International Journal of Life science & Pharma Research

A COMPARATIVE RANDOMISED CONTROLLED PARALLEL GROUP STUDY OF EFFICACY AND TOLERABILITY OF LABETALOL VERSUS METHYLDOPA IN THE TREATMENT OF NEW ONSET HYPERTENSION DURING PREGNANCY

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ABSTRACT

Hypertensive disorders in pregnancy remain one of the major causes of maternal and perinatal mortality in developing as well as developed countries and can result in hospital admission, pre-eclampsia and possible premature delivery. Antihypertensive drugs are often used to lower blood pressure to prevent this progression to adverse outcomes for the mother and the fetus. Methyldopa has often been used as control while comparing the effects of different dugs. Labetalol has also been successfully used for treatment of hypertensive disorders in pregnancy. Hence, we wanted to compare the efficacy and tolerability of labetalol versus methyldopa in pregnancy induced hypertension (PIH) in an Indian population. We carried out a prospective randomised controlled parallel group study on 90 outpatients as well as inpatients of the antenatal ward of Obstetrics and Gynaecology department of our tertiary care teaching hospital. Pregnant patients (20-40 weeks gestational age) newly diagnosed with blood pressure of ≥140/90mmHg and single ton with vertex presentation were included in the study. All patients with a history of hypertension, diabetes, Rh iso-immunisation, depression, congestive heart failure, heart block or bronchial asthma, patients at risk of major obstetric complications - antepartum haemorrhage, malnutrition, twins and hydramnios during the current pregnancy and patients who had already received antihypertensive drugs were excluded. 45 patients each were randomised to either of the two treatment arms – oral methyldopa or oral/IV labetalol. Difference in BP measurements pre- and post-treatments (on 8th day) were analysed by applying paired‘t’ test for the difference in pre- and post-treatment values. For inter group analysis, we applied chi-square test, using Epi Info statistical software version 3.3. A *P*-value < 0.05 was regarded as significant with 95% confidence limits. Adverse events were documented and subjected to causality analysis by Naranjo’s scale. There was no statistically significant difference in antihypertensive efficacy between the methyldopa and labetalol groups. Adverse drug reactions were possible to probable and occurred less with labetalol. However, despite equal efficacy and better tolerability, effect on fetal and maternal outcomes determines whether labetalol is better than methyldopa in PIH.

Key words: Pregnancy, Hypertension, Methyldopa, Labetalol, Efficacy, Tolerability

INTRODUCTION

Hypertension during pregnancy is defined as a diastolic blood pressure of 90 mmHg or greater on two occasions more than 4 hours apart or a single diastolic blood pressure above
110 mmHg. (Davey DA and MacGillivray I, 1988) Hypertensive disorders during pregnancy occur in women with pre-existing primary or secondary chronic hypertension, and in women who develop new-onset hypertension in the second half of pregnancy. Hypertensive disorders in pregnancy remain one of the major causes of maternal and perinatal mortality in developing as well as developed countries. (Magee LA and von Dadelszen P, 2004) Mild hypertension, which is defined as systolic blood pressure (BP) of 140 to 159 mmHg or diastolic blood pressure of 90 to 109 mmHg or both, is common during pregnancy. In some women, it can become more serious, resulting in hospital admission, pre-eclampsia and possible premature delivery. Antihypertensive drugs are often used to lower blood pressure with the aim of preventing this progression to adverse outcomes for the mother and the fetus. Severe hypertension, conventionally defined as a BP of >160/110 mmHg, should be treated to prevent severe maternal complications. (Podymow T and August P, *et al*, 2008) Even though a recent systematic review found that there was not enough evidence to show the benefit of antihypertensive drugs for mild hypertension during pregnancy, the risk of developing severe hypertension is reduced to half by using antihypertensive medications, (Abalos *et al*, 2007) so more research is needed. Many antihypertensive agents have been used to determine the possible benefits, risks and side-effects of drug treatment for women with pregnancy induced hypertension and to compare the differential effects of alternative drug regimens. Methyldopa has often been used as control while comparing the effects of different dugs. Labetalol has also been successfully used for treatment of hypertensive disorders in pregnancy. Though beta blockers have been found to be better in treating severe hypertension during pregnancy, there is insufficient evidence to support the same in case of mild hypertension in pregnancy. (Abalos *et al*, 2007) In this backdrop, we wanted to compare the antihypertensive drugs - labetalol versus methyldopa in pregnancy induced hypertension (PIH) in an Indian population.

Our objectives were:

1. To evaluate the efficacy of labetalol versus methyldopa as antihypertensive in the treatment of new onset hypertension during pregnancy
2. To evaluate the safety and tolerability of labetalol versus methyldopa in the treatment of new onset hypertension during pregnancy

MATERIALS AND METHODS

We carried out a prospective randomised controlled parallel group study on outpatients as well as inpatients of the antenatal ward of Obstetrics and Gynaecology department of our tertiary care teaching hospital. Ethical clearance for the study was obtained from the institutional human ethics committee. Patients were enrolled after informed consent was taken. A total of 90 patients were enrolled in the study as per selection criteria.

Pregnant patients newly diagnosed with systolic blood pressure of ≥140mmHg and a diastolic blood pressure of ≥ 90mmHg and gestational age between 20-40 weeks of pregnancy (calculated from the first day of last menstrual period) were included in the study. Only singleton pregnancy with vertex presentation was included. We did not keep edema or proteinuria as criteria for inclusion in the study, that is, they may or may not be present in the patients. All patients with a history of hypertension, diabetes, Rh iso-immunisation, depression, congestive heart failure, heart block or bronchial asthma, patients at risk of major obstetric complications - antepartum haemorrhage, malnutrition, twins and hydramnios during the current pregnancy and patients who had already received antihypertensive drugs were excluded.

Patients (45 each) were randomised using computer generated sequence of random numbers to either of the two treatment arms – labetalol and methyldopa, with bed rest for patients in each

group. The point of BP control was taken as a diastolic BP below 90mmHg in both groups. Labetalol was administered as oral/IV preparation and methyldopa as oral preparation in the respective groups. IV preparation was used to manage severe hypertension and eclampsia.

The starting dose of labetalol for patients with diastolic blood pressure 90-109 mmHg was 100mg stat and eight hourly. If diastolic pressure was ≥ 110mmHg, stat dose of 200mg was administered followed by 100mg eight hourly. Depending upon the response to treatment, the dose of labetalol was increased every 48 hours up to a maximum of 300mg eight hourly. Patients who failed to achieve the point of control seven days after initiation of therapy with a maximum of 900 mg/day of labetalol for at least 72 hours were labelled uncontrolled.

The starting dose of methyldopa for patients with a diastolic BP of 90-109 mmHg was 250mg stat and then six hourly. If the diastolic pressure was ≥ 110mgHg, dose was increased to 500mg six hourly up to a maximum of 2g/day. Patients who failed to achieve the point of control seven days after initiation of therapy with a maximum of 2g/day of methyldopa continued for at least 72 hours were labelled uncontrolled.

Measurement of blood pressure (BP) was done using mercury sphygmomanometer (auscultation method) taken after 15 minutes of rest. Readings were taken at least on two occasions six hours apart before diagnosing the patient as hypertensive. After removing any light clothing from the right arm, the patient was made to lie in the left lateral position with approximately 30 degrees of tilt towards the observer, with the right arm well supported at the level of the heart. The sphygmomanometer cuff of 12 cm was firmly applied over the right arm 2.5 cm above the elbow. Systolic BP corresponded to appearance of the first clear tapping sounds and diastolic BP was recorded at the point where the sounds first became muffled. (Korotkoff's phase IV). The mean of three recordings was taken as the value of BP.

Patients were followed up and BP, pulse rate and fetal heart rate were recorded every 15 minutes for two hours after initiation of treatment. Thereafter, the same parameters were recorded eight hourly during the period of hospital stay which depended upon the maternal response and gestational age. Patients close to term were followed up in the hospital whereas others were discharged after 10-14 days provided they had good control of BP, and did not show significant proteinuria or gross intra uterine growth retardation. On discharge, patients were advised to take the minimum dose of drug which kept the BP below 90mmHg, with advice to come for weekly follow up and get re-admitted if BP rose beyond the point of control.

Patients who remained uncontrolled in spite of therapy in both the groups were closely monitored in the hospital and attempt was made to continue the pregnancy up to 37 completed weeks followed by induction of labour and caesarean section, wherever induction was contraindicated or failed.

The primary efficacy end point was taken as change in baseline (pre-treatment) value of diastolic BP in left lateral position on the eighth day of treatment with the particular drug. Other end points included change from the baseline systolic BP.

Tolerability of the patients to labetalol and methyldopa was assessed by observing for adverse events and analysing for causality using Naranjo's scale. (Naranjo *et al*, 1981)

Statistical analysis was done by applying paired't' test for the difference in pre- and post-treatment values. For inter group analysis, we applied chi-square test, using Epi Info statistical software version 3.3. A *P*-value < 0.05 was regarded as significant with 95% confidence limits.

RESULTS

Age distribution of patients with PIH in both groups is shown in Table 1. Distribution of parity in both groups is shown in Table 2 and distribution of gestational age at which PIH is detected is shown in Table 3. Tables 4, 5 and 6 show the values of pre- and post-treatment mean systolic, mean diastolic and average mean BP.

Table 1: ***Age distribution of patients in group I (Methyldopa) and group II (Labetalol)***

Sl No	Age (Yrs)	Group I (Methyldopa)	Group II (Labetalol)	Total
		No of cases (%)	No of cases (%)	No of cases (%)
1	<18	3 (6.66%)	4 (8.8%)	7 (7.77%)
2	19-24	29 (64.44%)	23 (51.1%)	52 (57.77%)
3	25-30	12 (22.22%)	18 (40%)	30 (33.33%)
4	>30	1 (2.22%)	0 (0 %)	1 (1.11%)
Total No	of cases	45 (100%)	45 (100%)	90 (100%)

By Epi Info Statistical Software Version 3.3, Chi Square test $P > 0.05$ (Insignificant)

Table 2: ***Parity distribution of patients in group I (Methyldopa) and group II (Labetalol)***

Sl No	Parity	Group I (Methyldopa)	Group II (Labetalol)	Total
		No of cases (%)	No of cases (%)	No of cases (%)
1	G_1P_0	30 (66.66%)	24 (53.33%)	54 (60%)
2	G_2P_1	10 (22.22%)	13 (28.88%)	23 (25%)
3	G_3P_2	3 (6.66%)	4 (8.88%)	7 (7.77%)
4	G_4P_3	2 (4.44%)	4 (8.88%)	6 (6.66%)
Total No	of cases	45 (100%)	45 (100%)	90 (100%)

By Epi Info Statistical Software Version 3.3, Chi Square test $P > 0.05$ (Insignificant)

Table 3: ***Distribution of patients by Gestational age in group I (Methyldopa) and group II (Labetalol)***

Sl No	Gestational Age (Weeks)	Group I (Methyldopa)	Group II (Labetalol)	Total
		No of cases (%)	No of cases (%)	No of cases (%)
1	21-24	2 (4.44%)	1 (2.22%)	3 (3.33%)
2	25-28	1 (2.22%)	0 (0%)	1 (1.11%)
3	29-32	11 (24.49%)	12 (26.66%)	23 (25.55%)
4	33-37	31 (68.88%)	32 (71.11%)	63 (70%)
Total No	of cases	45 (100%)	45 (100%)	90 (100%)

By Epi Info Statistical Software Version 3.3, Chi Square test $P > 0.05$ (Insignificant)

Table 4: ***Shows mean systolic BP pre- and post-treatment values (8th day) in group I (Methyldopa) and group II (Labetalol)***

Sl No	Groups	Pre-treatment value of Systolic BP (mmHg)	Post-treatment value of Systolic BP (mmHg)	't' value	P value	Inference
1	Methyldopa	151.55±9.28	124.00±9.14	14.19	<0.05	Significant
2	Labetalol	149.70±9.16	126.20±10.28	11.45	<0.05	Significant
	't' value	0.95	1.07		>0.05	Insignificant

By Epi Info Statistical Software Version 3.3, Chi Square test P > 0.05 (Insignificant)

Table 5: ***Shows mean diastolic BP pre- and post-treatment values (8th day) in group I (Methyldopa) and group II (Labetalol)***

Sl No	Groups	Pre-treatment value of Diastolic BP (mmHg)	Post-treatment value of Diastolic BP (mmHg)	't' value	P value	Inference
1	Methyldopa	102.00±98.94	77.55±5.28	15.80	<0.05	Significant
2	Labetalol	101.77±10.06	78.44±8.24	12.04	<0.05	Significant
	't' value	0.11	0.61		>0.05	Insignificant

By Epi Info Statistical Software Version 3.3, Chi Square test *P* > 0.05 (Insignificant)

Table 6: ***Shows average mean BP pre- and post-treatment values (8th day) in group I (Methyldopa) and group II (Labetalol)***

Sl No	Groups	Pre-treatment value of Average mean BP (mmHg)	Post-treatment value of Average mean BP (mmHg)	't' value	P value	Inference
1	Methyldopa	118.51±7.53	93.03±7.08	16.54	<0.05	Significant
2	Labetalol	117.74±8.63	94.36±8.04	13.30	<0.05	Significant
	't' value	0.05	0.83		>0.05	Insignificant

By Epi Info Statistical Software Version 3.3, Chi Square test *P* > 0.05 (Insignificant)

In the methyldopa treated group, the mean systolic BP prior to treatment was 151.55 ± 9.28 mmHg. After treatment, systolic BP reduced to 124.00±9.14mmHg on the eighth day of treatment. Reduction in systolic BP was statistically significant ($P < 0.05$), compared to pre-treatment value.

In the labetalol treated group, the mean systolic BP prior to treatment was 149.70 ± 9.16 mmHg. After treatment, systolic BP reduced to 126.20 ± 10.28mmHg on the eighth day of treatment. Reduction in systolic BP was statistically significant ($P < 0.05$), compared to pre-treatment value.

On comparing methyldopa and labetalol groups, difference in fall in systolic BP was not statistically significant. ($P>0.05$)

In the methyldopa treated group, the mean diastolic BP prior to treatment was 102.00 ± 98.94 mmHg. After treatment, diastolic BP reduced to 77.55±5.28mmHg on the eighth day of treatment. Reduction in diastolic BP was statistically significant ($P < 0.05$), compared to pre-treatment value.

In the labetalol treated group, the mean diastolic BP prior to treatment was 101.77 ± 10.06 mmHg. After treatment, diastolic BP reduced to 78.44 ± 8.24mmHg on the eighth day of treatment. Reduction in diastolic BP was statistically significant ($P < 0.05$), compared to pre-treatment value.

On comparing methyldopa and labetalol groups, difference in fall in diastolic BP was not statistically significant. ($P>0.05$)

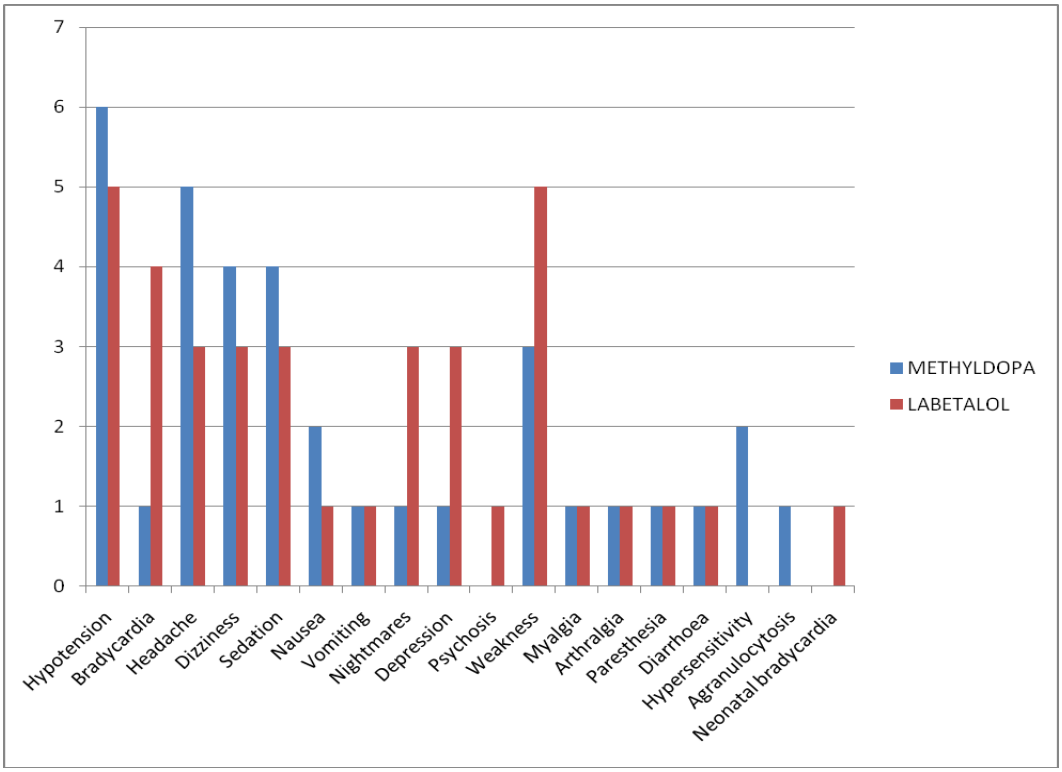
In the methyldopa treated group, the average mean BP prior to treatment was 118.51 ± 7.53 mmHg. After treatment, average mean BP reduced to 93.03 ± 7.08mmHg on the eighth day of treatment. Reduction in average mean BP was statistically significant ($P < 0.05$), compared to pre-treatment value.

In the labetalol treated group, the average mean BP prior to treatment was 117.74 ± 8.63 mmHg. After treatment, average mean BP reduced to 94.36 ± 8.04mmHg on the eighth day of treatment. Reduction in average mean BP was statistically significant ($P < 0.05$), compared to pre-treatment value.

On comparing methyldopa and labetalol groups, difference in fall in average mean BP was not statistically significant. ($P>0.05$)

Incidence of severe hypertensive crisis and eclampsia was 4.44% in methyldopa group and 6.66% in labetalol group. Difference between groups is not statistically significant.

Adverse events observed with both drugs are shown in Fig 1. These were lower in the labetalol treated group compared to the methyldopa group. By applying Naranjo's Causality analysis scale, we could assign a score of 4 to all the adverse reactions except for hypotension, bradycardia, neonatal bradycardia and hypersensitivity which were assigned a score of 5. We did not attempt dechallenge (except where clinically warranted) or rechallenge in the interest of the mother and fetus.



Numbers 0 to 7 depict the number of occurrences of the specific adverse event

Figure 1: ***Adverse events observed with Methyldopa and Labetalol in the respective groups***

DISCUSSION

Age distribution shows maximum patients between 19-24 years in both groups (64.44% in methyldopa group and 57.77% in labetalol group) and there was no significant difference in age distribution in both groups. Most common age group is in contrast to the findings of a large database study wherein there was a linear relationship between age and incidence of PIH. (Guzick DS *et al*, 1987).

Parity distribution shows maximum patients of PIH with G_1P_0 (primigravidae) in both groups (66.66% in methyldopa group and 53.33% in labetalol group) and there was no significant difference between groups in terms of parity distribution. This finding is similar to previous studies. (Walker JJ *et al*, 1982; Redman CWG *et al*, 1984; Plouin PF *et al*, 1988). Most patients with PIH (71.11% in methyldopa group and 68.88% in labetalol group) belonged to 33-37 weeks gestational age and there was no statistically significant difference between groups. This finding of the most common gestational age at which PIH developed is supported by other studies. (Walker JJ *et al*, 1982; Redman CWG *et al*, 1984; Lardoux H *et al*, 1988) However, according to another observation, the majority of cases of mild gestational hypertension develop at or beyond 37 weeks' gestation. (Sibai BM, 2003).

Both labetalol and methyldopa significantly reduce systolic and diastolic BP. However, control of BP by labetalol as well as methyldopa is comparable after eight days of treatment. That labetalol is an effective antihypertensive which decreases both systolic and diastolic BP in pregnancy induced hypertension was proved earlier. (Pickles CJ *et al*, 1992; Mahmoud TZ *et al*, 1993) Also, the comparable effect of methyldopa and labetalol on BP control in hypertensive disorders of pregnancy is supported by previous studies. (Redman CWG *et al*, 1984; Sibai BM *et al*, 1987; Plouin PF *et al*, 1988; Pickles CJ *et al*, 1989; Sibai BM *et al*, 1990) However, one study says that labetalol provides more efficient control of BP than methyldopa in the treatment of mild hypertension in pregnancy. (El-Qarmalawi *et al*, 1995) Hypertensive crisis and eclampsia occurred in both groups, but no significant difference was observed between methyldopa and labetalol groups.

Adverse effects seen with both drugs are of known types and labetalol caused fewer adverse effects compared to methyldopa. The adverse drug reactions were grouped in possible category except for hypotension, bradycardia, neonatal bradycardia and hypersensitivity which were assigned probable causality. Causality association could not be made stronger due to the lack of information on dechallenge and rechallenge, which were avoided for the safety of the mother and fetus.

The effect on fetal and maternal outcomes, for example, the incidence of prematurity, intra-uterine growth retardation, perinatal death, need for intensive nursery care in the baby or effect on hepatic and renal functions, incidence of eclampsia and incidence of elective or caesarean section in the mother must be considered before pronouncing that labetalol may be preferred in PIH on account of equal efficacy and better tolerability.

Labetalol is a third generation beta blocker with alpha adrenergic receptor blocking property and it has an additional arteriolar vasodilating mechanism for lowering peripheral vascular resistance. It causes selective blockade of α1 as well as β1and β2 receptors and also has partial agonist activity at β2 receptors. α1 receptor blockade contributes to the relaxation of arterial smooth muscle and vasodilatation, particularly in upright position. Blockade of β1 receptors prevents reflex sympathetic stimulation of the heart following fall in blood pressure and intrinsic sympathomimetic activity of labetalol at β2 receptors also contributes to the vasodilatation and subsequent fall in BP. (Brunton L *et al*, 2011).

CONCLUSION

Labetalol is equally efficacious and better tolerated compared to methyldopa in the treatment of new onset hypertension during pregnancy. However, the effect on fetal and maternal outcomes must be considered before selecting labetalol over methyldopa in the treatment of hypertensive disorders of pregnancy.

ACKNOWLEDGMENTS

We express our deepest thanks to Dr. Seetesh Ghose, Professor and Head of the Department of Obstetrics and Gynaecology of Mahatma Gandhi Medical College & Research Institute, Pondicherry, India for reviewing our manuscript.

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