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Original article

Study of effect of add on L-Arginine therapy on working capacity and Fatigability in hypertensive patients in tertiary care center of rural hospital

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Abstract:

Background: Hypertension is the third most important risk factor for attributable burden of disease. The aim of present study was to examine the effects of oral L-arginine supplementation on working capacity and fatigability as add on to standard antihypertensive therapy as L-arginine may increase blood flow to myocardium and skeletal muscle

Materials & Methods: This was a Randomized, open labeled clinical trial conducted in all patients with hypertension visiting the Medicine Out-Patient Department (OPD) of Pravara Rural Hospital, Loni. 149 hypertensive patients were enrolled in study after satisfying inclusion and exclusion criteria and randomized in Intervention Group (n=74) and Control Group (n=75). The participants in the Intervention group received antihypertensive therapy along with add on L arginine oral supplementation for 14 days. The participants in the Control group received only standard antihypertensive therapy and had followed up similar to that of the participants of Intervention group. The questionnaire was prepared to observe the effect of L-arginine on working capacity and Fatigability and responses of participants from both groups were recorded in pre-structured proforma

Results: In our study we found that add on L-arginine supplementation at a dose of 3g/d (L-arginine 5gm sachet) for 2 weeks in patients of hypertension resulted significant improvement in working capacity and significant reduction in fatigability in intervention group on first, second and third follow-up visits compared to control group.

Conclusion: L-Arginine supplementation may be considered for short period as add on with standard antihypertensive therapy in patients of hypertension.

Keywords: Fatigability, Hypertensive patients, L-arginine, Nitric oxide, working capacity,

Introduction

Hypertension is state of elevated systolic and/or diastolic blood pressure & is diagnosed when persons systolic BP is ≥140 mm of Hg and Diastolic BP ≥ 90 mm of Hg following repeated examination.[1]Hypertension is the third most important risk factor for attributable burden of disease in south Asia (2010)[2].

The WHO rates hypertension as one of the most important causes of premature death worldwide[3]. HTN is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease (CHD) deaths in India[4] . Review of epidemiological studies suggests that the prevalence of hypertension has increased in both urban and rural subjects and presently is 25% in urban adults and 10-15% among rural adults[5].

Endothelial dysfunction and decreased nitric oxide (NO) bioactivity represent prominent pathophysiological abnormalities associated with hypertensive cardiovascular disease.[6] The endothelium plays an important role in the maintenance of vascular tone and structure. One endothelium-derived vasoactive mediator with major importance is nitric oxide (NO), which is formed from the amino acid precursor L-arginine by the enzyme endothelial nitric oxide synthase (eNOS).[7]Arginine is a semiessential amino acid involved in several metabolic pathways and the production of a number of biologically active compounds[8].Specifically, arginine contributes to the removal of excess ammonia from the body and the synthesis of muscle protein, other amino acids, and creatine.[9],[10],[11],[12]Perhaps of most physiological significance, arginine is the precursor of nitric oxide (NO) and thus plays an important role in endothelium-dependent vasodilation.[9,11,13]Therefore, one of the proposed benefits of arginine supplementation is increased blood flow to the myocardium and skeletal muscle.[8,9,10] The majority of studies that have examined the effects of arginine on measures of exercise capacity, cardiac performance, and hemodynamics have used subjects with cardiovascular.[14,15,16,17,18]or pulmonary diseases[19,20].In general, these investigations have reported improvements in time to exhaustion, exercise tolerance, endothelial function, and blood flow.[14]

In particular, previous studies have demonstrated that arginine supplementation in a dose of 5.2–6.0 g/day improved performance related variables such as upper body strength [10], resistance to fatigue during repeated isokinetic muscle actions[21], and the anaerobic threshold [22], and peak [10]and mean power [23] during cycle ergometry. Though the findings of these previous studies have indicated that arginine supplementation can improve vascular function and exercise capacity in clinical populations, still we need to do larger and longer-term studies to confirm that L-arginine supplements can improve working capacity and reduce fatigability in hypertensive patients already on standard antihypertensive therapy. Thus, the aim of present study was to examine the effects of oral L-arginine supplementation on working capacity and fatigability as add on to standard antihypertensive therapy.

Methodology

This was a Randomized clinical trial conducted in department of pharmacology in collaboration with Department of General Medicine and Family Medicine. The study was started after the registration with Clinical Trial Registry of India (CTRI) Registration number CTRI/2019/03/018026 and

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ethical approval from Institutional Ethics Committee Registration Number: PIMS/DR/Phd/2018/94 Registration date: 21/1/2019. This study was completed as a part of Ph.D in our Institute. All patients with hypertension visiting the Medicine Out-Patient Department (OPD) of Pravara Rural Hospital, Loni, of age between 18-60 years and either gender, willing to give written informed consent 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.

All patients satisfying the eligibility criteria were allocated randomly to Group - I (Intervention) and Group -II (Control) by lottery method. Total 180 patients were enrolled for the study. At the end of the study, 31patients (16 from Intervention and 15 from control group) dropped out of the study and finally 149 patients completed the study i.e. 74 in Intervention Group and 75 in Control Group.

The participants in the Intervention group received antihypertensive therapy along with add on L arginine oral supplementation in a dose of 3g/day once daily. (Sachet of L-arginine was available in a packet of 5gm in which 3gm was active ingredient and 2gm was excipient). One sachet was administered every day for 14 days for participants in intervention group**.** Patients 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 at four times points interval by investigator: At the baseline (0 day),1st follow up (7th day),2nd follow up (14th day) & 3rd follow up (21st 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 Control group received only standard antihypertensive therapy as advised earlier by physician and had follow up visits similar to that of the participants of Intervention group i.e., at the baseline (0 day),1st follow up (7th day),2nd follow up (14th day) & 3rd follow up (21stday). During each follow up, from baseline to 3rd follow up, working capacity and fatigability was measured by interview in both the groups.

The questionnaire was prepared to observe the effect of L-arginine on working capacity and fatigability and responses of participants from both groups were recorded in pre-structured proforma.

Statistical analysis

Instat 3 Software was used for statistical analysis. Data was collected in pre-structured proforma and unpaired t-test and fishers exact test was applied to measure effects on working capacity and fatigability in Intervention and Control group.

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Results

Table 1: Comparison (Mean ± SD) of baseline characteristics between two groups

Variables	**Intervention Group (n=74)**	**Control Group (n=75)**	**P-value**
Age (years)	48.87 ± 7.69	50.97±7.45	0.096* (unpaired t-test)
Weight (kg)	68.31±10.58	67.40±11.01	0.607* (unpaired t-test)
Duration of Hypertension (months)	31.13 ± 14.82	28.84 ± 14.25	0.337* (unpaired t-test)
Gender- Male	44	42	0.67* (chi-square test)
Female	30	33	
*P-value not significant, Values are Mean ± SD, SD-Standard deviation			

Table 1. shows the comparison of baseline characteristics between two groups i.e Intervention and Control Group. At the baseline, the Mean ± SD age was 48.87 ± 7.69 in Intervention Group & 50.97±7.45 years in Control Group (P-value 0.096). Baseline weight (in Kg) was 68.31±10.58 in Intervention Group & 67.40±11.01 kg in Control Group (P= 0.607). Duration of hypertension (in months) in Intervention Group was 31.13 ± 14.82 & 28.84 ± 14.25 months in Control Group (P: 0.337). In our study there were 44 males & 30 females in Intervention Group & 42 males & 33 females in Control Group (P-value 0.67). This clearly shows that both groups are comparable in demographic data at the baseline levels and did not differ significantly from each other.

Table 2: Working Capacity in Intervention Group vs Control Group

Number of patients with better Working capacity			
Follow up visit	**Intervention Group out of 74**	**Control Group out of 75**	**P-value by Fishers Exact Test**
Baseline	24 (32.43%)	26 (34.66%)	0.7646
1st F/up	60 (81.08%)	23 (30.66%)	< 0.0001
2nd F/up	64 (86.48%)	24 (32%)	< 0.0001
3rd F/up	40 (54.05%)	21 (28%)	0.0003

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Figure 1: Working Capacity in Intervention Group vs Control Group

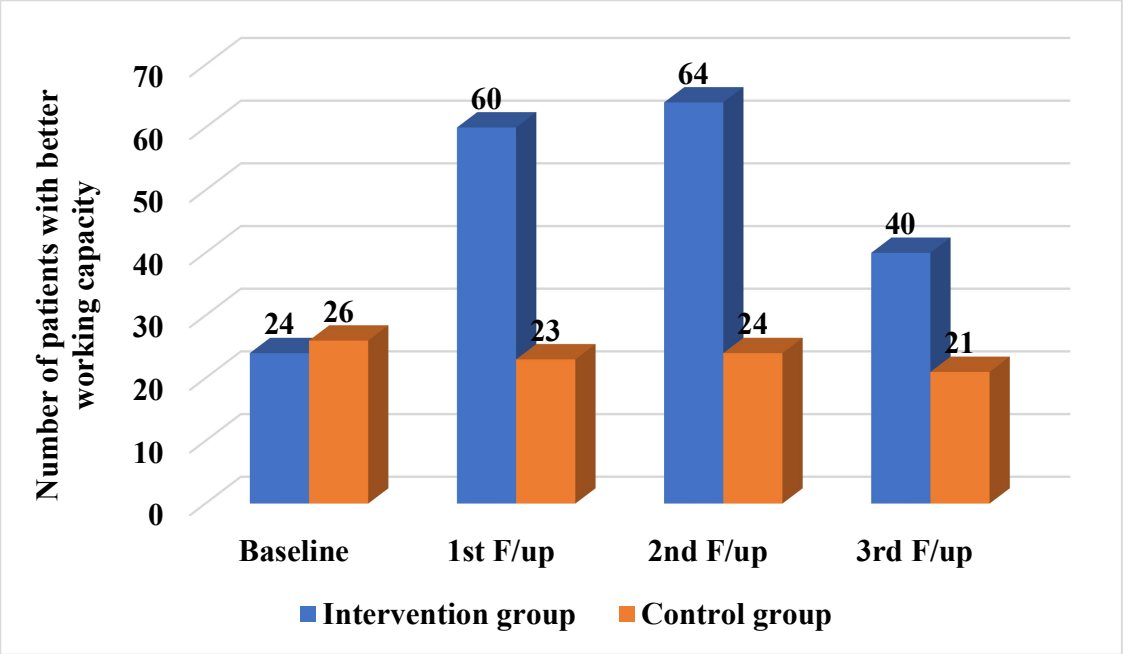

Figure 2: Line graph showing working capacity in Intervention Group vs Control Group

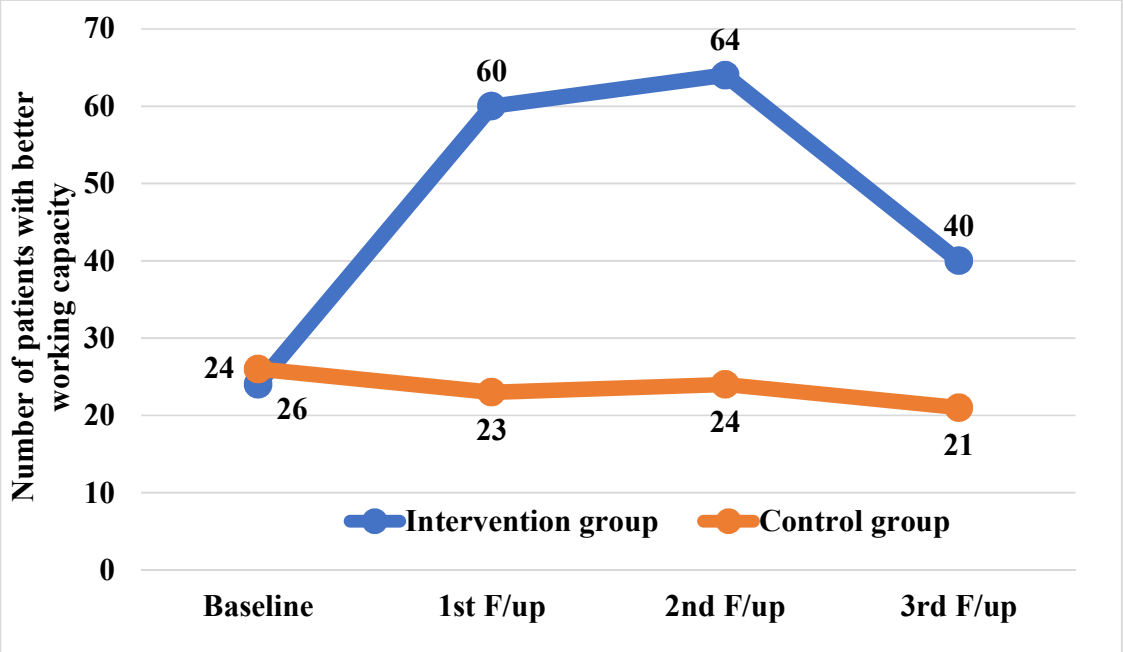

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Table 2 and figure 1 have shown number of patients with better working capacity of participants in Intervention Group as compared to participants in the Control Group. Both the groups are comparable at baseline with no statistically significant difference observed (p-value= 0.7646). On first follow-up visit, Intervention Group has shown statistically significant difference in the number of patients with better working capacity as compared to Control Group (p-value < 0.0001). On Second follow-up visit, Intervention Group again has shown statistically significant difference in the number of patients with better working capacity as compared to Control Group (p-value < 0.0001). On third follow-up visit, though there was statistically significant difference between Intervention and Control Group (p value= 0.0003), there was decline in the number of patients with better working capacity in Intervention Group (54%) as compared to first (81%) and second (86%) follow-up visits as evident from Figure 2.

Table 3: Fatigability in Intervention Group vs Control Group

Number of patients with Fatigability			
Follow up visit	**Intervention Group out of 74**	**Control Group out of 75**	**P-value by Fishers Exact Test**
Baseline	49 (66.21%)	47 (62.66%)	0.7677
1st F/up	12 (16.21%)	46 (61.33%)	< 0.0001
2nd F/up	9 (12.16%)	48 (64%)	< 0.0001
3rd F/up	30 (40.54%)	45 (60%)	0.0405

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Figure 3: Fatigability in Intervention Group vs Control Group

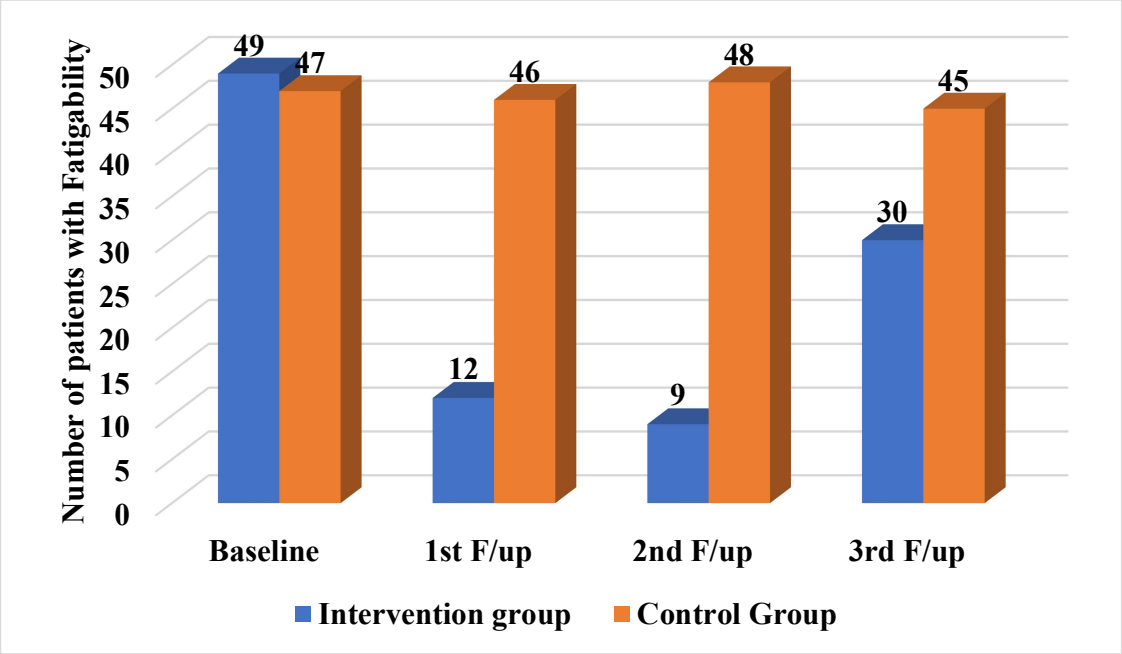

Figure 4: Line graph showing Fatigability in Intervention Group vs Control Group

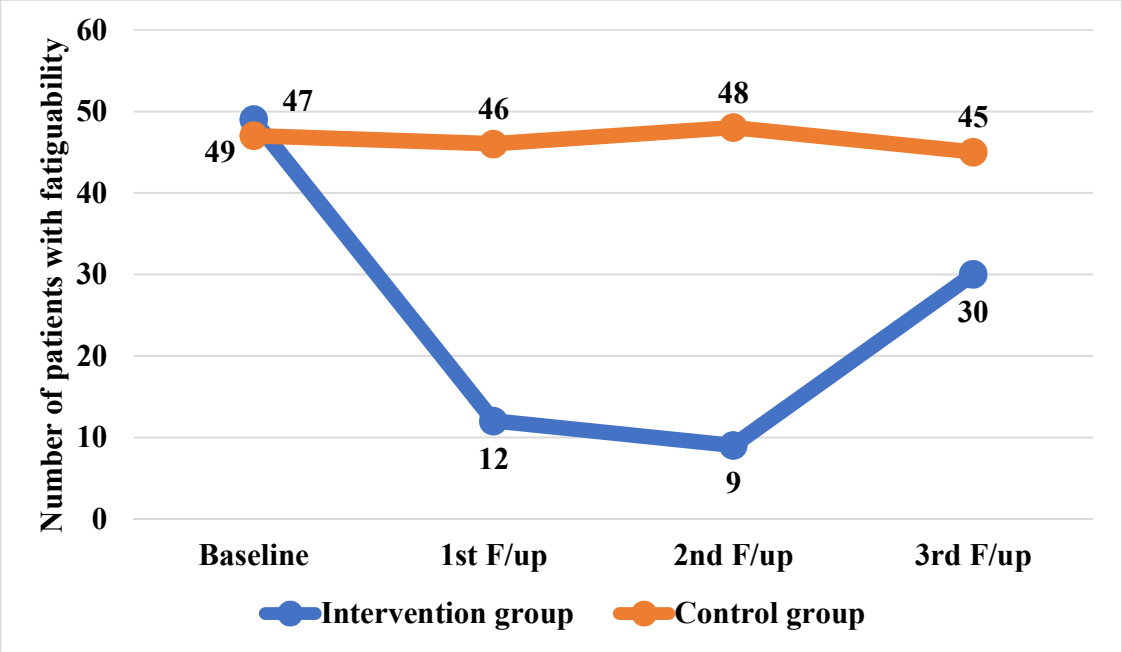

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Table 3 and Figure 3 has shown number of patients with fatigability of participants in Intervention Group as compared to participants in the Control Group. Both the groups are comparable at baseline with no statistically significant difference observed (p-value= 0.7677). On first follow-up visit, Intervention Group has shown statistically significant difference in the number of patients with fatigability as compared to Control Group (p-value < 0.0001). On Second follow-up visit, Intervention Group again has shown statistically significant difference in the number of patients with fatigability as compared to Control Group (p-value < 0.0001). On third follow-up visit, though there was statistically significant difference between Intervention and Control Group (p value= 0.0405), there was increase in the number of patients with fatigability in Intervention Group (40.54%) as compared to first (16.21%) and second (12.16%) follow-up visits as evident from Figure 4.

Discussion

The semi-essential amino acid, L-arginine, is a natural constituent of dietary proteins. L-arginine is particularly abundant in watermelon juice, seafood, nuts and meat proteins. Dietary intake of L-arginine is ~4–5 g/d but L-arginine can also be synthesized in the kidney and liver, where it is formed from L-citrulline. L-arginine can also be taken up by endothelial cells and oxidized to produce NO.[24]

NO has received significant attention in exercise physiology and sports nutrition, with many NO "supplements" being sold as potential ergogenic aids. This is based on the important role of NO in many physiological processes related to exercise and recovery, including the regulation of muscle contraction, mitochondrial respiration and blood flow.[25] Hence we have planned the study with the objective that L-arginine supplementation as add on to standard antihypertensive therapy may improve working capacity and reduce fatiguability in hypertensive patients.

In our study we found that add on L-arginine supplementation at a dose of 3g/d (L-arginine 5gm sachet) for 2 weeks in patients of hypertension resulted improvement in working capacity in intervention group on first, second and third follow-up visits compared to control group as shown in Table 2, Figure 1 and Figure 2.This is in agreement with Bailey SJ et al (2010) in which 9 men demonstrated that those who drank a beverage containing 6 grams of L-arginine 1 hour before intense exercise had significantly increased blood levels of nitric oxide and were able to exercise longer, compared with a placebo group.[26] Similar findings were observed by Pahlavani N et al (2017) that treatment with 2 grams of L-arginine daily for 45 days significantly increased sport performance, compared with a placebo group in 56 male soccer players.[27]Maxwell et al. administered oral arginine supplementation in a dose of 6.6g/day for2 weeks and examined the effects on vascular function and exercise capacity in patients with coronary artery disease and reported significantly greater flow-mediated vasodilation (5.5± 4.5 to 8.0 ± 4.9%) and total exercise time (545 ± 239 to 664 ± 763 seconds) during incremental treadmill walking compared with placebo.[18] and our results are also in accordance with Maxwell et al. Thus, the findings of these previous studies have indicated that arginine supplementation can improve exercise and working capacity in study subjects.

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However, number of patients with better working capacity reduced in number in intervention group on third follow- up visit (n=40) as compared to first (n=60) and second (n=64) follow-up visits. This might be explained by the fact that we have administered L-Arginine in intervention group for only first 14 days and not for the third week. So, the better effect observed in third week as compared to control group may be due to L-arginine supplementation already given for the first two weeks.

In our study, we also found that there was significant reduction in fatigability in intervention group as compared to control group on first, second and third follow-up visits as shown in Table 3, Figure 3 and Figure 4.

Similarly, number of patients with fatigability increased in number in intervention group on third follow- up visit (n=30) as compared to first (n= 09) and second (n=12) follow-up visits. The same hypothesis which we have put forward for the effect of L-arginine in third week on better working capacity in intervention group may be applicable in fatigability parameter also.

Limitations of Study

1) We have administered L-arginine supplementation for short period i.e for 14 days and in a dose of 3g/day (L-arginine 5gm sachet) in intervention group. In future, studies with longer duration and higher doses of L-Arginine supplementation may be warranted.
2) 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 working capacity & fatigability in hypertensive patients.

Conclusion

Findings of our study indicate that the daily intake of 3g/day of L-arginine supplementation (L-arginine 5gm sachet) as add on with standard antihypertensive therapy for 2 weeks in patients of hypertension led to a significant improvement in working capacity and significant reduction in fatigability. Henceforth, L-Arginine supplementation may be considered for short period as add on with standard antihypertensive therapy in patients of hypertension.

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