applying tests for cognitive functions, the systolic and diastolic blood pressure was recorded by auscultatory method in study group at both the occasions, i.e. during recruitment and then subsequent assessment after 3 months. In control group blood pressure measured at the time of recruitment.

All the cognitive functions tests were conducted in Gujarati language. They were conducted in particular sequence and this sequence was maintained for every subject.

TESTS
TESTS FOR MEMORY:

The PGI memory scale (PGIMS) [8,9] was employed to assess memory function of patients. PGI memory scale consists of ten sub- tests. These tests measure different aspects of memory and employ different methods of recall. These tests are –

Remote memory: It comprises of six simple questions relating to the past events of personal life.

Recent memory: It consists of five questions that assess the patient's ability to recall information and events in the recent past.

Immediate recall: This test includes sequential reproduction of the sentences in verbatim.

Mental balance: This test gives an idea of balance over ones mental functioning. The learned material (alphabet and numbers) were recalled in backward and forward series.

Attention and concentration: This function was evaluated by the test of digit span forward and backward repetition.

Word list memory test: In this test the investigator reads out the names of common objects (two series of five each) at a uniform interval. The patient was instructed to recall the same after one minute and score of correct recall recorded.

Paired associate test: A series of similar and dissimilar

associative pairs of words were administered to the patient. Patient was asked to mention the associate words in response to the stimulus word.

Rays figure test: This is non-verbal visuomotor test for memory. Subjects are supposed to draw a geometrical figure which was shown to them for 30 seconds.

Recognition: In this test the investigator showed a card containing common objects. The patient was allowed to observe this card for 30 seconds. Two minutes later a second card containing another set of pictures having some picture appeared in first card shown to the patient. Patient was asked to identify and name the picture that appeared in both the cards. Correct responses were recorded and scores allotted accordingly.

SIX LETTER CANCELLATION TEST (SLCT)

It is a psychomotor function test in which perceptual processing of sensory information can be readily assessed. It is a pencil and paper test, easy to replicate. It is a useful indicator of drug induced changes. The worksheet for this test was prepared in Gujarati, English or Hindi. The worksheet of this test consists of three parts: First part consists of Name, age, sex of a patient with date and instructions. Second part includes the key that mentioned six target letters, while the third part is having working section. The working section displays randomized alphabets arranged in 22 rows and 14 columns. Within 90 seconds, patient asked to cancel as many as many target alphabets as possible. The letter cancellation was undertaken in a horizontal, vertical or randomized manner. Total number of cancellations and wrong cancellations were scored. To avoid the effect of memory, parallel worksheets were prepared by changing the 6 letter key.

LINE TEST:

This test comprise of judgment of length of line and drawing the line of same length.

12. Delayed recall test:

Subjects were asked to recall the three sentences of earlier immediate recall test. So it is the extension of immediate recall test.

Statistical analysis: Data obtained in the various tests was analyzed using SPSS version 12. Analysis of distribution of data was done using Komolgorov smirnov test and Shapiro wills test. Unpaired student t test was used to compare blood pressure and cognitive function between case and control.

Paired t test used to compare blood pressure and cognitive functions at baseline and after 3 months.

Results: To see the effect of hypertension on cognitive functions, the cognitive functions are compared between hypertensive patients (study group) and healthy volunteers (control group). A total of 50 subjects were enrolled in each group.

Figure 1

Table 1. Baseline characteristics of case and control

	Cases N=50	Controls N=50
Age (years)	51.02± 7.7	46.0± 7.1
SBP(mmHg)	149.1±6.73	123.05±6.2
DBP(mmHg)	98.71±3.7	78±4.4

(All data are expressed in mean±SD)

Mean systolic blood pressure in cases was 149±6.73 and in controls was 123.05±6.18. There is significant difference between systolic blood pressure between study population and control population (P<0.001).

Mean diastolic blood pressure was also found to be statistically significant. (P<0.001).

It was observed that all the cases were prescribed Atenolol in the dose of 25-50 mg per day. Some of the patients were prescribed other antihypertensives like Amlodipine (n=5), Chlorthalidone (n=7) and antiplatelets like low dose aspirin (n=14) or Clopidogrel (n-6).

Figure 2

Table 2- Comparative test score showing cognitive fuctions between cases and controls:

Test	Cases group score	Controls group score
Remote memory	5.82 ± 0.44	5.81 ± 0.44
Recent memory	5.00 ± 0.00	4.95 ± 0.20
Immediate recall	8.80 ± 1.28	9.77 ± 1.50***
Mental balance	6.13 ± 0.96	6.63 ± 1.12*
Forward digit span	4.77 ± 0.79	5.15 ± 0.96*
Backward digit span	3.28 ± 0.66	3.43 ± 0.69
Word list memory	4.88 ± 0.95	5.63 ± 0.83***
Paired associate test	3.13 ± 0.99	3.47 ± 1.32
Ray's figure test	5.82 ± 2.08	6.31 ± 1.73
Recognition	10.73 ± 1.07	11.34 ± 0.88**
Six letter cancellation test	14.11 ± 3.9	17.31 ± 3.48***
Line test	8.48 ± 0.75	8.34 ± 0.91
Delayed recall test	3.48 ± 1.16	3.84 ± 1.41

(All data are expressed in mean±SD)

* P value < 0.05   ** P value < 0.01   *** P value < 0.001

UNPAIRED T TEST

Result shows that score of some subtests of cognitive functions in study group are significantly less than the control group. In the immediate recall test mean score in study group is 8.80 ± 1.28 while in control group it is 9.77 ± 1.50 which is significantly higher than study group (P<0.001). In the same way in mental balance test there is significant difference between study and control group score (6.13± 0.96 Vs 6.63 ± 1.12, P < 0.05). Score of forward digit span in study group is 4.77 ± 0.79 and in control it is 5.15 ± 0.96 which is also significantly differ (P<0.05). Significant change also seen in word list memory test (4.88 ± 0.95 Vs 5.63 ± 0.83, P < 0.001), Recognition test (10.73 ± 1.07 Vs 11.34 ± 0.88, P < 0.01) and six letter cancellation test (14.11 ± 3.9 Vs 17.31 ± 3.48, P < 0.001).

Results clearly indicate that hypertension may be responsible for the cognitive decline in patients of hypertension.

Effect of antihypertensive therapy on cognitive functions of hypertensive patients:

Baseline memory tests and blood pressure of cases was measured twice. Firstly, at the beginning of treatment, at day one and second at the end of three months. Adherence assured by checking the empty blister packet and checking the unused medicines. 5 subjects are lost to follow up during the study. It is seen that there was significant decrease in both systolic (149.11± 6.73 Vs 132.97 ± 7.77, P < 0.001) and diastolic (98.71 ± 71 Vs 84.62 ± 4.62, P < 0.001) blood pressure after three months of follow up.

After 3 months of therapy of antihypertensives there is significant improvement in some subtests of cognitive functions.

The score of immediate recall test at baseline is 8.80 ± 1.28 and after 3 months it became 9.42 ± 1.28. This is the significant improvement in immediate recall (P<0.001). Improvement also seen in the recognition test (initial score =10.73 ± 1.07 and subsequent score =11.42 ± 0.72, P<0.001), Six letter cancellation test (14.11 ± 3.9 Vs 16.77 ± 3.57, P<0.01) and delayed recall test (3.48 ± 1.16 Vs 4.06 ± 1.13, P < 0.001).

Improvement also seen in word list memory test where baseline score is 4.88 ± 0.95 and after 3 months it became 5.17 ± 0.77 which is also significant (P<0.05).

Figure 3

Table 3- Cognitive function test scores of cases at the start of therapy and after the follow up of three months.

Test	Study group initial score (n-50)	Study group score after 3 months (n-45)
Remote memory	5.82 ± 0.44	5.75 ± 0.48
Recent memory	5.00 ± 0.00	4.97 ± 0.14
Immediate recall	8.80 ± 1.28	9.42 ± 1.28***
Mental balance	6.13 ± 0.96	6.28 ± 0.96
Forward digit span	4.77 ± 0.79	4.88 ± 0.48
Backward digit span	3.28 ± 0.66	3.31 ± 0.55
Word list memory	4.88 ± 0.95	5.17 ± 0.77*
Paired associate test	3.13 ± 0.99	3.13 ± 0.97
Ray's figure test	5.82 ± 2.08	6.13 ± 1.7
Recognition	10.73 ± 1.07	11.42 ± 0.72***
Six letter cancellation test	14.11 ± 3.9	16.77 ± 3.57***
Line test	8.48 ± 0.75	8.44 ± 0.69
Delayed recall test	3.48 ± 1.16	4.06 ± 1.13***

(All data are expressed in mean±SD)

* P value < 0.05   ** P value < 0.01   *** P value < 0.001

PAIRED T TEST

During comparison of cases and controls, it was found that

there is decline in cognitive functions as indicated by Immediate recall test, Mental balance test, Forward digit span test, Word list memory test, Recognition test and Six letter cancellation test. Out of these tests, Immediate recall test, Word list memory test, Recognition and Six letter cancellation test showed improvement after three months of antihypertensive therapy.

Some tests like Remote memory test, Recent memory test, Backward digit span test, Paired associate test, Ray's figure test, Line test, Delayed recall test showed no decline. Out of these, only Delayed recall test showed improvement after three months of antihypertensive therapy.

DISCUSSION:

In this study the baseline cognitive functions of patients who were recently diagnosed with hypertension was found declined as compared to control.

It is seen that mean scores of six subtests of cognitive functions were less as compared to control. This decline may be because of pathological effect of hypertension or anxiety and apprehension produced by recent diagnosis of hypertension. The relationship between diagnosis of hypertension and cognitive functions were explored in other studies [11]. There are other studies which shows that poor cognitive functions are because of pathological changes of hypertension. [4, 5]

After three months of antihypertensive therapy scores of five sub test were found to be increased. Among these five subtests, four were those which found declined at the baseline. This suggests that antihypertensive therapy for three months improve the score of those cognitive function tests in which hypertensive patients perform poorly during recruitment in comparison to the subject of control group. There was no deterioration of any test after three months of antihypertensive therapy.

All the subjects of study group received atenolol as one of the drug. So it may be postulated that the effect produced on the score of cognitive function tests are attributed to atenolol but there is no direct proof.

Atenolol is a beta-1 selective antagonist. It is very hydrophilic and appear to penetrate the brain only to limited extend. [12] Despite hydrophilic nature CNS effects of atenolol have been documented

TV Rogers and CE Bowman (1990) reported the case a case series patients presenting with insidious mental impairment

whilst receiving atenolol. In each case marked improvement occurred on drug withdrawal. But in present study we have not observed any deleterious effect of antihypertensive therapy (atenolol for three months) on the score of any of the cognitive function test. [13]

In a study done by Madden DJ et al, (1986) atenolol and propranolol were given to the patients of essential hypertension for two weeks. Although beta blocked occur in the patients but there was no effect on cognitive functions. Fletcher AE (1992) also concluded in their review that atenolol do not have any major effect on cognitive function of hypertensive patients.

In the present study, it was observed that that blood pressure was controlled within three months of antihypertensive treatment and no any deterioration in cognitive functions was observed. So it will not wrong to conclude that antihypertensive therapy (atenolol) preserve the cognitive decline likely to associated with hypertension.

The finding of this study does not correlate with study of Bellew et al. (2004). They observed that patients younger than 65 year with hypertension were more likely to have increased cognitive decline as compared to nonhypertensive control. But the treatment with antihypertensive did not appear to provide protection from cognitive decline. [14]

In present study, other antihypertensives (amlodipine, chlorthalidone) were also prescribed but because of few numbers of such patients, analysis of possible effect of these additional drugs on cognition was not possible. There are certain studies which shows that antihypertensive therapy and particularly calcium channel blockers improves the cognitive functions in patients of hypertension. [15]

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