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Efficacy and safety of oral Vitamin D (cholecalciferol) supplement therapy in Stage I primary hypertension: A prospective, randomized, double-blind, placebo controlled, clinical trial in a tertiary care hospital in central India

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Abstract

Introduction: Hypertension is one of the most common cardiovascular disorders. Almost all targets in its therapy are exploited and there is a growing need to search for newer targets. Vitamin D is gaining increasing attention in treatment of primary hypertension.

Objectives: To study the efficacy and safety of Vitamin D supplementation on systolic and diastolic BP in patients of primary hypertension (JNC 7 stage I) receiving conventional antihypertensive medications (namely Tab atenolol 50mg or Tab amlodipine 5mg).

Methods: It was a prospective, randomized, double blind, parallel, placebo controlled clinical trial with 2 groups of 33 patients each. Both groups had patients receiving conventional antihypertensives (Tab atenolol 50mg or Tab amlodipine 5mg). Group A patients were given placebo (lactose tablets) and Group B were given oral Vitamin D_3 (60,000 IU) once weekly at bedtime after meals, repeated every fortnightly for 12 weeks.

Results: Patients belonging to Group B showed a statistically significant ($p < 0.0001$) decline in both systolic blood pressure after 12 weeks of receiving vitamin D supplementation. There was no significant change in the safety parameters.

Conclusions: Thus, our study shows that Vitamin D supplementation has some role in safely reducing systolic blood pressure after 12 weeks of supplementation and hence it should be supplemented with antihypertensive drugs to the patients with hypertension.

Keywords: Vitamin D, Hypertension, Amlodipine, Atenolol.

1. Introduction

Hypertension is one of the most common cardiovascular disorders. Sixty to eighty percent of both men and women will develop hypertension by the age of 80. [1] Due to its high prevalence it has been extensively studied and almost all possible targets of therapy have been exploited till date. Quest for newer target areas to treat hypertension is the growing need of the day. Current day researchers are looking at vitamin D for a solution to this ever growing problem. Vitamin D is gaining growing popularity in the patho-physiology of various extra-skeletal conditions like hypertension, renal disease and insulin resistance. [2] This could possibly be due to identification of vitamin D receptors in almost all human cells.

Vitamin D being fat soluble in nature can get accumulated in the fat depots of the body leading to toxicity. Hence, assessment of its safety is also an essential parameter. Thus, with this background this study was undertaken to determine the efficacy and safety of oral vitamin D (cholecalciferol) supplement therapy in Stage I primary hypertension.

2. Material and Methods

2.1 Ethics

Ethics committee approval was obtained prior to the conduct of the study.

2.2 Trial design

It was a prospective, randomized, double blind, parallel, placebo controlled clinical trial. Patients were screened in medicine OPD and those found meeting the inclusion criteria, were enrolled in the trial.

2.3 Study duration

Study period was of 3 months (12 weeks) from approval of Ethics committee. Participants were enrolled during winter to minimize the effects of sun exposure on vitamin D levels.

2.4 Inclusion criteria

1) Patients suffering from primary hypertension (JNC Stage I) and receiving conventional antihypertensives (Tab atenolol 50 mg or Tab amlodipine 5mg) for more than 4 weeks.
2) Patients between 18-60 years of age, both sides.
3) Willing and able to provide written informed consent.

2.5 Exclusion criteria

1) Hyperlipidemic patients (total cholesterol levels >240 mg/dl or triglycerides >150 mg/dl)
2) Patient with H/o angina, Congestive Heart Failure and MI
3) Pregnant females (excluded by urine pregnancy test) and lactating mothers.
4) Hypersensitivity or allergy to cholecalciferol.
5) Patients with plasma calcium levels >10.5mg/dl
6) Patients with severe hypertension, or secondary hypertension.
7) Patient with H/o proteinuria
8) Patient with H/o diabetes mellitus
9) Patients with pre-existing renal disease

Table 1: Sample size and groups: There were two groups, A and B

Group A	Patients on conventional antihypertensives (Tab atenolol 50mg or Tab amlodipine 5mg) +Placebo (lactose tablets) for 12 weeks	33 patients
Group B	Patients on conventional antihypertensives (Tab atenolol 50mg or Tab amlodipine 5mg) + oral Vitamin D_3 (60,000 IU) administered once weekly at bedtime after meals ,repeated every fortnightly for 12 weeks	33 patients

Sample size was calculated by using level of significance α = 5% and power 80%. Sample size was calculated to be 31 in each group. So the study sample size was rounded to sixty six (33 patients in each group) considering noncompliance and future rate of drop outs. Graph Pad prism software **Version 6**, was used for calculation of sample size and statistician of the institution assisted in the calculations.

2.6 Study conduct

Written informed consent was taken from all participants. After initial screening, clinical examination and laboratory investigation, patients were randomly allocated by using block randomization procedure for random allocation to receive either group A or group B drugs to ensure uniform allocation ratio. The randomized treatment allocation sequence was generated by random allocation software.

Patients received tablets in the plastic container labelled with information such as, initials of patient, group code of drug study, patient code number, date of next follow up and instructions regarding administration of tablet. All drugs were indistinguishable, and both participants and research staff were blinded to treatment assignment.

2.7 Assessment of efficacy

Every fortnightly patient was asked to visit for BP measurement.

2.8 Assessment of safety:

Blood investigations including liver function test, renal function test and serum calcium were done at baseline and at the end of the study to assess safety of the drug.

2.9 Statistical analysis:

Normality of data was assessed using the Kolmogorov Smirnov test. Being non normally distributed, quantitative data [BP] was expressed as median and range. Inter group difference was assessed using Mann Whitney test. All analyses were done at 5% significance using Graph Pad Instat version 3.0 and Microsoft Excel 2013.

3. Results

The current study comprises 63 participants who were enrolled and randomized. One patient from group A and two patients from group B failed to follow up. Intention to treat analysis was used to calculate the results.

a) **Demographics:** Both the groups were comparable on the basis of demographic characteristics of age and gender at baseline.
b) **Safety parameters:** Both the groups were comparable on the basis of safety parameters like the liver function tests, renal function tests and serum calcium at baseline. There was no statistically significant change in them at the end of 12weeks.

c) Efficacy parameters

- Systolic BP: There was a statistically significant ($p < 0.0001$) decline in systolic BP after 12 weeks in group B (median [range] in mm of Hg) [138(0-144)] as compared to group A [140(0-144)].
- Diastolic BP: There was no statistically significant ($p > 0.05$) decline in diastolic BP (90[0-94]) after 6 (90[0-94]) and 12 (median [range] in mm of Hg) weeks in group B as compared to group A.

4. Discussion

Several previous studies [3,4] have claimed that low Vitamin D levels are associated with a higher risk of having hypertension and that vitamin D supplementation significantly reduces blood pressure after atleast 6 weeks of supplementation. Our study showed significant reduction in systolic BP after 12 weeks of Vitamin D supplementation. The most well-supported mechanism by which vitamin D may affect BP is its role as a negative regulator of the RAAS. Vitamin D receptor (VDR) null mice showed significant elevations in renin activity and circulating plasma angiotensin II concentrations and had hypertension and cardiac hypertrophy.[5] But it is not clear whether these significant effects observed in vitro are also of relevance in vivo, i.e. in clinical settings.[6,7] In experimental studies, VDR activation has been shown to exert a variety of anti-atherosclerotic effects like vitamin D induced decrease of endothelial adhesion molecules, increase of nitric oxide (NO) production and inhibition of macrophage to foam cell formation. Vitamin D supplementation also decreases parathyroid hormone (PTH) levels and helps in regulating calcium homeostasis which is involved in the regulation of peripheral vascular resistance and arterial tone by modulating contractility of vascular smooth muscle cells. It also has renoprotective actions including antiproteinuric and anti-inflammatory effects. Taken together, several plausible pathophysiological mechanisms exist that may account for the link between vitamin D supplementation and arterial hypertension.[8-10] Thus supplementation therapy with Vitamin D can be exploited as a safe and efficacious option for hypertension in the future.

Our study is limited by our sample size of only 33 patients per group. A multicentric study of a higher magnitude with greater sample size will help provide good evidence to our research question.

References

[1]. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens.* 2007; 20:713–719.

[2]. Benowitz NL. Antihypertensive Agents. In: Katzung BG, editor. Basic and Clinical Pharmacology, 12th edition, Chap 11, New York: McGraw-Hill; 2012; p. 167,168,183.

[3]. Martins D, Wolf M, Pan D. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med.* 2007; 167:1159–1165.

[4]. Pfeifer M, Begerow B, Minne WH, Nachtigall D, Hansen C. Effects of a short-term vitamin D3 and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab*.2001; 86:1633–1637.

[5]. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1, 25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest.* 2002; 110: 229–238.

[6]. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, *et al*. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 2008; 29: 726-76.

[7]. Li YC. 31. Molecular mechanism of vitamin D in the cardiovascular system. *J Investig Med* 2011; 59: 868-71.

[8]. Fitzpatrick LA, Bilezikian JP, Silverberg SJ. 32. Parathyroid hormone and the cardiovascular system. *Curr Osteoporos Rep* 2008; 6: 77-83.

[9]. Brewer LC, Michos ED, Reis JP. 40. Vitamin D in atherosclerosis, vascular disease, and endothelial function. *Curr Drug Targets* 2011; 12: 54-60.

[10]. Tare M, Emmett SJ, Coleman HA, Skordilis C, Eyles DW, Morley R, *et al*. Vitamin D insufficiency is associated with impaired vascular endothelial and smooth muscle function and hypertension in young rats. *J Physiol* 2011; 589: 4777-86.