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EFFECT OF ADD ON SUBLINGUAL VITAMIN D3 ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN PATIENTS OF HYPERTENSION ON ANTIHYPERTENSIVE TREATMENT

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ABSTRACT

Introduction: The aim of present study was to study effects of Sublingual Vitamin D3 on blood pressure of hypertensive patients on antihypertensive drugs. **Methods:** This study was Non-Randomized Clinical Trail, in which 110 Hypertensive Patients participated in the study, of which, 55 each were enrolled in Test and Control Group each. All the hypertensive patients visiting the Medicine OPD of Pravara Rural Hospital, Loni, of age between 18-60 years and either gender, willing to participate in study were included in the study. Patients on thiazide diuretics or on any other chronic medications other than antihypertensives were excluded from the study. After taking written informed consent of the study participants, the patients were assigned into Test group and Control group. The participants in the test group were given add on therapy of Sublingual vitamin D3 60,000IU every 15 days for 3 months and their blood pressure was measured. **Results:** There was statistically significant difference reduction in systolic blood pressure from baseline visit (134±13 mm of Hg) in comparison with Visit II, V, VI and VII (ANOVA with post hoc Tukey test). Also, there was significant reduction in systolic blood pressure when Visit II, III, and IV were compared with Visit VII. Statistically significant difference was seen on comparison of systolic blood pressure of participant in Test group with that of Control group during Visits II ($P<0.05$, Unpaired t test), IV, V, VI and VII ($P<0.05$, Mann-Whitney Test). **Conclusion:** Sublingual Vitamin D3 therapy causes average fall in systolic blood pressure of 15 mm of Hg. Sublingual Vitamin D3 may have an add on therapeutic role in treatment of hypertension.

KEYWORDS: Sublingual Vitamin D3,Blood pressure,Hypertensive patients.

INTRODUCTION

All over the world, cardiovascular disease accounts nearly one third tall of deaths among deaths due to all causes.[1] Of these deaths, complications of hypertension is responsible for 9.4 million deaths every year. Hypertension leads to deaths in 45% of instances due to heart disease and 51% of instances due to stroke.[2] South Asians living in Western countries have a higher burden of cardiovascular disease than other ethnicities.[3-5] In 2003, the prevalence of congestive heart disease (CHD) in India was estimated to be 3-4 per cent in rural areas which was two-fold higher compared with prevalence 40 years ago. Also, in Urban areas 8-10 per cent prevalence of CHD was observed as which was six-fold higher compared with prevalence 40 years ago. The total number of CHD patients amounts to 29.8 million affected (14.1 million in urban areas, and 15.7 million in rural areas) according to population-based cross-sectional surveys.[6,7]

Epidemiologic studies have linked vitamin D deficiency with increased risk of major adverse CV events.[8] Vitamin D plays an integral physiological role in non-skeletal tissues and have been implicated in a wide range of chronic pathology, including skin and autoimmune disease, diabetes mellitus, hypertension, cancer [9]. Interest in the role of vitamin D in CVD arose from evidence of adverse cardiovascular effects of vitamin D deficiency in animal models,[10] and epidemiological studies reporting the increase in cardiovascular events in winter and at increasing distance from the equator.[11,12]

Several RCTs on vitamin D supplementation and BP have already been performed but have shown mixed results with most studies reporting no significant effect and only some showing that vitamin D lowers BP.[13–32] In a metanalysis of RCTs, vitamin D supplementation resulted in a nonsignificant reduction in systolic and diastolic BP.14 A significant decrease in diastolic BP was observed among RCTs including participants with pre-existing cardiometabolic disease.[14] Most previous

RCTs were, however, not adequately designed to answer the question whether correction of vitamin D deficiency is effective for the treatment of arterial hypertension because these RCTs, except for 3 trials, did not include participants with both vitamin D deficiency and high BP.[15,17,22] The aim of present study was to study effects of Sublingual Vitamin D3 on blood pressure of hypertensive patients on antihypertensive drugs.

METHODOLOGY

This study was Non-Randomized Clinical Trail, registered in the Clinical Trial Registry of India, it is available in Website: CTRI Website URL - http://ctri.nic.in; Registration number: CTRI/2017/03/008033. The study was approved by Institutional Ethical Committee (Pravara Institute of Medical Sciences). In the present study, 110 Hypertensive Patients participated in the study, of which, 55 each were enrolled in Test and Control Group each. All the hypertensive patients visiting the Medicine OPD of Pravara Rural Hospital, Loni, of age between 18-60 years and either gender, willing to participate in study were included in the study. Patients on thiazide diuretics or on any other chronic medications other than antihypertensives were excluded from the study.

After taking written informed consent of the study participants, the patients were assigned into Test group and Control group. The participants in the test group were given add on therapy of Sublingual vitamin D3 60,000 IU every 15 days for 3 months and their blood pressure was measured. The participants had 7 visits including the including the baseline visit followed by 6 visits were vitamin D3 was administered. The participants in the Control group did not receive add on therapy and had visits similar to that of the participants of Test group. During each visit, from baseline to visit 6, the Blood pressure of volunteers was measured using (Omron7120 Automated). Statistical analysis was done using Graphpad instat Software version 2.

RESULTS

The study participants included in the study were 55 each in Test and Control group. The test group consisted of 15 males and 40 females, while the Control group had 23 males and 32 female participants.

Table No. 1. Systolic & Diastolic BP and Pulse pressure in mm of Hg (Mean±SD) of Test Group During Visits.

Group	Baseline	Visit-I	Visit-II	Visit-III	Visit-IV	Visit-V	Visit-VI	Visit-VII
Systolic BP								
Test group	134±13	129±14.6	126.8±13*#	127±18#	126±14#	124±13.6*	122±13.5*	119±18.4*
Control group	140±21.9	138±21	139±18$	133±13	134±15@	137±18$$	138±16**	136±13##
Diastolic BP								
Test group	87.8±9.61	83.7±10	82±9.9	84±11.8	82±10.6	81±9.5	84±9.9	80±8.7
Control group	86.6±10.7	85±10.5	86±11.7	83±9.3	85±10	83±11	85±9.7	83±8.2

*P<0.01 vs Baseline, # P<0.01 vs V -7 **(ANOVA with post hoc Tukey-Kramer Multiple Comparisons Test)**
$ **P**<0.05 vs Visit II Systolic BP of Test group (Mann-Whitney Test)
@ **P**0.05 vs Visit IV Systolic BP of Test group (Unpaired t test)
$$ **P**<0.05 vs Visit V Systolic BP of Test group (Mann-Whitney Test)
** **P**<0.05 vs Visit VI Systolic BP of Test group (Mann-Whitney Test)
P<0.05 vs Visit VI Systolic BP of Test group (Mann-Whitney Test)

Table no. 1 represents changes in Systolic BP and Diastolic BP of Test group and Control groups during the visits. There was statistically significant difference reduction in systolic blood pressure from baseline visit (134±13 mm of Hg) in comparison with Visit II, V, VI and VII (ANOVA with post hoc Tukey test). Also, there was significant reduction in systolic blood pressure when Visit II, III, and IV were compared with Visit VII (Figure 1). There was no statistically significant difference in Diastolic blood pressure during visits in the Test group (P = 0.2925, ANOVA with post hoc Tukey test). Statistically significant difference was seen on comparison of systolic blood pressure of participant in Test group with that of Control group during Visits II (P<0.05, Unpaired t test), IV, V, VI and VII (P<0.05, Mann-Whitney Test).

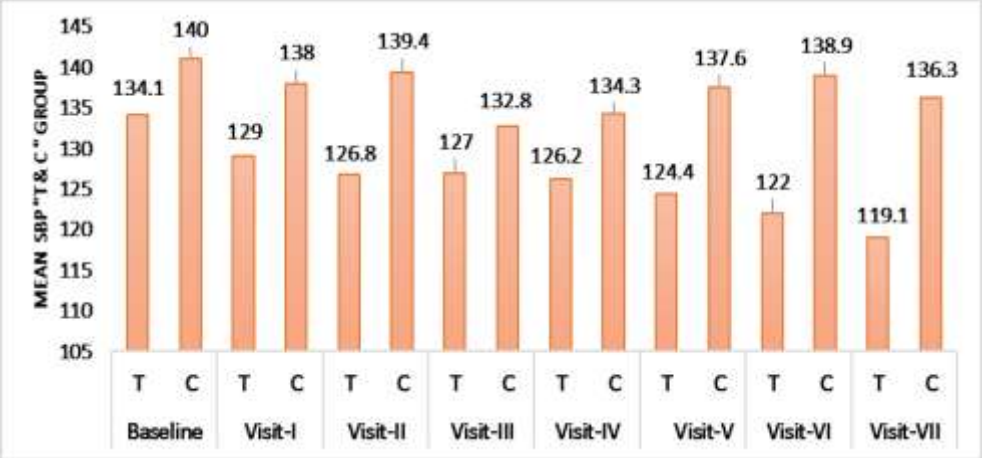

Figure No. 1: Systolic BP of Test & Control groups during Visits.

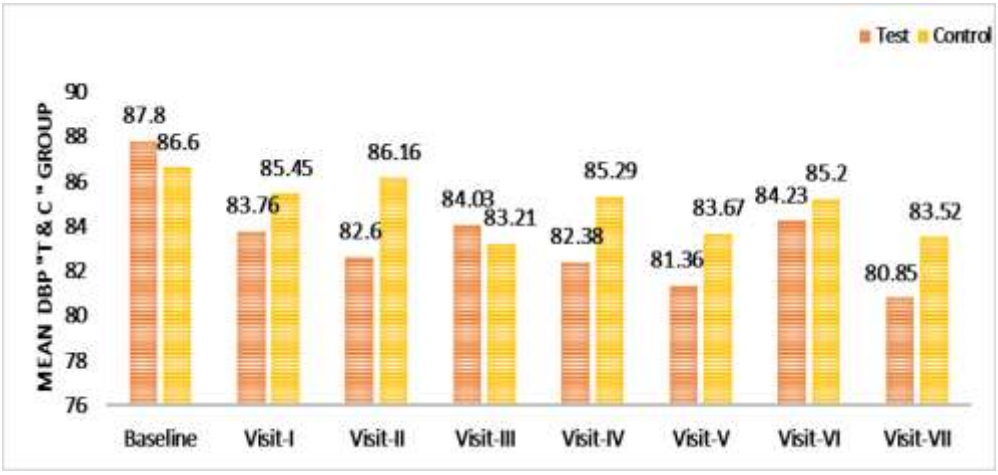

Figure No. 2: DBP of Test and Control group volunteers During Visits.

On intragroup comparison of Diastolic BP, during visits of Test group, there was no statistically significant difference observed. Similarly, observations were seen with the Control group. When Diastolic blood pressure of visits of Test group were compared with that of the Control group (Inter group comparison), there was no statistically significant difference (Figure No. 2).

DISCUSSION

Large observational studies and meta-analyses have shown that low 25(OH)D concentrations are a significant risk marker for arterial hypertension.[8,9] Molecular effects of vitamin D receptor activation, such as suppression of the renin–angiotensin– aldosterone system (RAAS), nephroprotective actions, or improvements in endothelial/vascular function, suggest antihypertensive properties of vitamin D.[6,9] Total number of participants in test & control group were 55each. Many studies evaluating effect of oral Vitamin D on blood pressure have been carried out.[13-32] These studies had varied doses, frequency as well as opposed to sublingual route in the present study.

Table No. 2: Comparison of studies evaluating effect of Vitamin D therapy on blood pressure.

Name of Authors	Schedule of Vitamin D	TEST GROUP Blood pressure(mmHg)				CONTROL GROUP Blood pressure(mmHg)			
		SBP		DBP		SBP		DBP	
		Before T/t	After T/t	Before T/t	After T/t	Before T/t	After T/t	Before T/t	After T/t
Hamid Nasri	50000 IU weekly /12 weeks	121±13	110±9#	80±8	76±7@	118±11	114±9$	80±7	79±4□
Wei Ren Chen	2000 IU Daily for 5months	132±9	128±9	75±8	74±8	131±9	130±11	75±8	74±8
Witham MD	100000IU 3 monthly for 1 year	153±11	151±19	82±10	82±8	155±14	146±16	86±9	80±11
Larsen T	3000 IU Daily for 20 weeks	132±10	130±11	77±6	76±7	131±9	132±11	77±6	77±7
Present Study	60,000 IU Every 15days for 3 Months	134±13	119±18*	87±9	80±8	140±21	136±8	86±10	83±8

SBP- Systolic blood pressure, DBP- Diastolic blood pressure, T/t- Treatment.

*P<0.05 vs Test group (ANOVA with post hoc Tukey-Kramer Multiple Comparisons Test), # P<0.05 vs SBP before T/t test group, @ P<0.05 vs DBP before T/t test group, $ P<0.05 vs SBP before T/t Control group, □ P<0.05 vs DBP before T/t Control group (paired t-test).

Vitamin D is a lipid soluble vitamin. It has been reported that only about 50% of a dose of vitamin D is absorbed.[33,34] The half-life of 1a,25(OH)2D3 in the plasma has two components. Within 5 min, only half of an administered dose of radioactive 1 α,25(OH)2D3 remains in the plasma. A slower component of elimination has a half-life of about 10 h. 1α,25(OH)2D3 is catabolized by a number of pathways that result in its rapid removal from the organism.[35] Considering the differences of pharmacokinetics of oral and sublingual routes of administration, the results of the present study cannot be directly correlated to the previous studies. The total amount of Vitamin D given to study participants in the previous studies varied from 350000 to 600000. Also, the dosing schedule was different in each study. In the present study amount of Vitamin D given to study participants was 360000IU. The AUC_{28} was 751.4 ±218.4 nmol/dL in the older group and 968.6 ±451.6 nmol/dL in the younger group.[36]

In a study by Hamid etal.,[37] there was statistically significant decrease in Systolic as well as Diastolic blood pressure in both Test and Control groups (Table no. 2). This implies that the reduction in blood pressure is similar in both groups. Also, although there was some reduction in the blood pressure, other studies did not find any statistically significant difference in systolic and diastolic blood pressure in both test and control groups. All these studies oppose the hypothesis of effect of vitamin D3 on reduction of blood pressure. In the present study, there was statistically significant reduction in systolic blood pressure in test group during various visits, while there was no reduction in systolic blood pressure in control group. On the other hand, there was statistically significant difference in the systolic blood pressure in the test and the control group (Table no. 1). On comparing the results of the above studies with the present study, there is some reduction in blood pressure in the previous studies, but there was no statistically significance. Also the average decrease in the systolic blood pressure was 11 and 12 mm of Hg in studies by Ansari etal and Wei Ran Chan respectively, while it was merely 2 mm of Hg in studies by Witham MD and Larsen T. The average fall in Systolic Blood Pressure in the present study was 15 mm of Hg. Hence, the fall in Systolic blood pressure was more as compared to previous study. This might be due to change in the route of administration of the drug. Nevertheless, the finding of the present study suggests that Vitamin D3 therapy by sublingual route is associated with fall in systolic blood pressure. The drawback of present study is that the antihypertensive medications that the patients received were not taken into account during the conduct of the study, which could have interfered with the results of the study.

CONCLUSION

Sublingual Vitamin D3 therapy causes average fall in systolic blood pressure of 15 mm of Hg. More studies aimed at comparing the effect of oral versus sublingual route of administration of Vitamin D3 may be required to confirm the findings of the present study. Sublingual Vitamin D3 may have an add on therapeutic role in treatment of hypertension.

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