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A Non randomised controlled trial of Eprosartan

KEYWORDS: Eprosartan, isolated systolic hypertension, non randomised control trial, JNC VII

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ABSTRACT *Isolated Systolic Hypertension is the most common form of hypertension in elderly which is a known risk factor for end organ damage. The aim of the present study was to study the role of Eprosartan in managing Isolated systolic hypertension (ISH) and its side effects. It was a Non randomised controlled trial conducted in Darbhanga Medical College & Hospital, Laheriasarai(Bihar) during March 2010 to December 2011. A total of 50 patients with experimental and control group was studied. The experimental group(20patients) with systolic blood pressure(SBP) less than 160 mmHg and the second experimental group(20patients) with systolic blood pressure more than 160 both showed significant decrease of SBP($p<0.001$) whereas control group patients showed no significant difference after 2 &4 weeks. Eprosartan is quite effective in controlling ISH with secondary prevention of cerebrovascular and cardiovascular events. This can be used by physicians considering its excellent long term safety and efficacy.*

Introduction

Hypertension is a major public health issue of both developed and developing countries as approximately 40% of adults aged 25 and above had been diagnosed with hypertension and it accounts for 9.4 million deaths worldwide.[1,2] The most common type of hypertension is Isolated systolic hypertension (ISH) which is defined as systolic blood pressure more than140 mm Hg and diastolic blood pressure less than 90 mm of Hg.[3] Isolated systolic hypertension is the most common form of hypertension in the elderly, present in nearly two-thirds of hypertensive individuals over age 60 years, and increasing linearly with age up to about the ninth decade of life. Elevated systolic blood pressure is a known risk factor for cardiovascular and renal disease.

Renin-angiotensin system (RAS) plays an important role in the pathogenesis of isolated systolic Hypertension. The derangement in RAS results in increased arterial thickening, stiffness and loss of contractility in arterial walls by increasing the collagen content and decreasing the elastin content which is the contributory factor in development of hypertension.The ARB(angiotensin II receptor blocker) help by decreasing the arterial stiffness in patients with isolated systolic hypertension.[4,5] Some of the ARBs approved by FDA are losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan, olmesartan and are currently in practice.[6] With a view to assess first hand the efficacy of eprosartan on ISH and to check its tolerability especially among the elderly patients age more than 50 years where ISH is more common the present study was designed.

Material and methods

The study was an open label Clinical intervention study (Non randomised control trial). Patients of ISH were selected from in-patient and out-patient medical department of Darbhanga Medical College & Hospital, Laheriasarai(Bihar). The patients were treated on an outdoor basis and were asked to report to the OPD once in fifteen days for follow-up for 4 weeks.

Inclusion criteria:

1. Age >50 years of either gender
2. Patients having ISH. Diagnosis of ISH was made on the basis of blood pressure. Since recommendations of JNC-VII (2003)[3] were followed hence patients with diastolic blood pressure (DBP) less than 90 mm of Hg and systolic blood pressure (SBP) of more than 140 mm Hg were included in present study.

Exclusion criteria:

1. Hypertension due to secondary causes of ISH such as thyrotoxicosis, severe anemia, aortic incompetence or arteriovenous fistula etc. after a meticulous clinical search aided by laboratory investigations.
2. Patients habituated to alcohol, tobacco smoking, pregnant women, patients with uncontrolled hypertension or those showing end stage organ damage, patients with renal impairment or liver dysfunction and those unwilling to participate in the study were excluded.
3. Patients already on antihypertensive therapy were also excluded from the study

This study enrolled 50 patients aged more than 50 years of either gender attending the medicine out-door in the Darbhanga Medical College Hospital, Laheriasarai, Bihar. The control group included 10 hypertensive patients with SBP less than 160 mmHg and were given a placebo (multivitamin pill) and life style changes with the advice to report for check ups. They were to be excluded from the study if at any time SBP became more than 160 mmHg. The other group included 40 hypertensive patients. 20 patients with SBP less than 160 mmHg and were given 400 mg of Eprosartan once daily. The other 20 patients with SBP more than 160 were given 800 mg of Eprosartan on once a daily basis.

An informed consent was obtained from all the patients.An initial work up on all patients was done collecting a detailed history followed by clinical examination and investigations. The arterial blood pressure of all patients enrolled in the study was recorded using a standard sphygmomanometer in the right upper limb in the sitting position registering the mean of the last two of three consecutive readings. This was recorded as the baseline value (phase 0). Follow up was done during the study period of 4 weeks for (1)Recording of the blood pressure of patients. (2)Side effects which developed during therapy with either Eprosartan or placebo were enquired for and appropriate laboratory investigations were performed. As regarding investigations, peripheral blood counts and routine examination of urine were frequently performed. Patients whose blood pressure could not be controlled satisfactory after 4 weeks of Eprosartan, would be treated by other conventional suitable drugs was contemplated.

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The study was approved by the institutional ethical committee. Data obtained during the study were recorded in structured questionnaire. It was entered in Microsoft excel 2010 and analysis was done using SPSS version 19. The range, mean, standard deviation (SD), standard error of mean(SE) and difference between the means before and after the therapy(intervention) was calculated.

Results

A total 50 subjects were studied and were grouped into experimental (40) and control arms (10).

The group with systolic blood pressure less than 160 mmHg had 20 patients with 5(25%) females. The age group ranged from 54-78 years. The range of systolic blood pressure was 140-158 mm of Hg (before therapy) with a mean of 151.6 mm of Hg (SD=5.8,SE=1.3). After the end of two weeks of starting therapy the mean systolic blood pressure decreased to 136.8 mm of Hg (SD=5.17 SE=1.15). The diastolic blood pressure was ranging from 80-90 mm of Hg with a mean of 83.4 mm of Hg (SD=2.6,SE=0.58) before therapy. After therapy at the end of two weeks, the mean diastolic blood pressure decreased to 81.6 mm of Hg (SD=1.79, SE=0.4). With the same treatment regimen after the end of 4 weeks the mean systolic blood pressure further decreased to 130.5 mm of Hg (SD=4.58, SE=1.02) and the diastolic blood pressure came down to78mm of Hg (SD=1.95, SE=0.43). Significance level is presented in Table 1 and 2.

Table 1. Comparison of Blood Pressure with base values

BP	T-value		P-value	
	After 2 weeks	After 4 weeks	After 2 weeks	After 4 weeks
SBP	8.53	12.78	<0.001(HS)	<0.001(HS)
DBP	2.55	7.43	<0.001(HS)	<0.001(HS)

Table 2. Comparison between therapy after 2 and 4 weeks

BP	T-value	P-value
SBP	4.08	<0.001(HS)
DBP	6.11	<0.001(HS)

The group SBP more than 160 mmHg had 20 patients with females 4(20%) in the the age group ranging from 53-77 years. The range of systolic blood pressure was from 160-178 before therapy with a mean of 168.6 (SD=6.12, SE=1.37). After the end of two weeks of therapy, the mean systolic blood pressure decreased to 153.3 mmHg (SD=5.52, SE=1.23). The diastolic blood pressure was ranging from 82-88 mm of Hg with a mean of 86.1 mm of Hg (SD=1.89 ,SE=0.42) before therapy. After therapy at the end of two weeks the mean diastolic blood pressure decreased to 81.8 mm of Hg (SD=1.58, SE=0.35).With same treatment regimen after the end of 4 weeks the mean systolic blood pressure further decreased to 146.3 mm of Hg (SD=6.75, SE=1.51). Diastolic blood pressure with same treatment regimen after the end of 4 weeks further decrease to 79.1 mm of Hg (SD=1.65,SE=037). Significance level is presented in Table 3 and 4.

Table 3: Comparison of Blood pressures with base values

BP	T-value		P-value	
	After 2 weeks	After 4 weeks	After 2 weeks	After 4 weeks
SBP	8.3	10.94	<0.001(HS)	<0.001(HS)
DBP	7.82	12.48	<0.001(HS)	<0.001(HS)

Table 4. Comparison between therapy after 2 and 4 weeks

BP	T value	P value
SBP	3.59	<0.01
DBP	5.29	<0.01

The control group had 10 Patients with 3(33.3%) females having SBP less than 160 mmHg. The age group of patients ranged from 57-77 years.Before placebo treatment, the mean systolic blood pressure was 145 mm of Hg (SD=2.87, SE=0.91). After treatment with a placebo for 2 weeks patients the mean SBP was found to be 145.2 mm of Hg (SD=2.53, SE=0.8). The changes was minimal and it was not significant. (P=0.10).The mean diastolic blood pressure was 85.60 (SD=2.63, SE=0.83) before the start of treatment with a placebo. After treatment with placebo for 2 weeks, the mean diastolic blood pressure was 84.4 mm of Hg (SD=3.37, SE=1.07). The difference was not significant. (P=0.8) .With the same placebo treatment for another 2 weeks mean systolic blood pressure did not decrease. It was 144.8 mm of Hg (SD=2.7, SE= 0.85).The mean diastolic blood pressure decreased to 84.2 (SD=3.58, SE=1.13) but not significantly. (P=0.3).

Table 5: Adverse effects with Eprosartan and Placebo.

Side effects	Placebo (N=10)	Study Group (N=40)
Dry Cough	1	1
Dizziness	1	2
Headaches	1	0
Upper Resp. Infection	0	0
Chest pain	0	0
Rhinitis	0	0
Myalgia	0	1
Sinusitis	0	0

Discussion and Conclusion:

Similar studies about Eprosartan have not been reported in India but since its approval there are many studies with similar findings that of this study. The POWER survey which used Framingham methodology reported that SBP declined by 22.4 mmHg and DBP declined 10.5 mmHg and significant reduction was seen in CHD risk as an impact of ARB based regimen comprising of Eprosartan 600mg/day as against 400mg in ISH patients having SBP less than 160mm Hg and 800mg/day in patients having SBP more than 160mm Hg in the present study .[7,8] In a RCT conducted at 35 primary care centres in Canada, it was found that Eprosartan alone was effective in controlling hypertension and there was no additional advantage of adding one more drug in controlling BP.[9] A meta-analysis of antihypertensives effects and safety of eprosartan compared with other antihypertensives concluded that Eprosartan monotherapy is equivalent to many first-line antihypertensive agents and is effective for the treatment of essential hypertension, especially for isolated systolic hypertension and can be considered by physicians.[10] A review done by Plosker demonstrated eprosartan (with or without hydrochlorothiazide) demonstrated superior antihypertensive efficacy to that of placebo. Eprosartan was generally well tolerated in clinical trials and had a lower incidence of persistent dry cough than enalapril.[11] In the present study also eprosartan was helpful in reduction of blood pressure significantly. But none of patients of with systolic blood pressure more than 160 mmHg achieved the level of normal blood pressure in spite of appreciable reduction in both systolic and diastolic blood pressure. It indicates that addition of another antihypertensive drug is necessary in stage II hypertension. Majority of patients with systolic blood pressure less than

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160 mmHg achieved reduction and came in prehypertension and a few became normotensive. In the control group of 10 patients on placebo therapy, the reduction in blood pressure was insignificant. The commonest side effects were dry cough(2.5%), dizziness(5%), but none of patients withdrew from the study because of its side effects.

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