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THE EFFECT OF BLOOD PRESSURE NORMALIZATION INTERVENTIONS ON COGNITIVE FUNCTION OF SENIOR CITIZENS WITH LOW BLOOD PRESSURE AND MILD COGNITIVE IMPAIRMENT.

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ABSTRACT

Background: Several observational studies have established positive correlation between low blood pressure and cognitive impairment, but no interventional study has proven this association.

Aims: To study the effect of blood pressure normalization interventions on cognition in senior citizens with low blood pressure and mild cognitive impairment and to assess the efficacy and safety of these interventions.

Methods and Material: This randomised clinical trial was done in a tertiary care teaching hospital and attached outreach clinics. 80 senior citizens with low blood pressure (JNC 8) and mild cognitive impairment (Kannada Translated Hindi MMSE/MOCA=20-27) were randomized to either intervention or control group. Antihypertensives were progressively withdrawn, or fludrocortisone added for participants in intervention group and antihypertensive therapy was continued for participants in control group. Participants of both the groups were followed up over a period of 8 weeks with regular blood pressure assessment every two weeks and cognitive assessments every 4 weeks following withdrawal of antihypertensives or addition of fludrocortisone.

Statistical analysis: Bonferroni test was used to compare change within, and Mann Whithney test was used to compare change between the groups.

Results: Both participants in intervention and control groups showed improvement in SBP, however the increase (95% CL) was greater in intervention (13.4 ±8.111 mm Hg, p=.0001) than control group (2.12 ±4.333 mm Hg, p= .004), similarly improvement was observed in DBP among intervention group (8.62 ±5.646 mm Hg, p=.0001) with no improvement in control group (0.43 ±2.995mm Hg, p=.375). Clinically significant improvement in cognitive function was seen in only intervention group.

Conclusions: Improvement in diastolic blood pressure in elderly with low blood pressure and mild cognitive impairment was associated with clinically and statistically significant improvement in cognitive function without any adverse events.

KEYWORDS : Senior citizens, low blood pressure, mild cognitive impairment.

INTRODUCTION:

The role of blood pressure as a modifiable risk factor for dementia has been extensively evaluated and midlife hypertension was found to be an important predisposing factor for dementia in later life[1]. However, the association between blood pressure, antihypertensive therapy and cognitive decline in the elderly is not clearly understood. Although several studies have shown a positive correlation between low blood pressure and cognitive decline in elderly, it is not clear whether the low blood pressure causing decreased brain perfusion, is the cause or effect of dementia [2-7].

Age related changes in cerebral blood vessels and impairment in autoregulatory mechanisms responsible for maintaining cerebral perfusion, may predispose elderly to repeated episodes of decreased cerebral perfusion and hypoxia leading to secondary amyloid deposition and dementia [8-11]. Hence a higher blood pressure (BP) may be needed in elderly to maintain adequate cerebral blood flow. Meta-analysis of studies evaluating the effect of antihypertensive treatment on cognitive function of elderly suggest that antihypertensive treatment does not reduce the risk for dementia [12, 13]. Aggressive antihypertensive treatment in elderly may compromise cerebral blood flow resulting in hypoperfusion and cognitive decline [14,15].

In the Effect of **B**lood **P**ressure **Norm**alization Interventions on **Cog**nitive function of Senior Citizens with Low Blood Pressure and Mild Cognitive Impairment (**BP Norm Cog**) Study, we evaluated whether temporary discontinuation of antihypertensive treatment or addition of Fludrocortisone improves cognitive functioning in persons 60 years or older with mild cognitive deficits and low blood pressure.

We hypothesized that there will be significant improvement in cognitive scores of senior citizens with mild cognitive decline after blood pressure improving measures and attainment of normal blood pressure needed for brain perfusion in the elderly.

SUBJECTS AND METHODS:

From September 2014, through July 2016 this randomized clinical trial was performed in Kasturba Medical College Hospital, a tertiary care centre attached to Kasturba Medical College Mangalore, and outreach clinics attached to KMC Hospital.

Participants were eligible for inclusion if they were 60 years or older, had a systolic blood pressure (SBP) of 130 mm Hg or less and/or a diastolic blood pressure of 70 mm Hg or less, and cognitive score of 20 to 27.

Patients with acute illness, moderate to severe dementia, uncontrolled diabetes, depression, heart failure, and myocardial infarction or a coronary reperfusion procedure less than 3 years ago, cardiac arrhythmias, history of stroke or transient ischemic attack and total illiteracy were excluded from the study.

Our study was approved by medical ethics Committee of Kasturba Medical College, Mangalore, Manipal University and was also was registered under ICMR Clinical trial registry with the number: CTRI/2014/12/005298.

Study procedures:

All the eligible senior citizens attending medical OPD/outreach clinics attached to Kasturba Medical College Hospital, Mangalore or senior citizens admitted in hospital for reasons other than acute illness for short or long term care who were found to have low blood pressure of <130/70 mm of Hg were approached for cognitive screening. After cognitive screening using either kannada translated Hindi MMSE or Montreal Cognitive Assessment (MOCA) those with SBP <130 and/or DBP <70mm of Hg and cognitive scores between 20-27 were informed about the study and were asked to provide an informed consent.

Depression was excluded using 15-point Geriatric depression scale. Patients were assessed for comorbidities such as DM, HTN, IHD and data on known risk factors for cognitive impairment such as educational status, family history of dementia, Obesity, physical activity were also collected. Blood pressure was measured as per JNC VIII (Joint National Committee) recommendations using calibrated Omron digital sphygmomanometer. Sitting blood pressure was recorded. A minimum of 3 readings were recorded and average of 2nd and 3rd reading were taken as the blood pressure. Patient's cognitive function was assessed using Kannada translated Hindi MMSE for patients with literacy state up to 12 years of schooling or Montreal cognitive assessment scale version 7.1 for baseline measurement and

for repeated measures version 7.2 and 7.3 for those with college education. Before the study MOCA was field tested in 50 senior citizens of Mangalore Senior Citizen Association and was found to be feasible to use in our seniors with college education.

Randomization and Masking:
After recruitment eligible subjects were given unique ID numbers, they were randomized to the control group or the intervention group according to the block randomization by chit method in blocks of two, one as control, and the other for intervention. Block of 2 chits with the allocated intervention with the number Code was kept in a sealed envelope and each time the sealed envelope was opened to randomize two patients by picking up the chit with the number. The investigator and the patients were not blinded. The intervention group was further classified into group with antihypertensive drugs and the group without antihypertensive therapy.

Masking: Cognitive scores were measured by the assessor who was not blinded.

Intervention:
Intervention group:
1. Withdrawal/reduction of antihypertensive agents in participants on antihypertensive therapy. Or
2. High salt diet, elastic crepe bandages and addition of fludrocortisone 50ug and titrated weekly to maximum of 100ug for participants not on antihypertensive therapy.

Control group:
Standard Care
Safety Measures: Patients were followed up every two weeks for Blood pressure measurements for early detection of high blood pressure.

Fludrocortisone group had weekly edema assessment and Potassium measurements at week 4 and end of therapy at week 8.
The following Withdrawal criteria were used:
1. Blood pressure of >160/90 mm of Hg.
2. Massive edema
3. Hypokalaemia with serum potassium <3 mg/dl.
4. Cardiac failure or elevated JVP.
5. Any other serious adverse event or severe adverse event.

Serious adverse event was defined as any event resulting in death, life threatening conditions, results in significant disability or results in hospitalization or leads to prolongation of hospital stay.

Severe adverse event is a non-serious adverse event of the highest grade e.g. severe edema.

Additional safety visits were made for participants in intervention group.

There was a total of 3 study visits as illustrated in [Figure 1].

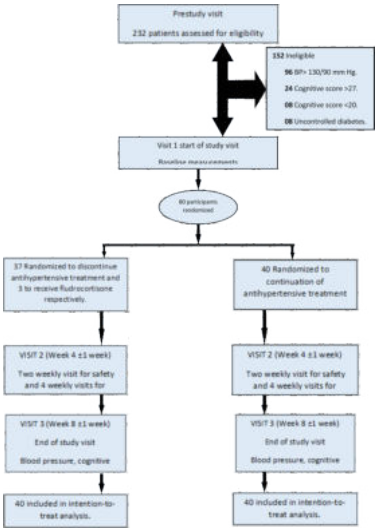

Figure 1. CONSORT Flowchart of the Study

Pre-study Visit:
In this visit eligible subjects with blood pressure< 130/70 mm of Hg with cognitive scores < 27, but ≥ 20 provided an informed consent. Informed consent of subjects with dementia whose signature was not valid was signed by first degree relative or a caregiver.

Study visit-1 Randomization visit:
Subjects were randomized to receive no intervention or blood pressure normalization intervention such as reduction in antihypertensive drug dosage or use of crepe bandage and increase in salt and water and/or addition of Fludrocortisone, which were supplied free of cost from the study grant. Comprehensive Geriatric assessment was done, and cognitive scores documented. Blood pressures were measured using digital sphygmomanometer and a minimum of 3 readings were recorded.

Study visit-2 (week 4±1):
In this visit blood pressures of participants were measured using standard methods, cognitive scores reassessed. Participants were also evaluated for adverse events and antihypertensives titrated accordingly.

Study visit-3 or End of therapy visit (week 8±1):
Blood pressure measurement and cognitive assessment was done for all the participants. Drug compliance as well as safety was assessed by Potassium measurement and edema assessment for participants receiving Fludrocortisone.

Participants with adverse events and those on fludrocortisone therapy were followed up at weekly intervals.

Outcomes: Improvement in mean and ≥ 3-point improvement in cognitive scores after intervention. Secondary outcomes were percentage of participants with adverse events.

Statistical analysis: Assuming that 50% of the subjects among cases will show clinically significant cognitive improvement and 10% of the controls will show clinically significant cognitive improvement, with the SD of the Cognitive scores for both cases and controls being +3, Sample size was calculated using the formula:

$n = 2(Z\alpha + Z\beta)^2 \times \sigma^2/d^2$.
Two tailed significance of 0.05 ($Z\alpha = 1.96$),
Power of 80% ($Z\beta = 0.84$),

Difference in mean cognitive scores of the two groups after intervention as 3, Standard deviation of the sample assumed as 3 (σ).

A sample size of 32 was calculated. If only 50% of the senior citizens can attain target blood pressure for cerebral perfusion with the interventions, a sample size of 64 was calculated. With an anticipated 20% drop out, additional 13 patients were needed giving us a total sample size of 77. We included 80 patients of which 40 got randomized to intervention and 40 remained as controls under standard care.

Chi square test and Fishers exact test were used to compare baseline characteristics between intervention and standard care groups. ANOVA was used for analysis of repeated blood pressure recordings, cognitive scores and post hoc analysis by Bonferroni test was used to compare the change within the groups.

Change between the intervention and standard care groups was compared with Mann Whithney test. All analyses were performed with SPSS software (version 13.0; IBM Corp).

RESULTS:
Among a total of 80 participants, 40 were randomized to intervention group and 40 to control group. There was no drop out of participants during the study. All the participants met the eligibility criteria and were available for follow-up measurements. As shown in [Table 1] baseline characteristics of intervention and control groups were well matched without any statistically significant difference.

Table 1: Baseline Characteristics of All 80 Participants *

Characteristic	Intervention Group (n = 40)	Control Group (n = 40)
1. Demographic:		
a. Age, mean (SD), y	68.95 (6.3848).	67.17 (5.7284).

b. Male sex	21(52.5%)	20 (50.0%)
c. Educational level, median (IQR), y	6^{th}-12^{th}	6^{th}-12^{th}
2. Clinical:		
a. BMI, mean (SD)	23.20 (3.3909)	22.79 (2.9700)
b. Current smoking	3 (7.5)	3 (7.5)
c. Alcohol consumption	7 (17.5)	3 (7.5)
d. CVD †	5 (12.5)	3 (7.5)
e. Hypertension	37 (92.5)	37 (92.5)
f. Diabetes mellitus	21 (52.5)	16 (40.0)
g. Obstructive airway disease	3 (7.5)	0
h. Hypothyroidism	2 (5.0)	2 (5.0)
i. Presence of other chronic diseases	6 (15.0)	2 (5.0)
3. Antihypertensives used:		
a. β-Blocker	10 (25.0)	10 (25.0)
b. Diuretic	1 (2.5)	2 (5.0)
c. Angiotensin-converting enzyme d. Inhibitor	12 (30.0)	11 (27.5)
e. Calcium channel blocker	25 (62.5)	25 (62.5)
f. Others	0 (0.0)	1 (2.5)
≥2 Agents	27 (67.5)	30 (75.0)
SBP, mean (SD), mm Hg	120.65 (7.241)	119.58 (7.317)
DBP, mean (SD), mm Hg	68.08 (5.370)	69.80 (4.536)
Baseline MOCA/KMMSE scores	22.85 (1.791)	22.38 (1.213)

* Data are expressed as number (percentage) of participants, unless otherwise indicated.

† Includes percutaneous coronary intervention, myocardial infarction, and coronary artery bypass graft more than 3 years ago.

Among the 40 participants in intervention group 37 were receiving antihypertensive agents at the start of the study. The 3 participants who were not on antihypertensive agents were given high salt diet, elastic crepe bandages and fludrocortisone to improve blood pressure. Among 40 participants in control group 37 were on antihypertensive agents and 3 were not on antihypertensive agents.

[Table 2] shows the systolic blood pressures (SBP) and diastolic blood pressures (DBP) in intervention and control groups at baseline and on subsequent follow-up. Increase in mean SBP and DBP by 8 weeks in the intervention group was 13.4 ± 8.111 mm Hg and 8.62 ± 5.646 mm Hg respectively, while increase in control group was 2.12 ± 4.333 mm Hg and 0.43 ± 2.995 mm Hg, respectively.

Table.2 Change in SBP among Intervention and control groups

SBP	Visit	N	Mean ± SD	ANOVA	p
Intervention group	1	40	120.65 ±7.241	77.936	.0001
	2	40	129.18 ±7.306		
	3	40	134.05 ±7.009		
Control group	1	40	119.58 ±7.317	5.304	.0001
	2	40	121.33 ±7.076		
	3	40	121.70 ±6.501		
DBP	Visit	N	Mean ± SD	ANOVA	p
Intervention group	1	40	68.08 ±5.370	21.520	.0001
	2	40	73.70 ±5.341		
	3	40	76.70 ±4.957		
Control group	1	40	69.80 ±4.536	1.306	.247
	2	40	70.70 ±4.195		
	3	40	70.23 ±4.335		

In the intervention group, improvement in both SBP and DBP was statistically significant (P =.0001) at all visits. In the control group, statistically significant improvement was seen only in SBP (P =.004) but not in DBP (P = 0.375) during subsequent visits. When the change in systolic and diastolic blood pressures between the two groups was compared using Mannwhithney test, statistically significant improvement was observed in intervention group for both SBP (Z=7.22) (P =.0001) and DBP (Z= 6.75) (P =.0001) as shown in [Table 3].

Table.3 Comparison of change in BP between Intervention and control groups.

BP	Group	Mean	SD	Mannwhitney test Z value	p
SBP1-SBP3	Intervention group	13.40	8.111	7.22	.0001
	Control group	2.125	4.333		
DBP1-DBP3	Intervention group	8.625	5.646	6.75	.0001
	Control group	.425	2.995		

[Table 4] shows cognitive scores in intervention and control groups at baseline and on subsequent follow-up. In intervention group, increase in mean cognitive score (95% CI) was 4.375 ±1.055, this was both statistically (P<0.0001) and clinically significant.

Table.4 Change in cognitive scores among Intervention and control groups.

Cognitive scores	Visit	N	Mean	SD	ANOVA	p
Intervention group	1	40	22.85	1.791	453.963	.0001
	2	40	25.28	2.038		
	3	40	27.23	1.609		
Control group	1	40	22.38	1.213	22.215	.0001
	2	40	23.13	1.285		
	3	40	23.13	1.343		

In control group, increase in mean cognitive score (95% CI) was 0.75 ±0.776, this was statistically significant (P<0.0001) but clinically not significant.

When the change in cognitive scores between intervention and control groups were compared using Mann whithney test, the improvement was statistically significant for intervention group (Z= 17.508) (P=0.0001) as shown in [Table 5].

Table.5 Comparison of change in cognitive scores between Intervention and control groups.

Cognitive scores	Group	Mean	SD	Mannwhitney test Z value	p
Visit 1-3	Intervention group	4.375	1.055	17.508	.0001
	Control group	.750	.776		

DISCUSSION:

Although there is enough evidence from several observational studies that low blood pressure in elderly predisposes to dementia and over treating hypertension in elderly may increase this risk, hardly any interventional studies were done except the DANTE study to evaluate the effect and efficacy of discontinuing antihypertensive treatment on cognitive functioning in older persons with cognitive impairment. Hence this study was conducted to test this hypothesis.

This randomized hospital and outreach based clinical trial in individual's ≥ 60 years with mild cognitive impairment and with low blood pressure, discontinuation of antihypertensive treatment or addition of Fludrocortisone to those without hypertension, was associated with significant improvement in cognitive function at the end of 8 weeks compared with continuation of antihypertensive treatment or standard care in the control group.

The baseline characteristics in our study were well matched between the two groups including several risk factors for dementia like gender, education status, BMI, smoking, diabetes, antihypertensives used for treatment. There was significant improvement in cognitive function, SBP and DBP among intervention group following discontinuation of antihypertensive treatment and this improvement was both clinically and statistically significant. Subjects in intervention group experienced ≥ 3-point improvement in cognitive scores.

Although there was some improvement in cognitive function, SBP and DBP among control group with statistical significance being achieved in case of cognitive function and SBP following discontinuation of antihypertensive treatment, this improvement was not clinically significant. Subjects in control group failed to achieve a ≥ 3-point improvement in cognitive scores. Statistically significant improvement in DBP was not observed in control group.

As proven by longitudinal community based observational studies by Qiu C *et al.* [16] Qiu C *et al.* [17] and Sabayan B *et al.* [18], DBP appears to be more important in maintaining cognitive function than SBP as clinically and statistically significant improvement in DBP was seen in only intervention group.

Results from the DANTE or Effect of Discontinuation of

Antihypertensive Treatment in Elderly People on Cognitive Functioning study, a similar community based blinded for outcome randomized study with 385 participants conducted recently by Moonen *et al.* [19] in Netherlands failed to show improvement in cognitive function with improvement in blood pressure following temporary withdrawal of antihypertensive medication in elderly above 75 years, over a period of 6 weeks following randomization.

When compared to the study by Moonen *et al*. [19] a positive association between increase in blood pressure and cognitive function might have been achieved in our study as, mean age of participants, baseline systolic, diastolic blood pressures and cognitive scores were lower. A greater increase in blood pressure from baseline and a large difference in change in blood pressure between the two groups following intervention can explain this improvement in cognitive scores.

As the participants in Moonen *et al*. [19] study already had a higher baseline systolic blood pressure of 148.8 ± 21.1mm Hg and diastolic blood pressure of 82.3 ±10.8 mm Hg further improvement beyond the threshold for cerebral perfusion did not improve cognitive scores. As our study included patients with low diastolic blood pressure and with blood pressure below the threshold for cerebral perfusion beneficial effects were evident after improvement in diastolic blood pressure.

The main strengths of the study were:

1. One of very few interventional studies till date to assess relation between blood pressure and cognitive function.
2. Low dropout rate.
3. Cognitive function was assessed with well validated tests.
4. Baseline characteristics of cases and controls were well matched thereby minimizing confounding factors.

Limitations of the study:

1. Neuroimaging was not done in the study.
2. Shorter follow-up.
3. Neuro psychiatry Battery of tests were not performed
4. Physicians and patients were aware of the treatment administered (not a double blinded study).
5. Effects of discontinuation of individual classes of antihy pertensives was not evaluated.

CONCLUSIONS:

1. Blood pressure improvement in patients with subnormal blood pressure and mild cognitive impairment (MCI) produced clinically and statistically significant improvement in cognitive scores in comparison with controls.
2. Blood pressure improvement measures like withdrawal of antihypertensives or addition of fludrocortisone or gradual reduction in blood pressure medication were safe for a short term of 8 weeks.
3. Long term safety of these interventions needs to be established.

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