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Original article

Effect of add on L-arginine on Mean arterial pressure in hypertensive patients on antihypertensive treatment

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Abstract:

Aim: Aim of our study was to find the effects of oral L-Arginine on Mean arterial pressure as an add on therapy in hypertensive patients on antihypertensive drugs**.**

Materials & Methods: This was a Randomized clinical trial, registered in Clinical Trial Registry of India (CTRI) Registration number: CTRI/2019/03/018026. All patients with hypertension visiting the Medicine Out-Patient Department (OPD) of Dr.Vitthalrao Vikhe Patil Pravara Rural Hospital, Loni, of age between 18-60 years and either gender, were included in the study. Patients on any drug that may affect nitric oxide synthesis or on any other chronic medications other than antihypertensives were excluded from the study. Total 149 hypertensive patients participated in the study and were randomized into Intervention group (I) and Control group (C) of which 74 were in I Group and 75 in C Group. The participants in the I group received standard antihypertensive therapy along with add on L-arginine oral supplementation for 14 days. The participants in the C group received only standard antihypertensive therapy and had followed up similar to that of the participants of I group.

Results: The Baseline Mean arterial pressure of I group and C group was statistically non-significant as analyzed by unpaired t-test, whereas in I group there was significant decrease in MAP on 1st,2nd and 3rd follow up visits compared to C group (Unpaired t-test).

Conclusion: The findings of the present study showed that add on L-arginine supplementation at a dose of 3g/d (Gyargin 5gm sachet) for 2 weeks in patients of hypertension resulted in significant decrease in the Mean arterial pressure.

Keywords: Mean arterial pressure, Hypertension, L-arginine, Nitric oxide.

INTRODUCTION

The leading cause of global mortality is cardiovascular disease with approximately 17.9 million deaths attributed to the disease in 2016 (31% of global deaths)[1]. An estimated 57% and 24% of stroke and coronary artery disease related deaths are caused by hypertension. Hypertension is associated with heart failure, stroke, chronic kidney disease and ischemic heart disease[2-3]. It is found that hypertension is the number one health related risk factor in India, with the largest contribution to burden of disease and mortality[4]. Increase resistance in the arteries leads to increase in blood pressure, so if there is reduction in arterial pressure, blood pressure also reduces. Mean Arterial pressure(MAP) is an average blood pressure in a person during a single cardiac cycle.[5] It is altered by systemic vascular resistance and cardiac output[6]. The radius of blood vessel is the prominent variable in determining systemic vascular resistance. The radius of blood vessel is influenced by both autonomic nervous system and local mediators. Endothelial cells produces either constriction or dilatation of blood vessels depending on body's needs in response to vasoactive substance[7].When

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there is rise in MAP, shearing forces on the walls of blood vessel induces nitric oxide (NO) synthesis in endothelial cells. In vascular endothelial cells NO is produced from a substrate - the amino acid L-arginine[8].NO diffuses into underlying vascular smooth muscle cells which activates guanylyl cyclase and causes dephosphorylation of GTP to cGMP. The cGMP acts as a second messenger which in turn causes relaxation of smooth muscle and vasodilation. Other locally produced vasodilating compounds are prostaglandins and bradykinin cause vascular smooth muscle relaxation by same mechanism[9]. Arginine is obtained exogenously from soybeans, lentils, fish, meat whole grain and nuts[10].It is produced in body in kidney and in liver via urea cycle and is also recovered from protein breakdown[11]. Arginine/NO pathway is a physiological mechanism of vasodilation in endothelial cells that impacts on the peripheral vascular resistance and thus can reduce the BP[12].Nolan Gokce demonstrated that nitric oxide is an important modulator for smooth muscle and it was confirm that the unavailability of the regulator or its synthetic enzyme nitric oxide synthase result a rise in arterial blood pressure. In multiple studies, it was found that inadequate production of the nitric oxide by the endothelium leads to endothelial dysfunction, which in turn causes hypertension [13]. Present study was designed to determine the effect of 3gm/day of L-Arginine supplement on MAP in hypertensive patients on antihypertensive therapy.

MATERIALS AND METHODS

This was a Randomized clinical trial conducted in Dr. Vitthalrao Vikhe Patil Pravara Rural Hospital (Dr.VVPPRH) Loni. All the known cases of hypertension coming to the department of General Medicine and Family Medicine of Dr.VVPPRH, Loni were enrolled for the study.

Ethical Consideration

The study was started after ethical approval from Institutional Ethics Committe. Registration Number: PIMS/DR/Phd/2018/94 Registration date: 21/1/2019 and was registered with Clinical Trial Registry of India (CTRI) Registration number: CTRI/2019/03/018026. Before starting the trial written informed consent of the participants, was taken.

Inclusion Criteria

All the hypertensive patient taking antihypertensive drugs, between the age group of 18 and 60 years, either gender, and patients ready to give written informed consent and willing to participate in the trial were included in the study

Exclusion Criteria

Patients on any drug that may affect nitric oxide synthesis or on any other chronic medications other than antihypertensives were excluded from the study. Patients with a history of recurrent herpes, patients suffering from gestational hypertension, diabetes mellitus, renal failure, transient ischemic attack, ischemic heart disease, peripheral arterial disease or stroke were excluded from the study.

Study Procedure

All the enrolled hypertensive participants were subjected to eligibility criteria. All patients satisfying the eligibility criteria were allocated randomly to I group and C group by lottery method. Total 180 patients were enrolled for the study from which 149 patients participated till the end of the study that is 74 in I Group and 75 in C Group and 31patients dropped out of the study (16 from I group and 15 from C group)

The participants in the Intervention group received add on L-arginine oral supplementation in a dose of 3g/day once daily for 14 days along with antihypertensive therapy**.** (L-arginine was available in a sachet of 5 g in which 3 g was active ingredient and 2 g was excipient). L-Arginine sachet used for the study were manufactured by Acme Life Tech-LLP (Jharmajri, Baddi, Dist. Solon, HP). Participants in I group received one sachet of L-arginine every day for 14 days and were given instructions to dissolve the whole content of sachet in half a glass of water (approx.100ml) and then need to be consumed by oral route. The participants were assessed by investigator at four times points interval: At the baseline (0 day), first follow up (7^{th} day), second follow up (14^{th} day) & third follow up (21^{st} day). Participants in the intervention group received L-arginine only for first 14 days and didn't receive from day 15 to day 21.

The participants in the C group received only standard antihypertensive therapy and had follow up similar to that of the participants of I group. During each follow up, from baseline to 3^{rd} follow up, blood

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Pressure recording was done using "DIAMOND MAKE" calibrated Sphygmomanometer. The mean arterial pressure (MAP) of the patients in both the group were assessed by using the values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the basis of suggested formulas:[14]

MAP = (SBP + 2 DBP) /3

Statistical analysis

The data were statistically analyzed by Statistical Package for Social Sciences Software using Friedman test, unpaired t- test and "Z" test of significance.

RESULTS

Table: 01 Comparison of baseline characteristics (mean ± SD) between I group and C group

Variables	Age (Years)	Gender		Weight (Kg)	Duration of hypertension in months
		Male	Female		
I group (n-74)	48.87 ±7.69	44	30	68.31±10.58	31.13 ± 14.82
C Group (n=75)	50.97±7.45	42	33	67.40±11.01	28.84 ± 14.25
P value	0.096*	0.67#		0.607*	0.337*
*Unpaird t-test, # Chi-square test					

Table:01 shows the comparison of baseline characteristics between I group and C Group. At the baseline there were no significant difference between age, gender, weight of participants and duration of hypertension between two groups.

Table:2 Comparison of MAP in Intervention Group & Control group at follow up visits

MAP (mmHg)	Baseline		1st F/up		2nd F/up		3rd F/up	
	Intervention Group	Control Group	Intervention Group	Control Group	Intervention Group	Control Group	Intervention Group	Control Group
Mean ± SD	115.68± 10.82	114.25± 10.66	106.72± 9.38	114.44± 9.82	104.59± 8.86	113.77± 9.02	108.14± 9.21	114.42± 9.16
Median	113.00	114.00	105.00	113.00	103.00	113.00	106.50	114.00
P-value Unpaired t-Test	P:0.416 Non-Significant		P < 0.0001 Significant		P < 0.0001 Significant		P < 0.0001 Significant	

Table:2 shows comparison of MAP between I Group & C Group from baseline to every 7 days follow-up of visit-1, visit-2, visit-3. The MAP in both the groups was comparable at baseline with no statistically significant difference observed (p-value=0.416) whereas, on first, second & third follow-up visit, I Group has shown statistically significant decrease in MAP as compared to C Group (p-value < 0.0001) as analyzed by unpaired t test & 'Z' test of significance.

Table:03 Within the group comparison of MAP in Intervention Group at follow up visits

Variable	Baseline	1st F/up	2nd F/up	3rd F/up
Mean±SD (mmhg)	115.68 ±10.82	106.72 ±9.38**	104.59 ±8.86**,$	108.14±9.12**,##,^^
Median	113.00	105.00	103.00	106.50
Friedman Test (Non-parametric Repeated Measures ANOVA) P<0.0001 Extremely Significant **P<0.001 vs Baseline, $P<0.0001 vs 1st F/up, ##P<0.05 vs 1nd F/up, ^^P<0.001 vs 2nd F/up (Dunn's Multiple Comparisons Test)				

Table:04 Within the group comparison of MAP in Control group at follow up visits

Variable	Baseline	1st F/up	2nd F/up	3rd F/up
Mean±SD (mmhg)	114.25 ±10.66	114.44 ±9.82	113.77±9.02	114.42±9.16
Median	114.00	113.00	113.00	114.00
Friedman Test (Non-parametric Repeated Measures ANOVA) P:0.2601 Non-Significant MAP: Mean Arterial pressure, SD: Standard deviation, F/up: Follow up				

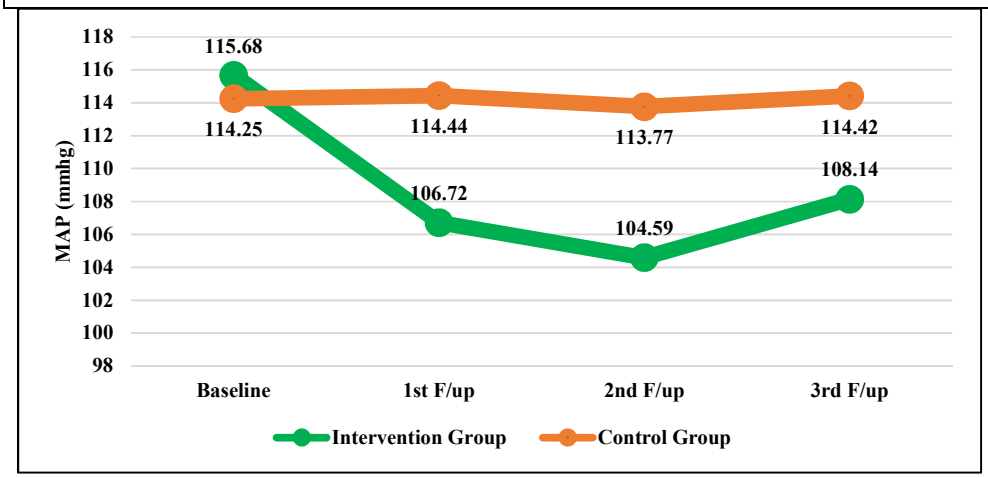

Figure 01: MAP of Intervention Group & Control Group at follow up visits

Within the group comparison of MAP in I Group showed that there was statistically significant decrease in MAP on follow-up of visit-1, visit-2, visit-3 as compared to baseline (Friedman test) Table:03 and Figure:02. Whereas, within the group comparison of MAP in C Group was found to be non-significant on followup of visit-1, visit-2, visit-3 as compared to baseline (Friedman test) Table:04 and Figure:01.

DISCUSSION

MAP provide information about both the systolic and diastolic blood pressure. So, it can be used in the management of hypertension to evaluated to ensure weather perfusion is maintained to the organs[15].Improper regulation of MAP can have important pathophysiological consequences. Raised MAP lead to increased oxygen demand by the heart, end organ damage, cardiac remodeling, vascular injury and stroke. On the other hand, low MAP can cause inadequate blood flow to organs, shock and syncope[16]. MAP is normally between 65 and 110 mmHg[17].

L-arginine serves as the principal substrate for vascular NO production. Reduction in nitric oxide

activity and endothelial dysfunction are involved in hypertension. Lack of availability or deficiency of arginine and changes in arginine metabolism have the potential to contribute to endothelial dysfunction and increased blood pressure[18].In the present study, at baseline visit both the groups are comparable with respect to age, gender, weight and duration of hypertension. The percentage of male patients suffering from hypertension was more than the females in our study. Amongst the 149 participants, 86 (58%) were male and 63 (42%) were female respectively. (Table:01) The mean age in our study was 49.92 ± 7.63 Yrs. This is in accordance with studies done by Asadi S, et al.[19] D. Bahrami et.al studies[20]. Maximum age in our study was 60 years, while minimum age in our study was 30 years. In Intervention Group it was 48.87 ± 7.69 Yrs. and in Control group the mean age was 50.97±7.45Yrs. (Table:01). In our study the mean duration of hypertension was 31.13 months(2.7yrs) in Intervention and in control group it was 28.84 months(2.4yrs) and it was found to be statistically non-significant as analyzed by unpaired t-test. (Table:01).

In our study we found that add on L-arginine supplementation at a dose of 3g/d (Gyargin 5 gm sachet) for 2 weeks in patients of hypertension resulted in significant decrease in Mean arterial pressure in I group compared to C group. The average reduction of MAP in Intervention group was 11 mm of Hg.

The MAP is a major determining factor of tissue perfusion regardless of the pulse pressure & influences properties of the vessel and heart function. Increased in level of MAP is linked with organ damage and cardiovascular disease[21]. The reduction of Mean arterial pressure in our study was in accordance with study done by D. Bahrami et.al[20] in their study L-Arginine supplementation was given in a dose of 5g/day for three months which resulted in significant reduction in mean arterial pressure (p:0.008).Also in a study done by Li H et al[22] after administration of L-arginine supplementation in a dose of 9 g/day for 2 weeks found significant reduction in systolic, diastolic and mean arterial pressure.

LIMITATIONS OF STUDY

In the present study we have administered L-arginine supplementation for a short duration of time that is for 2 weeks and in a dose of 3g/day in I group. In future, studies with higher doses and longer duration of L-arginine supplementation may be warranted. Furthermore, we have not studied L-arginine blood levels in patients of hypertension. In future, studies with L-arginine blood level estimation may give deeper insight about role of L-arginine on mean arterial pressure in hypertensive patients.

CONCLUSION:

Our finding indicates that L-Arginine in the dose of 3g/d for 2 weeks in patients of hypertension led to a significant decrease in MAP. So, this supplement may be used as an adjuvant to the existing treatment of hypertension. However, clinical trials with larger samples and longer duration are needed to know the long-term significance of L-Arginine supplementation in hypertensive patients.

SPONSORED BY:

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