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EFFECTS OF ANTIHYPERTENSIVE THERAPY ON COGNITIVE DECLINE AND BIOCHEMICAL MARKERS IN HYPERTENSIVE PATIENTS WITH INCREASED RISK FOR ALZHEIMER'S DISEASE

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Abstract
Hypertension is a modifiable risk factor for cognitive decline and Alzheimer's disease (AD). This randomized controlled trial aimed to evaluate the effects of antihypertensive therapy on cognitive function and biochemical markers in hypertensive patients at increased risk for AD. A total of 200 participants aged 60–80 years with diagnosed hypertension and mild cognitive impairment were randomized into two groups: one receiving standard antihypertensive treatment and the other receiving intensive antihypertensive therapy targeting lower blood pressure goals. Over 24 months, cognitive assessments and biochemical analyses, including amyloid-beta and tau protein levels, were conducted. The intensive therapy group showed a statistically significant improvement in cognitive scores ($p<0.01$) and a reduction in AD-related biomarkers ($p<0.05$) compared to the standard treatment group. These findings suggest that intensive blood pressure management may slow cognitive decline and modulate biochemical markers associated with AD in hypertensive patients. Further long-term studies are warranted to confirm these results.

Keywords: Hypertension, Cognitive Decline, Alzheimer's Disease

Introduction

Hypertension, a prevalent cardiovascular condition, has been increasingly recognized as a significant risk factor for cognitive decline and the development of Alzheimer's disease (AD). The pathophysiological mechanisms linking hypertension to cognitive impairment involve vascular damage, reduced cerebral perfusion, and the promotion of amyloid-beta accumulation, all of which contribute to neurodegenerative processes.[1] Recent studies have highlighted the potential of antihypertensive therapy not only in managing blood pressure but also in mitigating the risk of cognitive deterioration.[2-3]

The global burden of dementia, particularly AD, is escalating, with projections indicating a substantial increase in prevalence over the coming decades. This surge underscores the urgency of identifying modifiable risk factors and implementing preventive strategies. Hypertension, being both common and manageable[4], presents a viable target for such interventions. Epidemiological data have consistently demonstrated an association between elevated blood pressure and accelerated cognitive decline, emphasizing the need for effective blood pressure control in at-risk populations.[5-7]

Antihypertensive medications, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers, and diuretics, have been extensively studied for their cardiovascular benefits.[8] Emerging evidence suggests that these agents may also confer neuroprotective effects, potentially through mechanisms such as improved cerebral blood flow, reduction of oxidative stress, and attenuation of inflammatory pathways. Notably, ARBs have been associated with a lower incidence of AD compared to other antihypertensive classes, suggesting a class-specific benefit in cognitive outcomes.[9]

Clinical trials have begun to explore the cognitive effects of antihypertensive therapy. For instance, the Systolic Hypertension in Europe (Syst-Eur) trial demonstrated that antihypertensive treatment reduced the incidence of dementia in elderly patients with isolated systolic hypertension. Similarly, the SPRINT MIND study found that intensive blood pressure control was associated with a lower risk of mild cognitive impairment, although the effect on probable dementia was not statistically significant. These findings highlight the potential cognitive benefits of antihypertensive therapy but also indicate the need for further research to delineate optimal treatment strategies.[10]

Biochemical markers, such as amyloid-beta and tau proteins, play a crucial role in the pathogenesis of AD and serve as valuable indicators of disease progression. Investigating the impact of antihypertensive therapy on these biomarkers could provide insights into the mechanisms by which blood pressure control influences cognitive trajectories. Understanding these relationships is essential for developing targeted interventions aimed at preventing or delaying the onset of AD in hypertensive individuals.[11]

Given the existing evidence and the pressing need for effective preventive measures against cognitive decline, this study aims to evaluate the effects of antihypertensive therapy on cognitive function and AD-related biochemical markers in hypertensive patients at increased risk for AD. By conducting a randomized controlled trial with rigorous methodology, the study seeks to contribute to the growing body of literature on the intersection of cardiovascular health and cognitive function, ultimately informing clinical practices and public health policies.

Methodology

This case control study was conducted over 24 months to assess the impact of antihypertensive therapy on cognitive function and biochemical markers in hypertensive patients at increased risk for Alzheimer's disease (AD). The study enrolled 200 participants at ALLAMA IQBAL MEDICAL COLLEGE LAHORE aged 60–80 years with diagnosed hypertension and mild cognitive impairment (MCI), confirmed through standardized neuropsychological assessments. Participants were recruited from outpatient clinics and provided verbal informed consent before enrollment.

Sample size calculation was performed using Epi Info software, targeting a power of 80% and a significance level of 0.05 to detect a minimum difference of 2 points in cognitive scores between

groups. Accounting for a potential dropout rate of 20%, the final sample size was set at 200 participants, with 100 individuals allocated to each group.

Participants were randomized into two groups: the standard treatment group received antihypertensive therapy aiming for a target systolic blood pressure (SBP) of <140 mmHg, while the intensive treatment group aimed for a target SBP of <120 mmHg. Antihypertensive medications included ACEIs, ARBs, calcium channel blockers, and diuretics, administered based on individual patient profiles and tolerability.

Inclusion criteria encompassed individuals aged 60–80 years with diagnosed hypertension (SBP ≥140 mmHg or diastolic BP ≥90 mmHg) and MCI, defined by a Clinical Dementia Rating (CDR) of 0.5 and a Mini-Mental State Examination (MMSE) score between 24 and 27. Exclusion criteria included a history of stroke, significant psychiatric disorders, or use of medications known to affect cognitive function.

Cognitive assessments were conducted at baseline, 12 months, and 24 months using standardized tools, including the MMSE and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Biochemical analyses involved measuring plasma levels of amyloid-beta (Aβ42) and total tau protein at the same time points.

Data were analyzed using intention-to-treat principles. Continuous variables were compared using t-tests or ANOVA, while categorical variables were analyzed using chi-square tests. A p-value of <0.05 was considered statistically significant.

Results

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Standard Treatment (n=100)	Intensive Treatment (n=100)	p-value
Age (years)	68.2 ± 5.4	67.9 ± 5.6	0.68
Female (%)	52	55	0.72
SBP (mmHg)	148.5 ± 10.2	149.1 ± 9.8	0.54
MMSE Score	25.6 ± 1.2	25.7 ± 1.3	0.77
Aβ42 (pg/mL)	180.3 ± 25.4	179.8 ± 26.1	0.89
Total Tau (pg/mL)	75.6 ± 10.5	76.1 ± 11.2	0.65

Note: No significant differences were observed between groups at baseline.

Table 2: Cognitive Outcomes at 24 Months

Outcome Measure	Standard Treatment	Intensive Treatment	p-value
MMSE Score	24.8 ± 1.5	26.2 ± 1.3	<0.01
ADAS-Cog Score	15.4 ± 3.2	12.1 ± 2.8	<0.01

Note: The intensive treatment group showed significant improvement in cognitive scores compared to the standard treatment group.

Table 3: Biochemical Markers at 24 Months

Biomarker	Standard Treatment	Intensive Treatment	p-value
Aβ42 (pg/mL)	170.2 ± 24.5	185.6 ± 22.3	<0.05
Total Tau (pg/mL)	80.1 ± 9.8	72.4 ± 10.1	<0.05

Note: The intensive treatment group exhibited favorable changes in AD-related biomarkers.

Discussion

The findings of this randomized controlled trial indicate that intensive antihypertensive therapy targeting lower systolic blood pressure goals can lead to significant improvements in cognitive function and favorable modulation of biochemical markers associated with Alzheimer's disease (AD) in hypertensive patients with mild cognitive impairment (MCI). These results align with previous studies suggesting a link between blood pressure control and cognitive health.[12-13]

The observed cognitive benefits in the intensive treatment group may be attributed to improved cerebral perfusion and reduced vascular damage, which are critical factors in the pathogenesis of cognitive decline. The reduction in amyloid-beta and tau protein levels further supports the hypothesis that antihypertensive therapy can influence neurodegenerative processes beyond mere blood pressure reduction.[14]

Notably, the use of specific antihypertensive classes, such as ARBs and calcium channel blockers, has been associated with neuroprotective effects. These agents may exert their benefits through mechanisms involving the renin-angiotensin system and calcium homeostasis, which are implicated in neuronal function and survival.[15] The selection of antihypertensive medications with favorable central nervous system profiles could thus enhance cognitive outcomes in hypertensive patients.[16]

The study's methodology, including rigorous randomization, standardized assessments, and comprehensive biomarker analysis, strengthens the validity of the findings. However, certain limitations must be acknowledged. The study population was limited to individuals aged 60–80 years with MCI, which may restrict the generalizability of the results to other age groups or cognitive statuses.[17-19] Additionally, the 24-month follow-up period, while sufficient to observe significant changes, may not capture long-term outcomes related to dementia progression.[20]

Future research should aim to replicate these findings in larger, more diverse populations and explore the long-term effects of intensive blood pressure control on the incidence of AD. Investigating the differential impacts of various antihypertensive classes on cognitive function and neurodegenerative biomarkers will also be essential in optimizing treatment strategies.

In conclusion, this study provides evidence that intensive antihypertensive therapy can confer cognitive benefits and modulate AD-related biomarkers in hypertensive patients at increased risk for dementia. These findings underscore the importance of blood pressure management in preserving cognitive health and highlight the potential of antihypertensive therapy as a preventive strategy against cognitive decline.

Conclusion

Intensive antihypertensive therapy in hypertensive patients with mild cognitive impairment significantly improves cognitive function and favorably alters Alzheimer's disease-related biochemical markers. This study fills a critical gap by demonstrating the potential of blood pressure management in mitigating cognitive decline.

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