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Antihypertensive therapy is associated with improved visuospatial, executive, attention, abstraction, memory, and recall scores on the montreal cognitive assessment in geriatric hypertensive patients☆

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ABSTRACT

Background: The prevalence of Mild Cognitive Impairment (MCI) has increased over the past few decades. However, it can potentially be reversed if detected early. Early detection of MCI using the sensitive Montreal Cognitive Assessment (MoCA) might prove to be an important cog in the wheel in identifying and slowing down this morbid pandemic in hypertensive persons.

Objectives: To study the association of antihypertensive agents on cognitive scores and prevalence of MCI using the MoCA.

Materials and methods: This is a single-center, controlled, observational, cross-sectional study in a tertiary care teaching hospital in India. Cognitive assessment was done using the Montreal Cognitive Assessment. Data on MoCA scores were comprehensively analyzed.

Results: A total of $N = 210$ patients ($n = 105$ the in study and control groups) were included in the study. The median (IQR) MoCA score (out of 30 points) in patients taking antihypertensives was 26 (25 – 27), while it was 24 (22 – 25) in the control group. There was no difference in MoCA scores between patients taking lipophilic or hydrophilic antihypertensives. Similarly, there was no difference in MoCA scores between patients taking different drug regimens.

Conclusion: Anti-hypertensive therapy and lower blood pressure had a statistically significant positive association with visuospatial, executive, attention, abstraction, memory, and recall MoCA scores. Patients on antihypertensive therapy also had a lower prevalence of MCI. MoCA scores were similar in patients on either lipophilic or hydrophilic drugs and were similar between patients on different antihypertensive drug classes.

1. Introduction

Mild cognitive impairment (MCI) is a state of cognitive function that lies intermediate between the changes occurring in physiological aging and changes fulfilling the criteria for dementia. [1,2] There is no universal agreement on what exactly constitutes MCI, but one commonly used measure to identify it is the Montreal Cognitive Assessment (MoCA) score range between 18 and 25. Over the past few decades, the prevalence of MCI has increased due to an increase in life expectancy. [3] MCI is rapidly and worrisomely achieving the status of becoming a global non-communicable disease of major concern in both developing and developed countries, alongside diabetes mellitus and hypertension. [4] However, MCI is a disease whose progression can potentially be decelerated if detected early, before transitioning to dementia. Medication optimization and lifestyle modifications are treatments that are easy to follow and may give good results. [5] These interventions have the potential to drastically improve the quality of life and reduce the burden on society from this morbid condition. [6]

Assessing cognitive function objectively can be achieved using test-based scoring systems easily in the clinic. One of the most commonly used systems to detect cognitive impairment is the mini-mental status examination (MMSE). However, the MoCA has been developed as a brief and more sensitive test to detect MCI in the Western as well as the Indian context. [7,8] It is more sensitive than the MMSE to detect MCI

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(sensitivity of 90% for MoCA versus 18% for MMSE). [9] This is of significant importance because, with appropriate management, early detection of MCI may substantially improve patients' quality of life.

Hypertension, one of the most prevalent co-morbidities in the aging population, mainly affects people aged between 30 and 79 years; alarmingly, this prevalence has doubled from 1990 to 2019. [10] Nearly one-fifth of hypertensive patients have MCI – a significantly higher proportion than normotensives. [11] There is abundant evidence of the association between hypertension and MCI; however, there is a paucity of data on MoCA scores in different cognitive domains and the role of antihypertensive agents. With this background, the primary aim of our study was to establish the association between commonly prescribed antihypertensive drugs and MoCA scores. Secondary objectives included testing for MoCA scores in patients on either lipophilic or hydrophilic drugs and between different antihypertensive drug classes. This evidence will help clinicians take informed decisions on starting antihypertensive medications in geriatric patients to reduce and potentially stall the rapidly rising prevalence of MCI.

2. Materials and methods

2.1. Study design

This was a single-center, observational, controlled, cross-sectional study conducted in the Department of General Medicine in a tertiary care teaching hospital in Western India.

2.2. Study subjects

We recruited $n = 105$ patients in each of the study (patients taking antihypertensives) as well as control groups (total $N = 210$). In the study group we included patients who were between 60 and 80 years of age. Both men and women were recruited in inpatient and outpatient settings. These individuals had essential hypertension without clinical or laboratory evidence of secondary causes of hypertension. The patients were compliant with antihypertensive therapy for ≥ 2 years as assessed by self-reporting method. We excluded patients who could not see, hear, speak, communicate or were not fit to undergo MoCA test in any manner. Also excluded were patients on drugs with a potential to cause cognitive impairment (including anti-epileptics, anti-psychotics, benzodiazepines, anti-cholinergics, anti-depressants, anti-parkinsonian drugs, etc.) . Patients with known cases of psychiatric or other neurologic disorders, patients with a past history of stroke or head injury, patients in critical care, and patients who did not provide consent were also excluded. Subjects in the control group who had the diagnosis of essential hypertension but had not started or were noncompliant with anti-hypertensives were enrolled. Written informed consent was taken from all subjects. Institutional ethical committee clearance was obtained. The study period was from May 2022 to October 2022.

2.3. Data collection

Details of the patients regarding demographics, risk factors, education, blood pressure, and antihypertensive therapy were entered on a case sheet. All anti-hypertensive drugs were classified according to the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Their defined daily doses (DDDs) were calculated to make comparisons uniform and were classified as lipophilic or hydrophilic. [12]

2.4. Montreal cognitive assessment

After giving instructions, the Montreal Cognitive Assessment pen-and-paper-based test was then administered to the subject in the language of their choice. Total as well as domain-specific scores were noted. Cognitive domains assessed by MoCA include the visuospatial/executive, naming, orientation, memory & recall, language, abstraction, and attention domains. The maximum achievable score for the MoCA is 30 points. Subjects with ≤ 12 years of education were awarded an additional point to correct for educational differences. [13] Grading of the severity of cognitive impairment was done according to cut-off scores for the MoCA: scores ranging between 18 and 25 points were classified as mild cognitive impairment, scores between 10 and 17 points were classified as moderate cognitive impairment, and scores less than 10 points were classified as severe cognitive impairment. [13] Before starting the study, official training offered on the Montreal Cognitive Assessment website was acquired. Collected data were entered into an MS Excel sheet.

2.5. Statistical analysis

The data on categorical variables are shown as n (% of cases) and the data on continuous variables are presented as Median and Interquartile Range (IQR). The inter-group statistical testing for continuous variables is done using the Mann-Whitney U test (for 2 groups) and the Kruskal-Wallis H-test (for >2 groups). Multiple linear regression is performed adjusting for potentially confounding variables. Inter-group statistical testing for categorical variables is done using the chi-square test. Bivariate correlation analyses are done using Spearman's correlation. Underlying assumptions of normality (Shapiro-Wilk and Q-Q plots) and equality of variances (Levene) were tested. All the results are shown in tabular as well as graphical format to visualize statistically significant differences more clearly.

We calculated the estimated power achieved using Shieh et al.'s approach with sample sizes of $n = 105$ in each group (total $N = 210$) with a two-tailed α error of 5% and a probability ($P = 0.65$) that the MoCA score in the study group taking antihypertensive agents (study) was higher than those who were not (controls) for performing a two-sided Wilcoxon-Mann-Whitney test for two unpaired groups with normal parent distributions. [14] The achieved power was 97.1%.

P-values less than 0.05 are considered to be statistically significant. P-values have been corrected for multiplicity with the Bonferroni correction. Point estimates and effect sizes with their margins of error are provided along with P-values. For the Mann-Whitney test, the rank-biserial correlation is used as the estimate for effect size, the epsilon-squared statistic is used for the Kruskal-Wallis test, and rho is used for Spearman's correlation. The rank-biserial correlation value ranges from -1 to $+1$, with the null value lying at 1; values closer to -1 or $+1$ or values further away from 0 indicate a stronger effect size. The epsilon-squared statistic ranges from 0 to 1, with 0 to 0.01 indicating a negligible effect, 0.01 to 0.04 indicating a weak effect, 0.04 to 0.16 indicating a moderate effect, 0.16 to 0.36 indicating a relatively strong effect, 0.36 to 0.64 indicating a strong effect, and 0.64 to 1 indicating a very strong effect. The value of rho ranges from -1 to $+1$; values closer to -1 or $+1$ and further away from 0 indicate a strong effect. We used a multiple regression model to establish association of MoCA scores between the two groups after adjusting for age, sex, years of education, and duration of hypertension. All the hypotheses were formulated using two-tailed alternatives against each null hypothesis (hypothesis of no difference). Sample size calculation and statistical data analysis are done using SAS software, version 9.4 (SAS Institute), and R software, version 4.2.2 (R Project for Statistical Computing).

3. Results

From May 2022 through October 2022, we recruited $n = 105$ subjects in the study group and $n = 105$ controls using a random sampling method. Two hundred and eight patients requested the Marathi MoCA, and two patients requested the assessment in Hindi. Other characteristics of patients recruited in our study are shown in Tables 1 and 2.

Table 1
Patient demographic parameters.

Variable	Overall ($N = 210$)	Cases ($n = 105$)	Controls ($n = 105$)	p-value
Median age (IQR) – years	67 (63–72)	67 (63–71)	67 (63–72)	.721[*]
Gender: n (%)				.677[†]
Male	118 (56.2%)	61 (58.1%)	57 (54.3%)	
Female	92 (43.8%)	44 (41.9%)	48 (45.7%)	
Admission status:				.002[†]
Outpatients	110 (52.4%)	44 (41.9%)	66 (62.9%)	
Inpatients	100 (47.6%)	61 (58.1%)	39 (37.1%)	
Median education level (IQR) – years	6 (1–10)	6 (1–11)	6 (2–10)	.771[*]
Median BMI (IQR) – kg/m^2	23.1 (21.5–24.5)	23.4 (22–24.5)	22.6 (21.4–25)	.246[*]
Addiction: n (%)	72 (34.3%)	35 (33.3%)	37 (35.2%)	.504[†]
Alcohol	30 (14.3%)	16 (15.2%)	14 (13.3%)	
Smoking tobacco	29 (13.8%)	14 (13.3%)	15 (14.3%)	
Chewing tobacco	15 (7.1%)	7 (6.7%)	8 (7.6%)	
Median duration of addiction (IQR) – years[‡]	23.5 (15–34)	30 (20–40)	20 (15–25)	.023[*]

[*] Mann-Whitney U test.
[†] chi-square test of independence.
[‡] blood pressure taken on the day of assessment

IQR – interquartile range, AHA – American Heart Association, DM – diabetes mellitus, IHD – ischemic heart disease, COPD – chronic obstructive pulmonary disease.

Table 2
Current hypertensive and co-morbidity status.

Variable	Overall ($N = 210$)	Cases ($n = 105$)	Controls ($n = 105$)	p-value
Median duration of hypertension (IQR) – years	3 (1–7)	6.5 (4–12)	1 (0.25–2)	<0.001[*]
Median systolic blood pressure[‡] (IQR) – years	128 (118–138)	118 (114–126)	136 (132–144)	<0.001[*]
Median diastolic blood pressure[‡] (IQR) – years	78 (72–84)	72 (68–78)	84 (78–88)	<0.001[*]
Hypertension class[‡] (AHA): n (%)				<0.001[†]
Normal	55 (26.2%)	54 (51.4%)	1 (1%)	
Elevated	50 (23.8%)	29 (27.6%)	21 (20%)	
Stage I	61 (29%)	15 (14.3%)	46 (43.8%)	
Stage II	44 (21%)	7 (6.7%)	37 (35.2%)	
Co-morbidities: n (%)				.815[†]
DM	56 (26.7%)	36 (34.3%)	20 (19%)	
IHD	27 (12.9%)	15 (14.3%)	12 (11.4%)	
COPD	7 (3.3%)	3 (2.9%)	4 (3.8%)	
Asthma	3 (1.4%)	2 (1.9%)	1 (1%)	
Thyroid disorders	5 (2.4%)	3 (2.9%)	2 (1.9%)	

[*] Mann-Whitney U test.
[†] chi-square test of independence.
[‡] blood pressure taken on the day of assessment

IQR – interquartile range, AHA – American Heart Association, DM – diabetes mellitus, IHD – ischemic heart disease, COPD – chronic obstructive pulmonary disease.

Table 3
Antihypertensive therapy details.

Variable	Value
Median number of anti-hypertensive drugs per patient (IQR)	1 (1–2)
Median duration of anti-hypertensive drug therapy (IQR) – years	6 (4–10)
Median latent period between onset of hypertension and starting anti-hypertensive therapy (range) – years	0 (0–9)
Median number of lipophilic anti-hypertensive drugs per patient[*] (IQR)	1 (1–2)
Median number of hydrophilic anti-hypertensive drugs per patient[†] (IQR)	1 (1–1)
Antihypertensive drug therapy regimens: n (%)	
ARB	4 (3.8%)
ARB+BB	7 (6.7%)
ARB+CCB	13 (12.4%)
ARB+CCB+BB	1 (1%)
ARB+Diuretic	3 (2.9%)
ACEI	7 (6.7%)
ACEI+BB	5 (4.8%)
CCB	31 (29.5%)
CCB+BB	4 (3.8%)
CCB+Diuretic	1 (1%)
BB	25 (23.8%)
Diuretic	3 (2.9%)
Sympatholytic (alpha-2 agonist)	1 (1%)

[*] Out of a total $n = 114$ lipophilic anti-hypertensive drugs prescribed to $n = 86$ (81.9%) patients.
[†] Out of a total $n = 26$ hydrophilic anti-hypertensive drugs prescribed to $n = 26$ (24.8%) patients

IQR – interquartile range, CCB – calcium channel blocker, BB – beta blocker, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, mg - milligram.

Table 4
Details on lipophilic and hydrophilic antihypertensives in our study.

Variable	Value
Lipophilic anti-hypertensive drugs (DDD, ATC code)[*]: n (%)	
CCBs – Amlodipine (5 mg, C08CA01)	35 (31%)
Cilnidipine (10 mg, C08CA14)	10 (8.8%)
BBs – Metoprolol (150 mg, C07AB02)	26 (23%)
Carvedilol (37.5 mg, C07AG02)	4 (3.5%)
Nebivolol (5 mg, C07AB12)	1 (0.9%)
ACEIs – Ramipril (2.5 mg, C09AA05)	9 (8%)
ARBs – Telmisartan (40 mg, C09CA07)	27 (23.9%)
Valsartan (80 mg, C09CA03)	1 (0.9%)
Centrally acting alpha-2 agonists – Clonidine (0.45 mg, C02AC01)	1 (0.9%)
Hydrophilic anti-hypertensive drugs (DDD, ATC code)[†]: n (%)	
CCBs – Nifedipine (30 mg, C08CA05)	5 (4.8%)
BBs – Atenolol (75 mg, C07AB03)	11 (10.5%)
ACEIs – Enalapril (10 mg, C09AA02)	2 (1.9%)
Captopril (50 mg, C09AA01)	1 (1%)
Diuretics – Hydrochlorothiazide (25 mg, C03AA03)	5 (4.8%)
Chlorthalidone (25 mg, C03BA04)	2 (1.9%)

[*] Out of a total $n = 114$ lipophilic anti-hypertensive drugs prescribed to $n = 86$ (81.9%) patients.
[†] Out of a total $n = 26$ hydrophilic anti-hypertensive drugs prescribed to $n = 26$ (24.8%) patients

IQR – interquartile range, CCB – calcium channel blocker, BB – beta blocker, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, DDD – defined daily dose, ATC – anatomical therapeutic chemical classification, mg - milligram.

3.1. Antihypertensive therapeutic modalities

Details about the anti-hypertensive therapeutic regimens as well as drug classification and defined daily doses according to the WHO ATC/DDD index are provided in Tables 3 and 4.

The median defined daily doses of ACEIs, ARBs, diuretics, CCBs, and BBs were 2, 1, 0.5, 1, and 0.3 respectively. The median dosage frequency of each of these drug classes was once per day.

3.2. Comparison of MOCA scores between the two groups

Mann-Whitney U-tests were used to test the hypotheses that patients taking antihypertensive drug therapy result in a change in cognitive function. Total MoCA scores were superior in patients who took anti-hypertensives ($p < 0.001$). Further, on analyzing each cognitive domain, superior cognitive scores were found in the visuospatial/executive ($p < .001$), attention ($p = .008$), abstraction ($p < .001$), and memory & recall ($p = .009$) cognitive scores; however, there were no significant changes in the naming, language, and orientation scores. (Table 5, Fig. 1)

3.3. Cognitive impairment between the groups

A total of $n = 42$ (40%) patients suffered from cognitive impairment in the study group; $n = 40$ (38.1%) had mild impairment, $n = 1$ (1%) had moderate impairment, and $n = 1$ (1%) had severe impairment. In comparison, $n = 85$ (81%) patients had cognitive impairment in the control group; $n = 80$ (76.2%) had mild impairment, $n = 3$ (2.9%) had moderate impairment, and $n = 2$ (1.9%) had severe impairment. (Fig. 2)

A chi-squared test of independence was performed to evaluate the difference in the proportion of cognitive impairment in the study and control groups. Patients in the control group were more likely to develop cognitive impairment: χ^2 (1, $N = 210$) = 35.142, RR – 3.15, 95% CI – 2.1 to 4.85.

3.4. Association of lipophilic versus hydrophilic drugs on MOCA scores

Mann-Whitney U-tests were performed to assess the association of lipophilic and hydrophilic antihypertensive agents on cognitive function as assessed by MoCA. There was no statistically significant difference (all p-values >0.05 after correcting for multiplicity) between total as well as domain-specific MoCA scores between the two groups. (Table 6)

3.5. Difference in MOCA scores after adjusting for potential confounders

We used a multiple regression approach to establish association of MoCA scores with antihypertensive therapy. (Table 7) The effect of Group (Cases) is statistically significant and positive: beta = 1.46, 95% CI [0.30 to 2.62], t(204) = 2.48, $p = 0.014$. Patients who were treated with antihypertensive drugs had superior overall MoCA scores than untreated patients by 1.5 points (difference in estimated marginal means) after adjusting for age, sex, years of education, and duration of hypertension. This model explains 10% of the outcome variance (R2 = 0.10, F(5, 204) = 4.49, $p < .001$).

3.6. Association of antihypertensive drug classes on MOCA scores

A Kruskal-Wallis H-test was performed to assess the association of various antihypertensive drug therapy regimens (as described in Table 1) on cognitive function as assessed by MoCA. There was no statistically significant difference in the total MoCA score with different drug regimens: H (9) = 10.89, $\varepsilon^2 = 0.11$, 95% CI: −0.12 to 0.14, $p = .283$. Similarly, there exist no statistically significant differences in the visuospatial/executive domain ($p = .404$), naming domain ($p = .829$), attention domain ($p = .45$), language domain ($p = .395$), abstraction domain ($p = .412$), memory & recall domain ($p = .20$), or the orientation domains ($p = .494$). (Fig. 3)

4. Discussion

This study was an observational, single-center, cross-sectional, controlled study involving patients clinically diagnosed with essential hypertension sampled from the outpatient as well as inpatient departments of general medicine in a tertiary care teaching hospital in suburban India. The aim of this study was to assess cognitive impairment in geriatric hypertensive patients who were taking various antihypertensive drug regimens using the Montreal Cognitive Assessment. Patients who were treated with anti-hypertensive therapy for more than two years scored significantly better in the MoCA than patients who were hypertensive but had not yet started taking anti-hypertensive drugs. Even after adjusting for potential confounders, the result remained statistically significant. The proportion of patients who had mild cognitive impairment was also lower in the subjects who were receiving treatment for hypertension. In addition to having better overall MoCA scores, patients on antihypertensive therapy had superior visuospatial, executive, abstraction, attention, and memory & recall scores. There was no difference in total MoCA scores as well as domain-specific sub-scores in patients treated with either lipophilic or hydrophilic antihypertensives. Similarly, there existed no difference in MoCA scores between patients on different antihypertensive drug regimens.

Hypertension leads to cognitive impairment in diverse and complex mechanisms. Current literature suggests that the deterioration in cognitive performance in patients who are not on antihypertensive therapy is mainly due to structural changes such as atherosclerosis of larger cerebral arteries, arteriosclerosis, lipohyalinosis, and vascular remodeling in the setting of hypertension, white matter changes, disruption of neurovascular coupling, derangement of cerebral autoregulation, and other endothelium-dependent mechanisms. [15] The renin-angiotensin-aldosterone system (RAAS) also plays an important role in the pathophysiology of cognitive dysfunction. Chronic activation of the RAAS leads to endothelial injury, oxidative stress, and inflammation. [16] Recent research suggests that angiotensin-II in the brain acts on the angiotensin-I receptor and mediates most of its hypertensive effects. [16] The angiotensin-II receptor, however, produces completely

Table 5
Montreal Cognitive Assessment scores and cognitive impairment in the entire sample, as well as after grouping into those taking anti-hypertensive therapy for ≥2 years (cases) and those who were not on anti-hypertensive therapy (controls).

Variable	Overall ($n = 210$)	Cases ($n = 105$)	Controls ($n = 105$)*	Rank-Biserial Correlation† [95% CI]	p_{bonf}-value (adjusted)
Median total score (/30) (IQR)	25 (23–26)	26 (25–27)	24 (22–25)	0.47 [0.34 to 0.58]	<0.001
Median visuospatial/executive score (IQR)	3 (2–3)	3 (3–4)	2 (2–3)	0.39 [0.25 to 0.52]	<0.001
Median naming score (IQR)	4 (4–4)	4 (4–4)	4 (4–4)	−0.02 [−0.17 to 0.14]	.51
Median attention score (IQR)	4 (3–5)	5 (4–5)	4 (3–4)	0.26 [0.1 to 0.4]	.008
Median language score (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	0.01 [−0.15 to 0.16]	.65
Median abstraction score (IQR)	2 (2–3)	3 (2–3)	2 (2–3)	0.3 [0.15 to 0.43]	<0.001
Median memory & recall score (IQR)	3 (3–4)	4 (3–4)	3 (3–4)	0.25 [0.1 to 0.39]	.009
Median orientation score (IQR)	6 (6–6)	6 (6–6)	6 (6–6)	0.02 [−0.14 to 0.17]	.88

* The Hodges-Lehmann median difference estimate provides the difference between medians (e = exponent).

† The rank-biserial correlation value ranges from −1 to +1, with the null value lying at 1 (values closer to −1 or +1 or values further away from 0 indicate a stronger effect size)

IQR – interquartile range, CI – confidence interval, e – exponent.

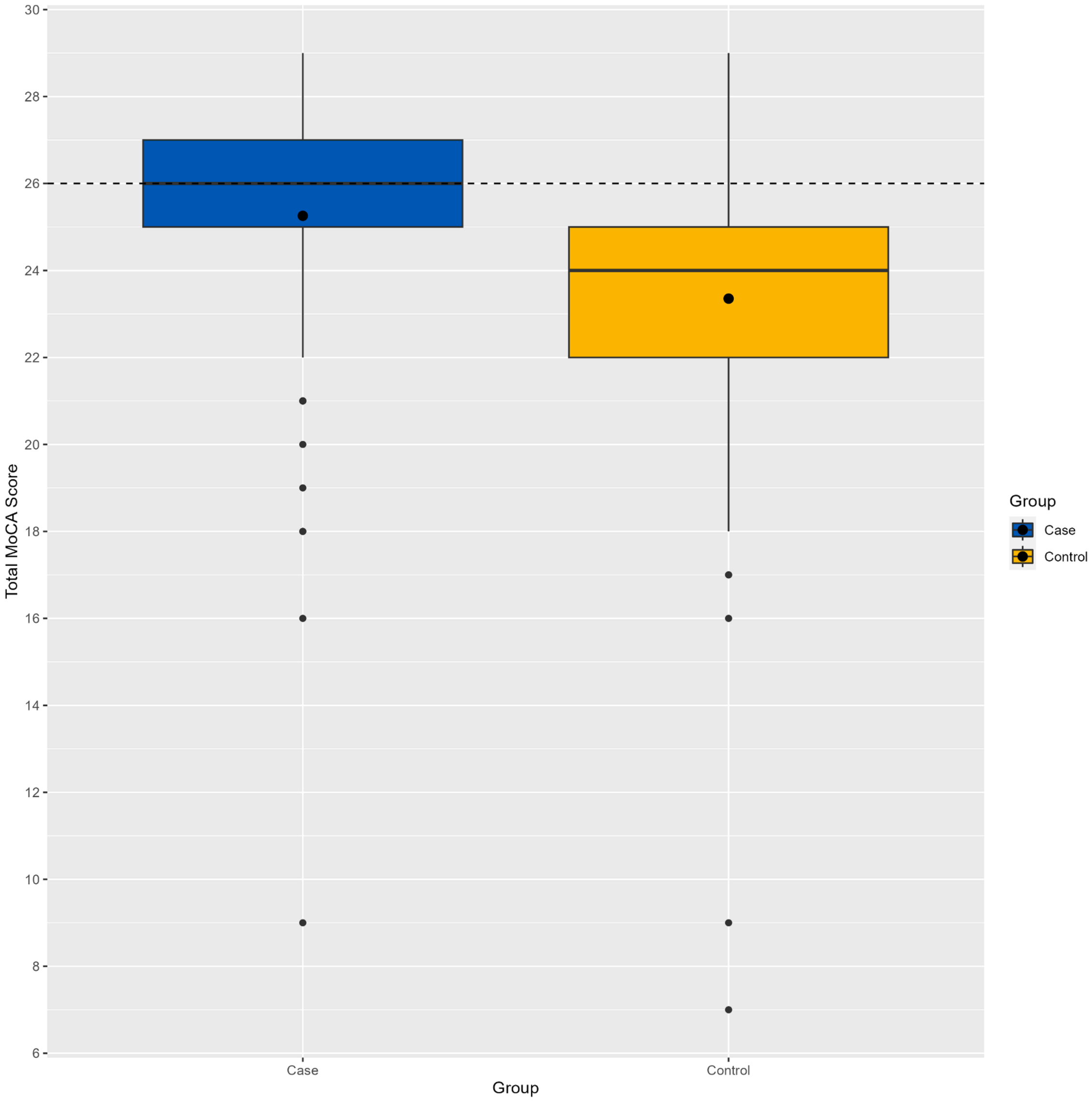

Fig. 1. Boxplot of MoCA scores for both study and control groups. The solid horizontal line represents the median. The lower and upper borders of the boxes represent the 25th and 75th centiles respectively. The black dot inside the box represents the mean. Outliers are denoted by group specific colours lying beyond the whiskers. The dashed line serves as a reference line for a MoCA score of 26 (the cut-off for MCI).

opposite effects by promoting vasodilation, anti-proliferation, and an increase in cerebral blood flow. [17] This may explain why antihypertensive therapy is effective to reduce cognitive impairment in hypertensives. In addition, blockade of the angiotensin-I receptor or angiotensin converting enzyme can improve the cerebrovascular dysfunction induced by hypertension, and also the endothelial cells' barrier function via activation of the angiotensin-II receptor signaling.

Griffiths et al. investigated the prevalence and risk factors associated with MCI among older people more than 60 years of age in rural Thailand. [18] They reported the prevalence of MCI in their study to be 71.4%. Along similar lines, our study reports an overall prevalence of MCI in 57.1% of patients. Out of these, a significantly higher proportion of hypertensive patients (76.2%) had MCI who were not on antihypertensive therapy in comparison to 38.1% of patients having MCI who were taking antihypertensive drugs. Our study suggests that antihypertensive therapy has a role in reducing cognitive decline, as evidenced by higher median MoCA scores in the group taking antihypertensive therapy. In a randomized, prospective, parallel-group trial with 1-year exposure to brain-penetrating ACEIs done by Ohrui et al., cognitive function was assessed using MMSE. [19] Their study showed that perindopril significantly improved MMSE scores. Similarly, results from the SCOPE and OSCAR trials have shown significant improvement in MMSE scores. [20,21] However, these trials have used the MMSE to assess cognitive function. A prospective cohort study performed in Western India which used the PGI memory scale to assess memory showed that patients taking antihypertensive therapy had significantly better immediate recall, delayed recall, and recognition scores after 3 months of antihypertensive therapy. [22] MMSE has important drawbacks including a low sensitivity to detect MCI and lower scores achieved in a rural/suburban setting. [9] Therefore, our study made use of the MoCA to overcome these drawbacks. To the best of our knowledge, ours is the first study in India to use the MoCA to assess cognitive function in geriatric patients taking antihypertensive drugs.

In a sub-study of the Systolic Blood Pressure Intervention Trial (SPRINT) trial, investigators studied the effects of intensive versus standard systolic blood pressure control on different domains of cognitive function. [23] The investigators did not find significant differences in different domains of cognitive function between the groups. In our study, we found that anti-hypertensive therapy given for at least 2-years confers protection against decline in the visuospatial/executive,

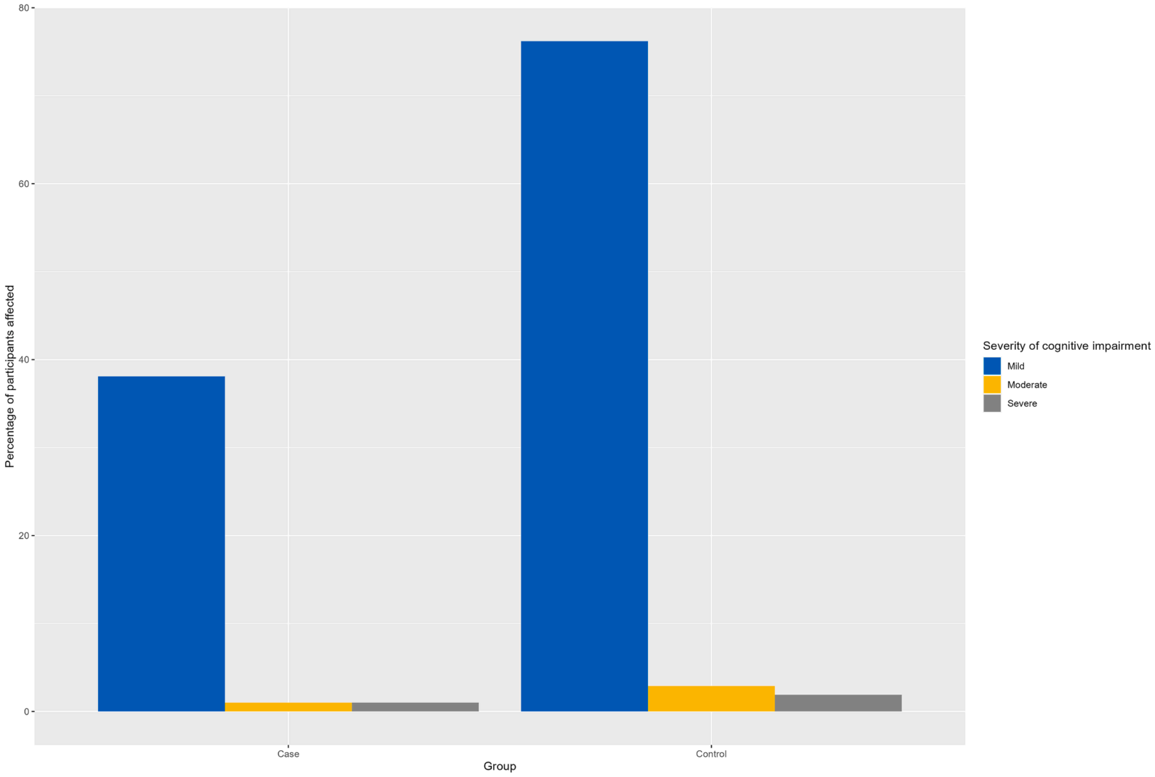

Fig. 2. Bar chart depicting the percentage of subjects affected with cognitive impairment in both study and control groups.

Table 6
Association of lipophilic and hydrophilic drugs on MoCA scores.

Variable	Lipophilic drugs ($n =$ 87): median (IQR)	Hydrophilic drugs ($n = 18$): median (IQR)[*]	Rank-Biserial Correlation[†] (95% CI)	p_{bonf}-value (adjusted)
Total MoCA score	26 (24.25–27)	26 (25–27)	−0.003 (−0.29 to 0.28)	.99
Visuospatial/ Executive score	3 (3–3.75)	3 (3–4)	−0.01 (−0.3 to 0.28)	.933
Naming score	4 (4–4)	4 (4–4)	0.01 (−0.27 to 0.3)	.917
Attention score	5.5 (4.25–6)	4 (3–5)	0.391 (−0.01 to 0.61)	.059
Language score	2 (1–2)	2 (1–2)	−0.141 (−0.41 to 0.15)	.248
Abstraction score	3 (2–3)	3 (2–3)	−0.001 (−0.29 to 0.29)	.996
Memory & Recall score	3 (2.25–4)	4 (3–4)	−0.201 (−0.46 to 0.09)	.165
Orientation score	6 (6–6)	6 (6–6)	−0.062 (−0.34 to 0.23)	.533

[*] The Hodges-Lehmann median difference estimate provides the difference between medians.

[†] The rank-biserial correlation value ranges from −1 to +1, with the null value lying at 1 (values closer to −1 or +1 or values further away from 0 indicate a stronger effect size)

IQR – interquartile range, CI – confidence interval, e – exponent.

memory/recall, attention, and abstraction domains in the MoCA. Findings are presented in a few studies where higher blood pressures negatively influenced global cognitive function, memory, processing times, attention, executive functioning, and visuospatial abilities. [24] In the brain, hypertension mainly affects the pre-frontal and frontal cortices, the parietal lobe, the hippocampus, and the amygdala. [25] The parietal cortex is largely responsible for visuospatial orientation and attention, the pre-frontal cortex and frontal lobe for executive functions, abstraction, and attention, while the hippocampus, amygdala, and other areas of the temporal lobe are responsible for memory formation and recall. [26–29] This may explain the protective role of blood pressure lowering therapy for these cognitive domains.

Lipophilic drugs are known to cross the blood-brain-barrier (BBB), which may lead to CNS effects. [30] In the case of antihypertensive drugs, although BBB-crossing potential is not a factor considered in clinical practice, lipophilicity may be desirable, especially in geriatric patients to reduce the risk of progression to MCI. However, our study did not show significant differences in the two classes of antihypertensives in overall or domain specific MoCA scores. A meta-analysis done by Ho et al. concurred with our findings. [31] They found that blood-brain-barrier crossing antihypertensive drugs acting on the RAAS did not seem to be more efficacious in improving cognitive scores than non-blood-brain-barrier crossing drugs acting on the RAAS. A substudy of the Cardiovascular Health Study (CHS), in contrast, showed that non-centrally active ACE inhibitors were associated with a greater risk of incident dementia. [32] Similarly, memory also has been shown to be preserved when BBB-crossing drugs have been used. [33] RAAS in the brain is believed to be involved in functions critical to cognition, including neuronal differentiation, nerve regeneration, and learning and memory. [15] Therefore, these drugs that can penetrate the BBB may influence cognition through both luminal and abluminal neurovascular effects, including neuronal effects.

In a comprehensive systematic review and meta-analysis by Peters et al. in 2020 which included 50,000 participants from 27 different studies to investigate the role of different anti-hypertensive drug classes

Table 7
Linear regression models explaining overall MoCA scores.

	Unadjusted				Adjusted		
Characteristic	N	Beta	95% CI[1]	p-value	Beta	95% CI[1]	p-value
Group	210						
Control		—	—		—	—	
Case		1.9	1.1 to 2.7	<0.001	1.5	0.30 to 2.6	0.014
Age	210	−0.02	−0.09 to 0.06	0.70	−0.02	−0.09 to 0.06	0.69
Sex	210						
Female		—	—		—	—	
Male		0.23	−0.64 to 1.1	0.60	0.15	−0.71 to 1.0	0.73
Years of education	210	0.03	−0.05 to 0.12	0.44	0.03	−0.05 to 0.11	0.47
Duration of hypertension (years)	210	0.17	0.08 to 0.26	<0.001	0.07	−0.06 to 0.20	0.28

[1] CI = Confidence Interval.

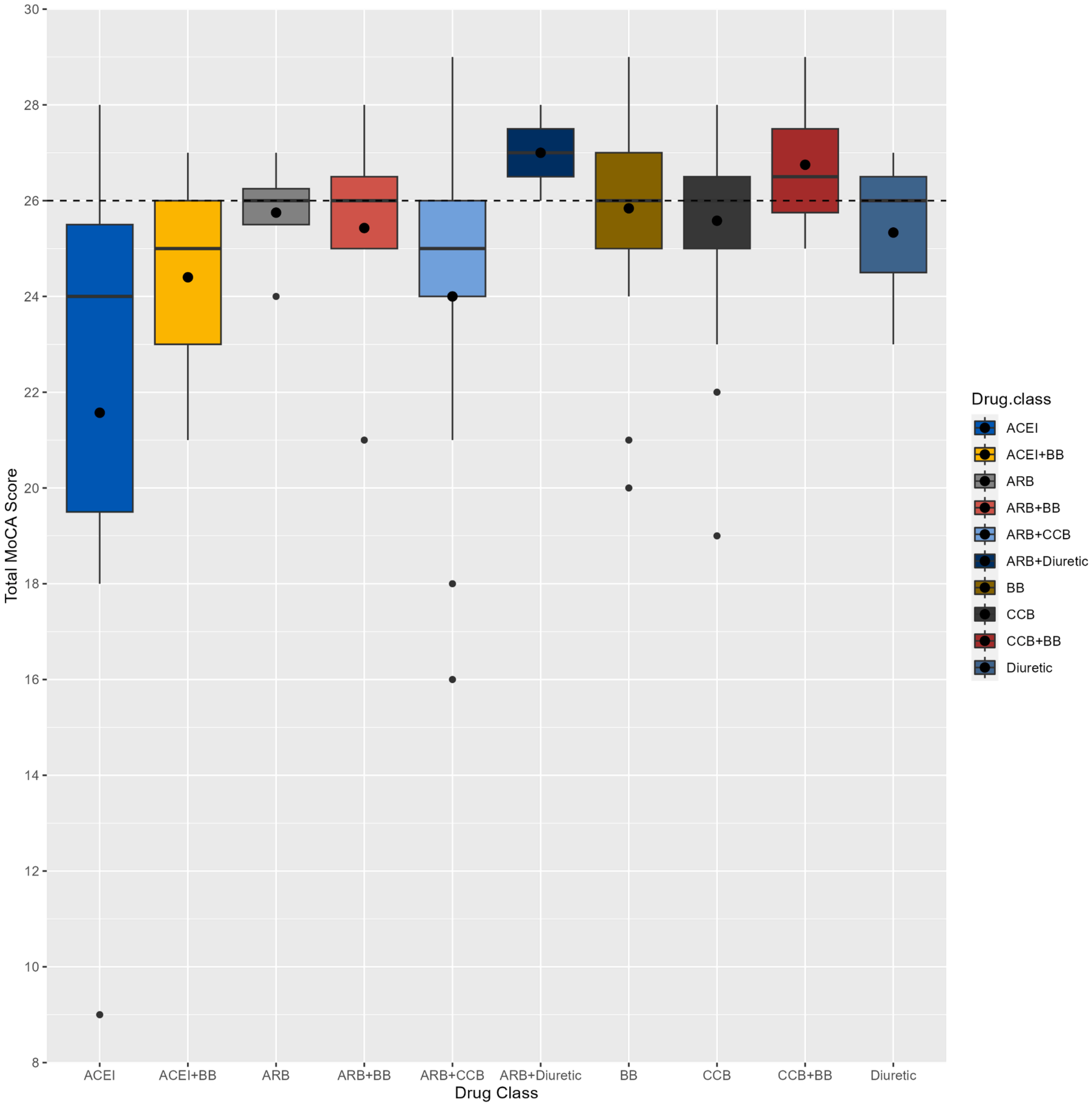

Fig. 3. Boxplots comparing cognitive function as tested by MoCA for different drug class combinations. ACEI – angiotensin converting enzyme inhibitor, BB – beta blocker, ARB – angiotensin receptor blocker, CCB – calcium channel blocker. Solid horizontal lines represent the medians. The black dot inside the box represents the mean. Outliers are denoted by drug class specific colours lying beyond the whiskers. The lower and upper borders of the boxes represent the 25th and 75th centiles respectively. The dashed line represents the reference line of a MoCA score of 26 (the cut-off for MCI).

and cognitive decline and dementia, it was found that no anti-hypertensive drug class was better than the others with respect to cognitive impairment. [34] Most of the studies included in this review assessed cognition with the MMSE. Similarly, Ding et al. in their meta-analysis of approximately 31,000 participants found that the hazard of developing dementia and Alzheimer's disease in patients taking antihypertensive drugs was 0.88 and 0.84 times that of patients not on antihypertensive regimens. [35] They also found that no single antihypertensive class was superior to the other in reducing the risk of dementia. The conclusions derived from our study are similar, where there were no significant differences in MoCA scores between subjects taking various antihypertensive drugs. However, den Brok et al. in their network meta-analysis concluded that ARBs or CCBs were associated with a lower risk of dementia in observational studies. [36] In a different sub-study of the SPRINT trial, exposures of at least 1 year to thiazide diuretics and RAAS inhibitors were found to reduce adverse events and cardiovascular mortality; on the other hand, the use of beta-blockers was found to increase cardiovascular mortality. [37] Thus, along with consideration of improved cognitive function, other protective as well as risk factors, especially cardiovascular risk factors, should also be kept in mind while prescribing antihypertensive drugs to geriatric patients. Classes including ACEIs, ARBs, and CCBs may be superior to other drug classes, with effects not just limited to lowering blood pressure.

Our study, being cross-sectional in design, restricted comparison of cognitive assessment to a single time-point as well as histopathological confirmation of the diagnosis. Prospective controlled studies that assess MoCA scores periodically after initiation of antihypertensive therapy might yield interesting results giving insight into the rate and pattern of slowing of cognitive decline. Studies evaluating differences in cognitive scores among patients on monotherapy with BBs or CCBs versus combination therapy where drugs acting on the RAAS are added to the backbone therapy would be helpful to design effective treatment regimens for the hypertensive elderly. It might also be noteworthy that even though the median difference in MoCA scores between those who were and weren’t taking antihypertensive drugs was modest, even a superior MoCA score by 2-points in geriatric hypertensive patients who are compliant with antihypertensive medications might lead to better patient quality of life and activities of daily living and reduced healthcare burden. Studies should be planned wherein these outcomes are assessed between groups with a trivial (2- or 3-point) difference in cognitive scores.

5. Conclusion

The results of our observational cross-sectional study in a tertiary care teaching hospital in suburban India showed that antihypertensive therapy had a statistically significant association with the total, visuospatial, executive, attention, abstraction, memory, and recall MoCA scores. Patients on antihypertensive therapy also had a lower prevalence of MCI. The beneficial effect of antihypertensive therapy seems to be associated with lower blood pressure, but brain-specific effects may also play an important role in patients taking ACEIs and ARBs. Patients taking hydrophilic versus lipophilic medications had similar MoCA scores. MoCA scores were similar between patients on different antihypertensive drug classes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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