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IMPACT OF ORAL L-ARGININE ON MENOPAUSAL SYNDROME

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ABSTRACT

As a substrate for nitric oxide synthesis, L-Arginine may have possible beneficial effect in treating menopausal syndrome due to its function as vasodilator. Therefore, its effects were investigated in a double-blind, placebo-controlled, randomized control trial. After randomization, Oral L-arginine or placebo (9gms) each were given daily for 3 months to 60 postmenopausal women. There was significant improvement in postmenopausal women after consumption of both L-arginine/placebo. However Compare with placebo, L-arginine has significant beneficial effect in menopausal syndrome.

INTRODUCTION

L-Arginine is a nutritional substance found in various food. It is a semi-essential amino acid partly synthesized by the body [1]. Under certain condition L-arginine administration can enhance the synthesis of nitric-oxide (NO). In the presence of nitric-oxide synthase it is converted to NO which causes vasodilation via stimulation of soluble guanylyl cyclase and subsequent rise in intracellular cyclic guanosine monophosphate (cGMP), which results in vasodilation and improves circulation [2]. It provides similar protection with oestrogen [3]. It acts as a neurotransmitter in the brain and plays a crucial role in learning and memory [4]. It also serves as neurotransmitter in the lower urinary tract [5]. Vascular aging, characterized by endothelial dysfunction and large elastic artery stiffening occurs across the stages of the menopause transition, beginning in early perimenopause and becoming more pronounced in the late perimenopause to early postmenopausal period. These notable observations in vascular function have been attributed to declines in ovarian function and oestrogen levels [6] Oestrogen therapy improves vascular NO bioactivity in the systemic circulation of postmenopausal women, but its side effects and concerns regarding cancer risk on long-term term use is not acceptable by many women [7]. Experimental Study showed the use of L-arginine, as a nitric oxide substrate, improved the experimental vasospasm in rats [8]. The objective of this study was to assess the effect of L-arginine on menopausal syndrome using modified Greene Scale. We also assessed the minimum duration of its significant effect. On the basis of the above knowledge L-Arginine is believed to have possible beneficial effect in menopausal syndrome. Therefore, in this study, if it is found to be effective. it can be routinely administered for treating women with menopausal syndrome.

MATERIALS AND METHODS

The study was conducted in accordance with declaration Helsinki after obtaining approval from Institutional Ethical Committee. In this study 60 postmenopausal women coming to menopausal clinic at Queen Mary hospital, Lucknow were recruited for Randomized control trial. A written consent was taken from each participants. They were randomly divided into study and control groups. In study group oral L-arginine (9g) was given three times daily one hour before meal for 3 months duration. Participants in the control group received placebo. Modified Greene scale was used to assessed menopausal symptoms at baseline and after consumption at 1,2 and 3 months respectively. Treatment effects between two groups were analyzed using paired Chi-square, Independent samples and paired 't'. A 'p' value less than 0.05 was considered to be indicator of significant association. Target score value was 10 or below.

RESULTS:

In study group, mean symptom scores were 17.27±2.98, 13.87±3.75, 10.03±3.85 and 6.03±2.88 respectively at baseline, 1 month, 2 months and 3 months as compared to 16.40±1.89, 14.83±1.72, 13.23±1.68 and 11.13±1.66 respectively at the corresponding time intervals in Placebo group. Except for baseline and 1month intervals, at both the subsequent follow-up intervals, mean value of target score in Placebo group were significantly higher as compared to that in Study Group ($p<0.001$). During the intervention period, a decline in mean value of target score of 11.23±2.00 was observed in Study Group as compared to 5.27±1.41 in Placebos. Statistically, both the groups showed a significant decline in mean symptom scores ($p<0.001$).

In Study group, 2 (6.7%) participants could not achieve the targeted score. A total of 2 (6.7%) achieved it within 1 month, 10 (33.3%) achieved it in 2 months and 16 (36.7%) achieved it in 3 months. In placebo group, none of the participants could achieve the mean value of target score within the study period. Statistically, this difference between two groups was significant ($p<0.001$). This reduction in mean symptom score and was accompanied by improved perceptions of wellbeing in study group.

DISCUSSION

Studies have shown that postmenopausal women have low nitric oxide level in the body and it often led to pathogenesis and progression of vascular dysfunction across menopausal and postmenopausal stages. L-Arginine, a semi-essential amino acid acts as a precursor of nitric oxide (NO) is believed to have beneficial effect as it is a potent vasodilator. Therefore, in this study its effect on menopausal syndrome were examined in post-menopausal women. The results showed that L-arginine supplementation significantly decreased the mean symptom score in study group compared to control group ($p<0.05$). There was significant improvement after consumption of L-arginine. By improving blood flow in the body it helps in alleviating hot-flushes.

The minimum effective period of Oral L-arginine supplementation

was one month, however only six percent showed effective results. At the end of second month thirty three percent reported effective results. Majority of the participants, thirty six percent showed improvement at the end of third months. Thus, L-Arginine is more effective on administration for longer period. Since it is a nutritional substance it requires longer duration of administration to enhance generation of NO.

In some other studies too, subjects exhibited improved symptoms after L-arginine supplementation, a result that is in line with our study. One study demonstrated that positive results exist for the use of supplements containing combinations of L-lysine and L-arginine as treatments for anxiety symptoms and disorders [9]. "Oral treatment with L-lysine and L-arginine reduces anxiety and basal cortisol levels in healthy humans" in one hundred eight healthy Japanese adults [10]. One study, showed that arginine bioavailability may be decreased in major depressive disorder. This could impair the production of nitric oxide, and add to oxidative stress in the central nervous system [11]. In a study conducted on women achieved menopause recently showed the absence of association of NO with the severity of hot flushes. But they did not detect any relationships of individual hot flushes and serum levels of estradiol that indicated that nitric oxide might not to be a factor in hot flushes and might not be related to their etiology. Although the results of many other studies are in line with our study, Some more detailed studies are needed to determine the effects of differing L-arginine doses on menopausal syndrome [12]. A study on premenopausal, early- or late- perimenopausal, and early- or late-postmenopausal showed that a decline in endothelial function with menopause transition in women is probably due to relative L-arginine deficiency. And relative L-arginine deficiency may be related to elevated levels of the methylarginine L-NMMA, which would compete with L-arginine for eNOS and for intracellular transport, reducing NO biosynthesis[13]. A study conducted in postmenopausal women observed that the mechanism for cutaneous vasodilation during hot flash episodes has a nitric oxide component. Increases in CVC despite the inhibition of prostaglandin synthesis suggested that prostaglandins had no contribution to cutaneous vasodilation during hot flash episodes [14]. study conducted in healthy postmenopausal women on Endocrine and lipid effects of oral L-arginine treatment observed that lack of effect of L-Arginine on major endocrine hormones and lipid profile support the safety of oral L arginine administration [15]

Table 1: Comparison of Symptomatic Profile of Study Group and Placebos (Placebo)

SN	Time interval	Study Group			Placebo Group			Statistical significance	
		n	Mean	SD	N	Mean	SD	't'	'p'
1.	At baseline	30	17.27	2.98	30	16.40	1.89	1.345	0.184
2.	At 1 month	30	13.87	3.75	30	14.83	1.72	1.283	0.204
3.	At 2 months	30	10.03	3.85	30	13.23	1.68	4.178	<0.001
4.	At 3 months	30	6.03	2.88	30	11.13	1.66	8.404	<0.001
Mean Change from baseline to last follow-up		-11.23±2.00			-5.27±1.41				
'p' value for baseline to last follow-up change (Paired 't'-test)		't'=30.85; p<0.001			't'=20.42; p<0.001				

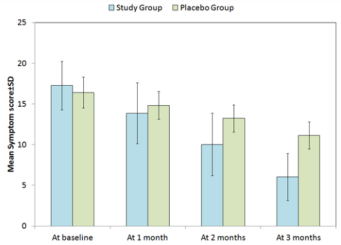

Fig. 1: Comparison of Symptomatic Profile of Study Group and Placebo Group

Table 2: Time taken to achieve Targeted Score between two groups

SN	Time interval	Study Group		Placebo Group		Statistical significance	
		No.	%	No.	%	χ^2	'p'
1.	Did not achieve at all	2	6.7	30	100	52.50	<0.001
2.	1 month	2	6.7	0	0		
2.	2 months	10	33.3	0	0		
3.	3 Months	16	36.7	0	0		

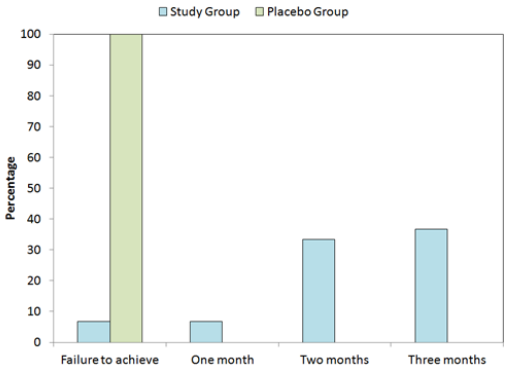

Fig. 2: Time taken to achieve Targeted Score between two groups

CONCLUSION

Oral administration of L-arginine could improve menopausal syndrome in postmenopausal women. Early beneficial effects were observed in thirty days. However further studies should be carried out to determine impact of oral L-Arginine on menopausal syndrome with a larger sample size to shed light on our findings.

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