Original Article

Indian Journal of Public Health Research & Development
Volume 13 Issue 3 July-September 2022
DOI: http://dx.doi.org/xxxxx/ijphrd.xxxx.13221.1

Effect of Antihypertensive Drugs Therapy Concognitive Functions and Asymmetric Dimethylarginine (Adma) Levels In Hypertensive Patients

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How to cite this article: Yavatesh Joshi T , Riddhi Gor et al. Effect of Antihypertensive Drugs Therapy Concognitive Functions and Asymmetric Dimethylarginine (Adma) Levels In Hypertensive Patients. Volume 13 Issue 3 July-September 2022

Abstract

The purpose of this study is to evaluate cognitive functions and its association with Asymmetric Dimethylarginine (ADMA) levels in hypertensive patients treated with antihypertensive drugs.

Methods: At least 100 subjects of hypertension were proposed for this study keeping in mind the time constraint and limitation of resources.

Results: Treatment with antihypertensive medications caused change in HMSE score from 24. 51 ± 2.27 at day 1 to 25.64 ± 2.31at four weeks Treatment with antihypertensive medications caused change in ADMA levels from 15519.65 ± 7311.63 ng/L at day 1 to 12314.47 ± 10696.09 ng/L at four weeks.

Conclusion: Treatment with antihypertensive medications caused change in HMSE score from 24. 51 ± 2.27 at day 1 to 25.64 ± 2.31at four weeks

Keywords: hypertension, dimethylarginine, drug therapy, concognitive

Introduction

Hypertension or raised blood pressure (BP) is a major public health problem and has emerged as the most important risk factor for morbidity and mortality globally. Hypertension is one of the well-established risk factor for cardiovascular and cerebrovascular disease and other associated complications. The prevalence of hypertension in urban areas of India is 24 – 30% and 12-14% in rural areas.[1] The rates for hypertension in percentage are projected to increase up to 22.9 and 23.6 for Indian men and women, respectively by the year 2025. Every fourth individual in India aged above 18 years have raised blood pressure.[2]

The available evidence indicates that hypertension may also acts as risk factor for the adverse cognitive outcomes. Several epidemiological studies had shown that hypertension may be associated with a range of adverse cognitive dysfunctions, including cognitive decline, mild cognitive impairment, and dementia. Although, studies suggest impairment of cognitive functions in hypertension however, there is still little consensus about the effectiveness of

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treating hypertension to prevent or slow this cognitive decline associated with raised blood pressure.[3,4] Thus, relationship between raised blood pressure (BP) and cognitive functions is biologically complex and is still not fully understood.

Asymmetric dimethyl arginine (ADMA) is an endogenous molecule and differs from arginine due to addition of two methyl groups. It is formed by the methylation of arginine residues in proteins via protein arginine methyl transferases. ADMA can be used as a marker for detection of endothelial dysfunction caused by oxidative stress. It is an endogenous inhibitor of nitric oxidase synthase (NOS), an essential enzyme for the synthesis of NO. It acts as endogenous competitive inhibitor of nitric oxide synthase (NOS) and physiologically generated during the methylation of protein arginine residues and released during proteolysis.[3] Previous studies have demonstrated that plasma ADMA concentration is increased in patients with hypertension and increased ADMA is correlated with cognitive impairment.[4] However, whether there is a relationship between the change of plasma ADMA levels and cognitive functions in patients treated with antihypertensive drug therapy remains unknown.

Various previous studies suggest that antihypertensive drugs used for control of raised BP can control the cognitive impairment associated with hypertension. While there are also other studies that suggest that antihypertensive drugs are not effective to provide protection from cognitive impairment. Furthermore randomized, controlled clinical trial data available on the efficacy of antihypertensive drug treatment on prevention of dementia are conflicting.[5,6] There are number of small studies available which show the association between ADMA concentrations and cognitive decline in older adults.

Keeping in the mind the association among ADMA, hypertension and cognitive dysfunctions, the present study was undertaken to examine the effect of antihypertensive drugs on cognitive function in hypertensive patients and on the serum levels of ADMA.

Methods

Study Design

Prospective clinical study.

Study Duration

The study wase conducted from November 2019 to October 2021.

Ethical Clearance

Ethical clearance to conduct study was obtained from Institutional Ethics Committee-Human Research (IEC-HR).

Subjects

At least 100 subjects of hypertension were proposed for this study keeping in mind the time constraint and limitation of resources. However, due to pandemic, enrolment of patients was not feasible for long duration of time so due to this situation inclusion of number of participants were reduced to at least 50 and duration of the follow up of study was modified to four weeks after duly permission for completion of work at time.

Inclusion Criteria

1. Newly diagnosed patients of essential hypertension or previously diagnosed patients of essential hypertension who were not taking or on irregular antihypertensive medication.
2. Patients of either sex with age between 30-55 years.
3. Patients willing to give written informed consent.

Exclusion Criteria

1. Patients of secondary hypertension
2. Patients known to have psychological and behavioural disorders or any other CNS disorder that could interfere with the memory and psychomotor functions
3. Patients on any other medications (e.g. sedatives, antipsychotics, antidepressants, antihistaminic) that may affect memory and psychomotor functions
4. Patient with metabolic syndrome, diabetes, dyslipidaemia, , inflammatory disease, liver damage, renal failure, history of coronary artery disease and history of cerebrovascular disease

5. Patient who required antihypertensive drugs (clonidine, methyldopa) that may have central effects.
6. Pregnant and lactating women.

Procedure

Participants

All newly diagnosed patients of essential hypertension or previously diagnosed patients of essential hypertension who were not taking or on irregular antihypertensive medication at time of enrolment and needed antihypertensive therapy, aged between 30 years to 55 years.

Methods: Subjects who fulfilled the inclusion criteria and sign the informed consent were recruited. Before applying HMSE cognitive score for cognitive functions the systolic blood pressure (SBP) and Diastolic blood pressure (DBP) was recorded using digital sphygmomanometer at first day and after four weeks in all the participants. Cognitive functions were assessed using HMSE cognitive score at first day and at four weeks.

Assessment of cognitive functions

Hindi Mental Status Examination (HMSE) cognitive screening test (Annexure 4) was performed to assess the cognitive functions of the participants at day 1 and after 4 weeks of treatment.

Estimations of biochemical parameters

Blood sample from each participant was taken with aseptic precautions for baseline investigations and for estimation of serum ADMA levels at day 1 (baseline) and the last day of 4 weeks of the treatment.

Baseline investigations: A complete clinical examination and investigations i.e., complete hemogram, liver function tests, renal function tests, blood sugar levels, ECG and lipid profile were carried out to rule out any disease referred to in exclusion criteria

Estimation of Asymmetric Dimethylarginine (ADMA) levels

For estimation of serum ADMA levels the samples were centrifuged at 4000 rpm for 10 minutes to remove serum and were stored at -20°C until analysis. Serum ADMA levels were evaluated using commercially available Human Asymmetric Dimethylarginine (ADMA) ELISA kits. Serum ADMA was estimated twice in the study i.e. day 1 and after 4 weeks of treatment.According to the manufacturer, the assay method is as follows:

Results

Subjects Enrolled

In this study total 54 newly diagnosed hypertensive patients or in hypertensive patients on irregular antihypertensive drug treatment were enrolled and followed up for 4 weeks.

Demographic characteristics of participants

A total of 54 patients were enrolled, of which 26 (48.2%) were males, and 28 (51.8%) were females. Mean age of participants was 46.88 ± 8.5 years

Maximum patients belonged to age group of 41-50 years [24 (44.4 %)] followed by 51-55 and 30-40 years [19(35.18%) and 11 (20.37%) respectively]

16 (29.62%) patients were newly diagnosed case of hypertension while 38 (70.37 %) were having previously diagnosed case with irregular treatment history.

20 (37.0%) patients were uneducated.

Class of Antihypertensive drugs prescribed in study subjects

Distribution of participants according to antihypertensive drugs prescribed :

Most commonly prescribed antihypertensive medication was telmisartan in 34 (61.8 %) patients. Enalapril was prescribed in 11(20%) patients while amlodipine was prescribed in 7 (12.7%) patients. Combination of enalapril and amlodipine was prescribed in two (3.63%) patients.

Mean HMSE score at baseline (Day 1) and follow up (4 weeks) in study subjects (n=54):

HMSE score	Day 1	At week 4
Mean ± SD	24.51 ± 2.27	25.64 ± 2.31

Mean HMSE score at day 1 before starting antihypertensive medications in all participants was

24.51 ± 2.27(mean ± SD), and it was 25.64 ± 2.31(mean ± SD), at week 4 after starting antihypertensive drug therapy (Table 3)

Mean ADMA levels (ng/L) at baseline (Day 1) and follow up (4 weeks) in study subjects (n=54):

ADMA (ng/L)	Day 1	At week 4
Mean ± SD	15519.65 ± 7311.63	12314.47 ± 10696.09

Mean ADMA levels (ng/L)at day 1 before starting antihypertensive medications in all participants was 15519.65 ± 7311.63 (mean ± SD), and it was 12314.47 ± 10696.09 (mean ± SD),at week 4 after starting antihypertensive drug therapy.

Mean HMSE score at baseline (Day 1) and follow up (4 weeks) in different group of antihypertensive drugs prescribed:

In telmisartan treated patients, mean serum HMSE score levels at the start of treatment was 24.57 ± 2.29 (mean ± SD), which were 25.97 ± 2.59 (mean ± SD) at four weeks after treatment.

In Enalapril treated patients , mean HMSE score at the start of treatment was 24.54 ± 2.5 (mean ± SD), which was25.91 ± 2.34 (mean ± SD) at four weeks after treatment.

In Amlodipine treated patients, mean HMSE score at the start of treatment was 23.57 ± 1.9 (mean ± SD), which were 25.57 ± 0.97 (mean ± SD) at four weeks after treatment.

Patients prescribed with combination of Enalapril + Amlodipine had mean HMSE scoreat the start of treatment 22.0 ± 1.41 (mean ± SD), which were 24.0 ± 0.0 (mean ± SD) at four weeks after treatment.

Mean ADMA levels (ng/L)at baseline (Day 1) and follow up (4 weeks) in different group of antihypertensive drugs prescribed:

In telmisartan treated patients , mean serum ADMA levels (ng/L) at the start of treatment was 14597.06± 7266.57 ng/L (mean ± SD), which were 10704.97 ± 5680.05 ng/L(mean ± SD) at four weeks after treatment.

In Enalapril treated patients , mean serum ADMA levels (ng/L) at the start of treatment was 14961.45 ± 4849.5ng/L (mean ± SD), which were 16948.82 ± 21275.2 ng/L (mean ± SD) at four weeks after treatment.

In Amlodipine treated patients , mean serum ADMA levels (ng/L) at the start of treatment was 20492.0 ±10.526.1 ng/L (mean ± SD), which were 13390.71 ± 6179.8 ng/L(mean ± SD) at four weeks after treatment.

Patients prescribed with combination of Enalapril + Amlodipine had mean serum ADMA levels (ng/L) at the start of treatment 14016.0 ± 1343.5 ng/L (mean ± SD), which were 9526.5 ± 2568.92 ng/L(mean ± SD) at four weeks after treatment.

Correlation between HMSE score and ADMA levels :

Correlations	HMSE (Day 1)	HMSE (at 4 Week)
ADMA (Day 1)	0.059	0.254
ADMA (at 4 weeks)	-0.085	-0.02

The Pearson correlation between the ADMA premedication was positive but not significant when compared with HMSE on day 1 and week 4. The ADMA levels during post medication were negative but not significant with HMSE on day 1 and week 4.

Discussion

Essential hypertension is considered as a multifactorial disease and various environmental and genetic factors contribute in its aetiology. Despite recent advances in understanding and treating hypertension, the prevalence of hypertension is continuously rising. Approximately 40% of the adult population aged 25 and above are affected with hypertension, worldwide.

Various previous studies suggest that antihypertensive drugs used for control of raised blood pressure can control the cognitive changes associated with hypertension. While there are also other studies that suggest that antihypertensive drugs are not effective to provide protection from cognitive impairment. [7]

Normal anatomical and functional integrity of the vascular endothelium is essential for the prevention of atherosclerosis, hypertension, and other cardiovascular diseases. Nitric oxide (NO) produced in endothelial cells by endothelial NO synthase (eNOS) is an important compound required for the anatomical and functional integrity of the vascular endothelium. eNOS enzyme mediates the conversion of the amino acid arginine into NO and citrulline. [8]

In present study use of Enalapril, an ACE inhibitor caused change of HMSE score from 24.54 ±2.31 to 25.91 ±2.34 Ohruit et al in their study showed that ACE inhibitor caused improvement in MMSE scores suggesting that central ACEIs may benefit cognitive function in patients with hypertension.115 In another study Yamada K *et al* showed that different types of ACE inhibitors have varying effects on cognitive impairment. [9] However studies also show contradictory results where, ACE inhibitors did not affect cognitive functions or accelerated the development of dementia.

In this study, angiotensin receptor antagonists, telmisartan also cause change in mean HMSE score form 24.57 ±2.29 to 25.97 ±2.59 Study shows that administration of losartan in elderly hypertensive patients affected memory function both the immediate as well as delayed one. Thus, angiotensin receptor antagonists can not only act as antihypertensive but also on impaired cognitive function. Also in animal models of learning and memory, drugs acting by inhibition of RAAS pathway, especially ACE inhibitors and angiotensin receptor antagonists have been demonstrated to have potential nootropic effects.[9]

One of the objectives of our study was to correlate the levels of ADMA level with cognitive dysfunction in hypertensive patients. In our study, we found insignificant correlation between HMSE score and ADMA level. Although there are studies showing correlation of MMSE scores with biomarkers but there is no study available correlating ADMA levels with HMSE score following treatment with antihypertensive medications.

Conclusions

In conclusion, the results of this study suggest

- Treatment with antihypertensive medications caused change in HMSE score from 24. 51 ± 2.27 at day 1 to 25.64 ± 2.31at four weeks
- Treatment with antihypertensive medications caused change in ADMA levels from 15519.65 ± 7311.63 ng/L at day 1 to 12314.47 ± 10696.09 ng/L at four weeks
- Mean HMSE cognitive score with telmisartan, amlodipine andenalapril class of antihypertensive medications were 24.57 ± 2.29, 23.57 ± 1.9, 24.54 ± 2.5 respectively at day 1 and 25.97 ± 2.59, 25.57 ± 0.97, 25.91 ± 2.34, respectively at four weeks.
- Mean ADMA levels with telmisartan, amlodipine andenalapril class of antihypertensive medications were 14597.06± 7266.57 ng/L , 20492.0 ±10.526.1 ng/L , 14961.45 ± 4849.5 ng/L respectively at day 1 and 10704.97 ± 5680.05 ng/L, 13390.71 ± 6179.8 ng/L, 16948.82 ± 21275.2ng/L, respectively at four weeks.

Ethical clearance- Taken from ethical committee of institution

Source of funding - Self

Conflict of Interest – Nil

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