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A CROSS-SECTIONAL STUDY ON THE EFFECT OF ANTI- HYPERTENSIVE DRUGS ON THE ARTERIAL STIFFNESS AMONG HYPERTENSIVE PATIENTS

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ABSTRACT
This study was conducted to assess the effect of various anti-hypertensive drugs on the arterial stiffness in hypertensive patients and to compare the effect of various anti-hypertensive drugs. Secondary objective was to assess the correlation between smoking, alcoholism, waist hip ratio, duration of hypertension and MAP with C-F PWV. Methodology-the study was a prospective cross-sectional multi-arm parallel-group observational study was conducted over a period of 6 months. Subjects were divided into 2 groups; Group one included hypertensive patients on regular treatment and group 2 had age-matched healthy controls with normal blood pressure. Results- The PWV, ASI, and pulse pressure vascular parameter were statistically higher in hypertensive patients than in controls. Different treatment groups were categorized based on the various anti- hypertensive therapies which were given to the study population and a comparison was done and there was no statistical significance between these groups concluding that arterial stiffness was equally high in both these sub-groups. The correlations were done between parameters like age group, smoking, alcoholism, duration of hypertension, waist-hip ratio and mean arterial pressure (MAP) with C-F PWV, and all the correlations were found to be statistically significant. Conclusion- Regardless of treatment status, non-diabetic chronic hypertensives subjects have higher PWV, ASI, and pulse pressure than controls.

KEYWORDS: Hypertension, Arterial stiffness, Cardiovascular diseases, Anti-hypertensive.

INTRODUCTION
Hypertension refers to persistently raised blood pressure in the blood vessels. A person with systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg is diagnosed as having hypertension according to the new ACC and American Heart Association (AHA) guidelines.[1]

Epidemiology
Hypertension contributes to nearly 7.1 million premature deaths, two-thirds of all strokes and half of myocardial infarction every year. The worldwide prevalence of hypertension in 2000 was 26.4% including approximately a quarter of the adult population and it is estimated to rise ʊ 29.2% by 2025. The overall average prevalence of hypertension in the world was estimated as 35% (37% in men and 31% in women.[2]

Hypertension and Cardiovascular risk
Among all risk factors for cardiovascular disease, hypertension is the strongest. All cardiovascular diseases are at risk of being acquired through hypertension, including coronary disease, cerebral stroke, left ventricular hypertrophy, cardiac arrhythmias, valvular heart diseases, and renal failure. In addition to the occurrence of end-organ damage, the uncontrolled rise in arterial pressure has been found to be associated with progressive increase in the risk of cardiovascular events. Major modifiable risk factors for cardiovascular disease include high blood pressure (BP), smoking, diabetes, and abnormal cholesterol levels (CVD). Among these, high BP is associated with the strongest evidence for causation and has a high prevalence of exposure.[3]

Arterial stiffness
Arterial stiffness explains the elasticity of the arterial wall. Vascular smooth muscle tone, elastin and collagen, as well as transmural distending pressure, determine

arterial stiffness. A major contributor to arteriosclerosis is inflammation, which also contributes to stiffening of the large arteries. The AS has been found to play a role in both the pathogenesis and prognosis of hypertension, with increased blood pressure being an important cardiovascular risk factor causing arterial wall damage.[4]

Pulse wave velocity

The pressure pulse generated by ventricular ejection is propagated along the arterial tree at a speed determined by the geometric and elastic properties of the arterial wall which constitutes the basic principle of PWV measurement. PWV is determined from measurement of the distance travelled by the pulse between two recording sites and the pulse transit time, according to the following formula: PWV (m/sec) = distance (m)/transit time (sec).[5] Aortic PWV has been demonstrated to be forceful marker and predictor of cardiovascular risk in both normotensive and hypertensive patients. It is closely correlated with the presence and extent of atherosclerosis.[6]

Correlation between PWV and Arterial stiffness

There is a positive linear correlation between PWV and arterial blood pressure or age. Higher PWV and stiffness index were observed in patients with borderline, white-coat or sustained hypertension than in age-matched normotensive individuals. Elevated PWV and increased arterial stiffness are not only related to the stretching effect of elevated blood pressure but also to early changes and abnormalities in the arterial wall in hypertension.[7]

Anti-hypertensive drugs

In addition to treating hypertension, antihypertensive drugs also reduce cardiovascular risks. The arterial stiffness must be measured to determine its efficacy.

The Anti-hypertensive drugs include Calcium channel blockers (amlodipine), Angiotensin-converting enzyme inhibitor (enalapril), Angiotensin-2 receptor blockers (telmisartan), and Beta-blockers (metoprolol).

MATERIALS AND METHODS

A prospective cross-sectional multi-arm parallel-group observational study was conducted over a period of 6 months in the Department of Pharmacology of ESIC medical and super specialty hospital, Sanathnagar.500 subjects were screened on the basis of inclusion and exclusion criteria. Subjects were divided into 2 groups; Group one included hypertensive patients on regular treatment (250 subjects) and group 2 had age-matched healthy controls with normal blood pressure (250 subjects). Only hypertensive patients on anti-hypertensive drugs for 1 year or more were taken in the study. The hypertensive subjects with other co-morbid conditions such as renal disease and diabetes were excluded from the study. The subjects were interviewed and explained the purpose of the study. All subjects gave written informed consent. Confidentiality of the data has been assured to the subjects.

A questionnaire was used to obtain the patient's medical information data such as medical and medication history, and social history. To start the periscope test- the patient was allowed to relax for 5-10 mins before starting the test. Four Blood pressure Cuffs and ECG electrodes are connected to the patient. All the 4 cuffs inflate and starts recording the test. After the end of the test, the results will be displayed on the computer screen. The result shows Cardiovascular Risk Analysis (CVRA) which gives an interpretation of the whole test.

Statistical methods

The effect of anti-hypertensives on arterial stiffness was estimated after compilation and analysis of data. The categorical data between the groups was compared using chi square test. The PWV, ASI and pulse pressure was compared by using one way analysis of variance (ANOVA) with post hoc analysis or Kruskal Wallis test whichever was appropriate. The data related to vascular parameters of the study (PWV, ASI and pulse pressure) will be presented as mean ± standard deviation (SD). All categorical data (gender, smoking etc.) were presented as percentages. Correlation parameters like age group, smoking, alcoholism, duration of hypertension, waist hip ratio and mean arterial pressure (MAP) with C-F PWV among the subjects were done using Spearman rank correlation. Statistical analysis was carried out at 5% level of significance and P value < 0.05 was considered significant.

RESULTS

Table 1: Blood pressure wise distribution.

Blood pressure	Cases	
Stages	**Subjects**	**Percentage %**
Normal	2	9.2
Elevated	32	12.8
Stage 1	60	24
Stage 2	121	48.4
Hypertensive crisis	09	3.6

Table 2: Prescription wise distribution of antihypertensive drugs in study population.

Drugs	No. of subjects	Percentage %
Amlodipine	71	28.4
Telmisartan	65	26
Metoprolol	18	7.2
Telmisartan –amlodipine combination therapy	54	21.6
Telmisartan-hydrochlorothiazide combinationtherapy	34	13.6
Telmisartan -amlodipine-hydrochlorothiazidecombination therapy	07	2.8

Table 3: Therapy wise distribution of antihypertensive drugs in the study population.

Therapy	No. of subjects	Percentage %
Monotherapy	154	61.6%
Dual therapy	88	35.2%
Triple therapy	07	2.8%

Table 4: Demographic and Other characteristics of study subjects.

Characteristic	Case (n=250)	Control (n=250)
Age (years)	49.42± 10.70	35.94± 11.23
Gender male Female	125(50%) 125(50%)	115(46%) 135(54%)
Bmi (kg/m2)	27.95± 5.346	25.90± 5.089
Waist circumference(cm)	M= 100.62± 9.63 W= 99.938± 11.35	M= 95.183±10.272 W= 92.05±11.51
Hip circumference(cm)	107.53±11.14	102.68±12.79
Waist hip ratio male female	0.963 ± 0.072 0.907 ± 0.085	0.918 ± 0.049 0.900 ± 0.062
Smokers male female	56(44.8%) 0(0%)	44(38.2%) 0(0%)
Alcoholics male female	36(28.8%) 0(0%)	56(48.6%) 0(0%)
Mean arterial pressure(mmhg)	105.13 ± 13.68	91.021 ± 10.20
Mean duration (years)	2.44 ± 1.11	-
Sbp (mmhg)	139.18 ± 19.89	118.54 ± 13.28
Dbp (mmhg)	88.11 ± 12.04	77.26 ± 9.20

Inference

- Other characteristics are presented as mean ± SD.
- ANOVA was used for the comparison of data among the groups.

Table 5: Parameters of PWV, ASI and pulse pressure among Hypertensive and Control groups.

Parameters	Case	Control	P- value
Carotid femoral pwv (cm/s)	1327.9±433.4	816.9±478.5	0.0001
Left brachial pwv (cm/s)	922.3±598.8	1278.5±652.9	0.0001
Right brachial pwv (cm/s)	1803.6±611.1	1195.2±307.7	0.0001
Left brachial asi (mmhg)	30.90±12.48	23.34±7.29	0.0001
Right brachial asi (mmhg)	32.06±12.33	23.85±8.38	0.0001
Left ankle asi (mmhg)	44.53±12.72	33.85±10.30	0.0001
Right ankle asi (mmhg)	43.02±13.19	33.12±9.28	0.0001
Pulse pressure (mmhg)	50.82±13.21	41.25±7.34	0.0001
Right abi	1.04±0.09	1.45±6.70	0.0001
Left abi	1.04±0.07	1.02±0.08	0.008

Inference

- Data are presented as mean ± SD; Kruskal Wallis test was used for comparison of thedata.
- All the parameters are statistically significant as p value is <0.05 except the RightABI parameter.

Table 6: Comparison of vascular parameters between the patients receiving various Monotherapies and Polytherapies.

Parameters	Amlodipine monotherapy	Telmisartan monotherapy	Metoprolol monotherapy	Telmisartan + Amlodipine dual therapy	Telmisartan + Hydrochlorothiazide dual therapy	Telmisartan + Hydrochlorothiazide + Amlodipine triple therapy
Carotid femoral PWV (cm/s)	1289.40± 458.99	1348.74± 464.33	1317.27± 309.07	1336.97± 430.90	1373.35± 391.63	1260.07± 323.82
Left brachial PWV (cm/s)	1857.00± 676.13	1966.52± 656.59	1823.85± 347.24	1908.41± 491.57	2070.96± 606.38	1813.61± 410.33
Right brachial PWV (cm/s)	1761.34± 681.44	1839.89± 637.83	1861.11± 455.31	1823.26± 622.49	1761.29± 509.41	1799.17± 424.26
Left brachial ASI (mmHg)	30.78± 11.72	31.58± 14.37	29.03± 10.98	33.63± 13.20	27.27± 9.69	26.82± 7.45
Right brachial ASI (mmHg)	30.16± 12.68	34.32± 13.83	29.87± 11.73	34.01± 11.18	29.60± 10.12	32.80± 11.42
Left Ankle ASI (mmHg)	43.79± 12.76	45.22± 13.56	46.70± 11.02	47.47± 12.78	39.56± 11.43	41.20± 7.84
Right Ankle ASI (mmHg)	43.10± 13.00	44.16± 12.19	41.69± 12.50	46.01± 15.26	36.74± 11.51	41.98± 8.69
Pulse Pressure (mmHg)	50.11± 14.98	53.18± 13.23	48.53± 13.76	51.74± 11.81	48.23± 11.33	47.42± 11.17
Right ABI	1.04± 0.12	1.05± 0.08	1.05± 0.06	1.05± 0.08	1.04± 0.07	1.05± 0.09
Left ABI	1.04± 0.07	1.03± 0.07	1.04± 0.08	1.04± 0.07	1.03± 0.07	1.04± 0.11

Inference

- PWV: pulse wave velocity; ASI: arterial stiffness index; ABI: Ankle brachial index;data are presented as mean ± SD and Mann Whitney test was used for comparison.
- There was no statistical significance between these groups inferring that arterial stiffness was equally high in all these sub-groups which was in accordance withprevious study.

Table 7: Correlation between various parameters and c-f pwv.

Parameters	Case Carotid femoral pwv (r value)	P- value	Control Carotid femoral pwv (r value)	P- value
Age groups	0.495	0.0001	0.498	0.0001
Waist hipratio	0.043	0.001	0.145	0.002
Smokers	0.049	0.001	0.343	0.0001
Alcoholics	0.167	0.008	0.214	0.001
Duration ofhtn	0.173	0.006	_	_
Map	0.426	0.0001	0.448	0.0001

Inference

- The above table depicts the Correlation between parameters like age group, smoking, alcoholism, duration of hypertension, waist hip ratio and mean arterial pressure (MAP) with C-F PWV. All the correlations were found to be statistically significant and showed positiveassociation.

DISCUSSION

One of the main causes of morbidity and mortality in the Indian population is now recognized to be cardiovascular diseases. Hypertension, diabetes mellitus, smoking, hypercholesterolemia, and a family history of coronary artery disease are the main risk factors for cardiovascular diseases. The strongest or one of the strongest risk factors for all cardiovascular illnesses among the many risk factors is hypertension.[8]

Out of 250 subjects, 50% were male and 50% were female from the sample population and in 250 control subjects, 46% were male and 54% were female. The majority of subjects were found in the overweight category of BMI whereas least no. of subjects was found in the obese class III category in sample population. Whereas in the control population, most no. of subjects was found in the normal range BMI and the least no. of

subjects were found in the obese class III category, according to the latest WHO BMI classification. It was found that most subjects were at risk of cardiovascular diseases (84.8% in the case group and 82.4% in the control group) according to the latest WHO classification on waist-hip ratio.

We also found that in the sample population, 44.8% of males were smokers and 55.2% were non-smokers whereas, 100% of the female population were non-smokers. In the control population 34.2% of males were smokers and 61.2% were non-smokers whereas 100% of the females were non-smokers. in the study population 28.8% of males were alcoholic and 71.2% were non-alcoholic in comparison with, female population, where 100% were non- alcoholic. In the control population, 48.6% of males were alcoholic and 51.4% were non-alcoholic on the other hand, 100% of the female population were non-alcoholic.

In our study, hypertensive subjects compared to controls, the vascular measures PWV, ASI, and pulse pressure were all considerably higher. These findings were in accordance with a previous study done by Kola, s et al., titled "Assessment of Arterial Stiffness Index in Hypertensive Patients in Relation to Their Treatment Status Attending a Tertiary Care Center in South India". When compared the therapy of Anti-hypertensive drug in study population, the most of the hypertensive patients were given monotherapy such as (Telmisartan (40mg), Amlodipine (5mg) and Metoprolol over dual therapy and triple therapy. New studies confirm that carotid femoral pulse wave velocity as the gold standard for noninvasive assessment of aortic stiffness.

Different treatment groups were categorized based on the various anti-hypertensive therapy which was given to the study population and comparison was done between Amlodipine monotherapy, Telmisartan monotherapy, Metoprolol monotherapy, Telmisartan + Amlodipine dual therapy, Telmisartan + Hydrochlorothiazide dual therapy, Telmisartan + Hydrochlorothiazide + Amlodipine triple therapy. There was no statistical significance between these groups inferring that arterial stiffness was equally high in both these sub-groups.In our study, we have also considered BMI, waist circumference, hip circumference, waist hip ratio, smoking, alcoholics and mean arterial pressure. Correlation was done between parameters like age group, smoking, alcoholism, duration of hypertension, waist hip ratio and mean arterial pressure (MAP) with C-F PWV. All the correlations were found to be statistically significant.

Both acute and chronic arterial stiffness may also be influenced by body mass index (BMI). Alcohol and smoking both have a negative impact on vascular stiffness. Hypertensives shows increased arterial stiffness, which underlines the significance of early diagnosis of blood pressure and arterial stiffness in addition to effective blood pressure control. For the time being, there are no recommendations for the use of certain medications to combat and reduce arterial stiffness. However, there is proof that achieving proper blood pressure control is a necessary initial step in treating arterial stiffness.

Recommendation

In order to establish guidelines for the use of medications that target arterial stiffness and the value of these parameters in the long-term prognosis of hypertension, larger studies are required to determine the normal reference values of vascular parameters of arterial stiffness in the Indian population.

CONCLUSION

Regardless of treatment status, hypertensives patients have higher PWV, ASI, and pulse pressure than controls. This study supplements the requisite for establishing rational guidelines for the use of medications that target arterial stiffness and the value of these parameters in the long-term prognosis of hypertension, larger studies are required to determine the normal reference values of vascular parameters of arterial stiffness in the Indian population.

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