EFFICACY AND TOLERABILITY OF TRANDOLAPRIL IN MILD TO MODERATE HYPERTENSION: A DOUBLE BLIND COMPARISON WITH ENALAPRIL

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ABSTRACT

Objectives : To compare the efficacy and tolerability between Trandolapril and Enalapril in mild to moderate hypertension.

Materials & Methods: This was a prospective, double blind, parallel, comparative clinical trial involving 120 patients with mild to moderate hypertension. Patients were randomized to receive trandolapril 2 to 4 mg once daily and enalapril 5 to 10 mg once daily. The participants were followed for 8 weeks.

Results : Both the drugs achieved effective control of blood pressure at the end of 8 weeks. The mean reduction in SBP was 22.17 mmHg with trandolapril and 21.47 mmHg with enalapril group; the mean reduction of DBP was 9.57 mmHg with trandolapril and 11.13 mmHg with enalapril. Adverse events were developed in 11 (18.3%) and 12 (20%) patients in trandolapril and enalapril group. Conclusion: The efficacy and tolerability of trandolapril was comparable to enalapril in mild to moderate hypertension with minor adverse events.

(c) Keywords: Hypertension; ACEIs; Trandolapril; Enalapril

(d) Running Title: Efficacy of Trandolapril in Mild to Moderate Hypertension

INTRODUCTION

Hypertension is one of the most prevalent vascular diseases in the world and posses a major public health problem. Angiotensin converting enzyme inhibitors (ACEIs) are accepted as first line therapy in the treatment of hypertension and heart failure[1]. The principle antihypertensive effect is through renin-angiotensin-aldosterone (RAA) mechanism[2]. They offer distinct advantages such as preventing or reversing cardiovascular remodeling[3], diabetic complications[4], improving endothelial function[5] and also enhancing fibrinolysis[6]. The American Heart Association and American College of Cardiology recommends ACEIs as standard therapy in patients who are at high risk for cardiovascular morbidity and mortality[7]. In recent years, there has been a rapid growth in the number of ACEIs entering the market. Most have claimed some sort of advantages based on differences in pharmacokinetics, metabolism or tissue ACE binding.

Trandolapril is a new non-sulfhydryl lipophilic ACEI. The main pharmocodynamic effects of trandolapril are achieved by reduction in plasma angiotensin–II levels, which leads to a reduction in total peripheral vascular resistance, blood pressure, and decreased sodium and water retention by the kidney[8]. It has an effective long duration of action in the dose of 2 to 4 mg daily and is well tolerated with minor adverse events[9]. Few studies were done in Indian population to compare its efficacy and tolerability with other ACEIs. The present study was under taken to compare the efficacy and tolerability of trandolapril with enalapril in mild to moderate essential hypertension.

MATERIAL AND METHODS

The present study was a randomized, double blind, parallel, comparative clinical trial carried out in Kempegowda Institute of Medical Sciences Hospital and Research Centre, Bangalore, over a period of one year. The study protocol was approved by the Institution Ethical Committee (IEC), and conducted in accordance with the Declaration of Helsinki. After obtaining written informed consent, 120 patients of either sex in the age group of 20 to 60 years with mild to moderate hypertension (sitting DBP between 90 to 110 mmHg) were recruited for the study. Patients who were previously receiving antihypertensive medication were given 2 weeks' washout prior to entry into the study. Patients with the following conditions were excluded from the study; pregnant and lactating women, patients with history of drug allergy or intolerance to ACEIs, patients unwilling to comply with the protocol

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requirement, patients with severe hypertension, patients already on antihypertensive drugs or other medications known to affect the outcome of the study, patients who had participated in other clinical trials in the past one month, patients with history or evidence of renal, hepatic or neurological disease, patients with uncontrolled diabetes and patients with suspected bilateral renal artery stenosis or single kidney. A detailed medical history, clinical examination, anthropometric measurements and baseline laboratory investigations were carried out.

Patients fulfilling the study criteria were randomly assigned to two groups of 60 each to receive either trandolapril 2 mg or enalapril 5 mg. The BP was recorded at baseline, at 2, 4 and 8 weeks. BP was recorded 3 times at each visit after 5 minutes of rest in a sitting posture. Compliance was monitored by pill count method. Patients were monitored for adverse events throughout the study period.

Laboratory investigations like Hb%, WBC count, blood urea, serum creatinine, lipid profile, serum electrolytes (sodium and potassium), FBS, urine analysis, and ECG were done at baseline and at the end of 8 weeks. Romhilt-Esters point score system10 was used to detect LVH by using ECG.

Data was expressed in percentages and mean ± SD. Student't' test was used to find the significance of SBP and DBP between the two groups. ANOVA was used to find the significance of SBP and DBP during the study period within each group.

RESULTS

Out of 120 patients, 64 were men and 56 women. The mean age in trandolapril and enalapril group was 51.21±6.0 and 50.57±6.16 years respectively. 68 (56.66%) patients were from urban and 52 (43.33%) from rural area.

The mean SBP at baseline in the trandolapril group was 151.57±7.63 mmHg compared with 151.07±7.14 mmHg in the enalapril group. The mean DBP at baseline in the trandolapril group was 98.40±4.49 mmHg compared with 100.53±5.66 mmHg in the enalapril group (Table-1). There were no significant differences between the two groups with respect to demographic and baseline characteristics.

The most frequent comorbid conditions present in both groups included type 2 diabetes mellitus in 16.66% (n = 20), obesity (BMI ≥ 25 kg/m2) in 28.33% (n = 34),

Table-I: Demographic and Basic Characteristics

Characteristics	Trandolapril	Enalapril
Age (years)	51.20±6.01	51.57±6.16
Sex – Male/Female (N)	33/27	31/29
Location– Urban/Rural (N)	28/32	40/20
Basal SBP (Mean±SD) mmHg	151.57±7.63	151.07±7.14
Basal DBP (Mean±SD) mmHg	98.40±4.49	100.53±5.66

n=60 in each group. Values are mean± Standard Deviation (SD)

Table-II: Comorbid Conditions in Study Groups

Co morbid Conditions	Trandolapril	Enalapril
Type 2 diabetes mellitus	11 (18.3)	9 (15)
Obesity	18 (30)	16 (26.7)
Diabesity	5 (8.3)	6 (10)
LVH	5 (8.3)	6 (10)

Numbers in parenthesis indicates percentage

Table-III: Changes in SBP and DBP in Trandolapril and Enalapril Group during the Study

Visits	Trandolapril		Enalapril	
	SBP	DBP	SBP	DBP
Basal	151.57±7.63	98.40±4.49	151.07±7.1	100.53±5.6
2 Weeks	144.30±7.12	94.27±4.58	143.73±7.3	95.80±4.75
4 Weeks	137.13±6.16	91.45±3.02	136.23±6.1	91.87±2.85
8 Weeks	129.40±1.12	88.83±1.34	129.60±0.8	89.23±1.17

Values are mean± standard deviation (SD). No statistical significance between two groups

Table-IV: Adverse Events in the Study Group

Adverse Events	Trandolapril	Enalapril
Cough	4 (6.66)	3 (5)
Giddiness	1 (1.66)	4 (6.66)
Headache	2 (3.33)	2 (3.33)
Fatigue	1 (1.66)	2 (3.33)
Myalgia	2 (3.33)	1 (1.66)
Abdominal Discomfort	1 (1.66)	0 (0)
Total	11 (18.33)	12 (20)

Numbers in parenthesis indicates percentage

diabesity in 9.16% (n = 11) and left ventricular hypertrophy based on ECG changes in 9.16% (n = 11) of patients (Table-2). At the end of 2 and 4 weeks, 38% and 75% of the study subjects in trandolapril group and 27% and 58% in the enalapril group achieved reduction in DBP to < 90 mmHg and reduction in DBP at 4 weeks was shown to be significant (P<0.05). The dose of trandolapril was increased from 2 to 4 mg in 25% (n = 15) and enalapril from 5 to 10 mg in 41.7% (n = 25) of patients at the end 4 weeks in patients who did not show DBP reduction to < 90 mmHg with the initial dose.

The mean SBP/DBP in the trandolapril group was 151.57±7.63 / 98.40±4.49 at baseline, 144.30±7.12 / 94.27±4.58 after 2 weeks, 137.13± 6.16/ 91.45±3.02 after 4 weeks and 129.40±1.12/ 88.83 ±1.34 after 8 weeks. Mean fall in SBP and DBP was shown to be 22.17 and 9.57mmHg (Table-3). The mean SBP/DBP in the enalapril group was 151.07 ± 7.14 / 100.53 ± 5.66 at baseline, 143.73 ± 7.34 / 95.80±4.75 after 2 weeks, 136.23 ± 6.19 / 91.87 ± 2.85 after 4 weeks and 129.60 ± 0.81 / 89.23 ± 1.17 after 8 weeks. Mean fall in SBP and DBP was shown to be 22.17 and 9.57mmHg (Table-3). Mean fall in SBP and DBP was shown to be 21.47 and 11.23 mmHg. There was no significant difference in mean fall in SBP and DBP in both groups.

ECG was recorded in all patients at baseline and at the end of 8 weeks. 11 patients from both groups had preexisting changes suggestive of LVH. Out of 11, one patient in trandolapril group showed partial reversal of LVH. All laboratory parameters both at baseline and at the end of 8 weeks were within normal limits.

Adverse events were encountered in 18.33% (n = 11) and 20% (n = 12) of patients in trandolapril and enalapril group respectively. Cough (6.6%), headache (3.3%) and myalgia (3.3%) were experienced in the trandolapril group. Giddiness (6.6%), cough (5%), headache (3.3%), and fatigue (3.3%) were seen in the enalapril group (Table-4). The most common adverse event from both groups was cough in 5.8% (n = 7). All the adverse events were mild, transient, and did not require any treatment, discontinuation of medication or withdrawal from the study.

DISCUSSION

In the present study, reduction in DBP to < 90 mmHg was achieved in 75% of patients who received trandolapril 2 mg and 58% who received enalapril 5mg for 4 weeks. All patients achieved target DBP reduction by the end of 8 weeks after doubling of dose in both groups. Similar findings were observed in studies carried out by Pinakini K. Shankar et al,11 they had shown that 98.4% patients with trandolapril and 93% with enalapril achieved target DBP reduction at the end of 8 weeks. In the present study, mean reduction in SBP and DBP was 22.17 and 9.57 mmHg in trandolapril group.

In two non-comparative trials where trandolapril was administered for a period of 2 weeks to 12 months in mild to moderate hypertension, mean reduction in SBP ranged from 7 to 31 mmHg and in DBP from 8 to 20 mmHg[12,13]. Many controlled clinical trials have found that trandolapril produces clinically significant blood pressure reduction and achieves target blood pressure level in patients with hypertension[14,15]. The observations reflects that trandolapril is equally efficacious and comparable to enalapril and that trandolapril offers a satisfactory approach for reduction of blood pressure in mild to moderate hypertension. In this study, one patient from trandolapril group with LVH showed partial reversal.

Roland E16 observed in a meta-analysis that ACEIs brought about early and significant decrease in LVH mass and wall thickness in 13% of patients with a mean duration of 25 weeks. In this regard, there is a need to conduct further studies to confirm the observation.

In the present study, cough was the common adverse event in both the groups which accounted for 6.66% and 5% of patients. Many studies have proposed that bradykinin and substance P were responsible for the production of cough[17,18]. In many studies, it was observed that the incidence of cough ranged from 2.3% to 39.1% and drug withdrawal was minimal[19,21]. In the present study, we observed that cough was mild, transient and did not require discontinuation of medication or withdrawal from the study.

CONCLUSION

The present study suggests that the efficacy and tolerability of trandolapril were comparable to enalapril in mild to moderate hypertension. Both drugs effectively controlled systolic and diastolic blood pressure at the end of 8 weeks and were well tolerated with few minor adverse events.

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