Comparative Efficacy of Labetalol and Methyldopa in the Treatment of New Onset Hypertension during Pregnancy

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ABSTRACT

BACKGROUND

Hypertensive disorders in pregnancy remain one of the major causes of maternal and perinatal morbidity and mortality particularly in developing countries like India and can result in hospital admission, preeclampsia also premature delivery. Antihypertensive drugs are often used to lower blood pressure with the aim of preventing its progression to adverse outcomes for the mother and the foetus. The risk of developing severe hypertension is reduced to half by using antihypertensive medications. Methyldopa has often been used as control while comparing the effects of different drugs. Labetalol has also been successfully used for the treatment of hypertensive disorders in pregnancy. The study was planned to assess and compare efficacy of labetalol and methyldopa in the treatment of new onset hypertension during pregnancy.

METHODS

A total of 120 women was enrolled in the study as per selection criteria. Pregnant patients newly diagnosed with systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥ 90 mmHg on two separate occasion 6 hours apart, proteinuria 1+ dipstick in two midstream urine samples collected 4 hours apart, between 20-40 weeks of pregnancy (calculated from the first day of last menstrual period) were included in the study. Only singleton pregnancies with vertex presentation were included. Out of 120 women, 60 were given Methyldopa and 60 were given Labetalol. After randomization they were divided into two groups, Group A received methyldopa 250 mg TID and Group B received labetalol 100 mg TID. Mean Arterial Pressure (MAP) was calculated according to formula systolic BP +2 diastolic BP /3. Mothers were subjected to 6 hourly BP monitoring. Comparison of two drugs was done daily by calculating MAP of two groups. After collection of data, statistical analysis of the data was done by using Student's Sample Independent Test (either paired or independent) (SPSS version 20).

RESULTS

Significant fall in MAP was seen in patients receiving Labetalol. Labetalol reduces BP more rapidly (<48 hrs) compared to Methyldopa. Adverse drug reactions were more in methyldopa group compared to labetalol group.

CONCLUSIONS

Freedom from maternal and foetal side-effects, efficient hypotensive action indicate that labetalol is suitable for treatment of new onset hypertension during pregnancy.

KEYWORDS

Pregnancy, Hypertension, Methyldopa, Labetalol, Efficacy

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BACKGROUND

Hypertensive disorders seem to complicate approximately 10% of pregnancies and are important causes of maternal and foetal morbidity and mortality.[1] Hypertension is the most common medical problem encountered during pregnancy.[2] It is estimated that globally 6-8% of pregnancies are complicated by hypertension.[3] 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. 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 its progression to adverse outcomes for the mother and the foetus. The risk of developing severe hypertension is reduced to half by using antihypertensive medications. Methyldopa, labetalol and long-acting nifedipine are acceptable oral antihypertensive agents used in pregnant women with mild to moderate hypertension. 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).[4] 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 background, we wanted to compare the antihypertensive drugs methyldopa versus labetalol in pregnancy induced hypertension in an Indian population.

We wanted to compare efficacy of methyldopa and labetalol in the treatment of new onset hypertension during pregnancy.

METHODS

A prospective randomised controlled parallel group study on outpatients as well as inpatients of the antenatal ward of Obstetrics and Gynaecology Department, Burdwan Medical College, Burdwan from January 2017 to June 2018 for a period of one and half years. Ethical clearance for the study was obtained from the institutional human ethics committee. After taking informed consent total 120 women were enrolled in the study as per selection criteria. Pregnant patients newly diagnosed with systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg on two separate occasion 6 hours apart, Proteinuria 1+ dipstick in two midstream urine samples collected 4 hours apart 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. Multifetal pregnancy, eclampsia, and women with pre-existing or concurrent medical disorders like diabetes mellitus, cardiac diseases, renal disease, thyrotoxicosis and chronic hypertension attributable to hypertension during their pregnancy were excluded from the study. Out of 120 women 60 were given Methyldopa and 60 were given Labetalol after taking history, general and systemic examination. After randomization they were divided into two groups, Group A received methyldopa 250 mg TID and Group B received labetalol 100 mg TID. Mean Arterial pressure (MAP) was calculated according to formula systolic BP +2 diastolic BP/3. Mothers were subjected to 6 hourly BP monitoring. Comparison of two drugs was done daily by calculating MAP of two groups. If there was no fall in BP even after 48 hrs of drug therapy, dose of the drug was doubled. Response in lowering BP was assessed over a period of 7 days. Observations were made as regards fall in BP with methyldopa/ labetalol, time required to control BP, onset of labour spontaneous/induced, neonatal outcome in terms of 5 minutes Apgar score and SNCU admission also the side effects of drugs. The starting dose of labetalol for patients with diastolic blood pressure 90-109 mmHg was 100 mg stat and eight hourly. If diastolic pressure was ≥110 mmHg, stat dose of 200 mg was administered followed by 100 mg eight hourly. Depending upon the response to treatment, the dose of labetalol was increased every 48 hours up to a maximum of 300 mg 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 250 mg stat and then sixth hourly. If the diastolic pressure was ≥110 mgHg, dose was increased to 500 mg six hourly up to a maximum of 2 g/day. Patients who failed to achieve the point of control seven days after initiation of therapy with a maximum of 2 g/day of methyldopa continued for at least 72 hours were labelled uncontrolled.

Categorical variables are expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Continuous variables are expressed as Mean, Median and Standard Deviation and compared across the groups using Mann-Whitney U test. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

RESULTS

Figure 1 and 2 shows age and gravida distribution in both groups. Maximum numbers of patients were in the age group of 18-25 years and majority of them were primigravida. Table 1 compared mean arterial pressure on admission and after treatment in both groups. In the present study, the mean arterial pressure in patients treated with

methyldopa on admission was 116.78 mmHg while on day 7 it reduced to 105.52 mmHg, with a statistically significant p value <0.05. With labetalol, the mean arterial pressure on admission was 117.99 mmHg which reduced to 95.25 mmHg on day 7. Reduction in MAP was statistically significant. On comparing the two drugs, MAP on admission were comparable but on day 7, significant fall in MAP was seen in patients receiving labetalol. Table 2 compared the time taken to control the BP in both the groups. Labetalol reduces BP more rapidly (<48 hrs) compared to methyldopa (p <0.001). Figure 3 shows adverse drug reactions. There were significantly more cases with adverse drug reactions in methyldopa group compared to labetalol group. So, more patients will accept labetalol to control BP. The commonest side effects noted in methyldopa group in our study were headache (18.33%) followed by drowsiness (10%) and nasal stuffiness (8.33%). The commonest side effects noted in Labetalol group is dyspnoea (8.33%). Gastrointestinal symptoms in the form of nausea or vomiting were encountered in about 8.33% in methyldopa group and 6.67% in labetalol group.

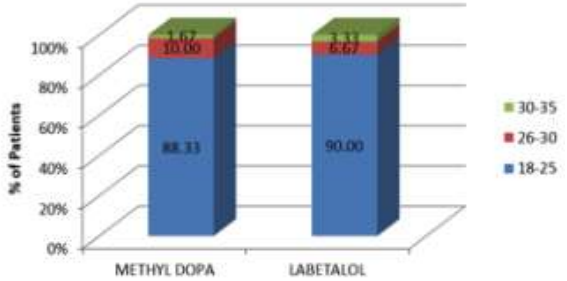

Figure 1. Age Distribution in Both Groups

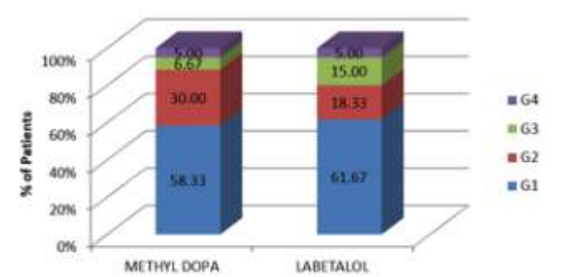

Figure 2. Distribution of Gravida in Both Groups

	Group							
	Methyl DOPA			Labetalol				
	Mean	Median	S.D.	Mean	Median	S.D.	p	Significance
Map on Admission	116.78	116.34	5.03	117.99	117.67	5.60	0.263	Not Significant
Map after Treatment	105.52	104.67	9.54	95.25	95.00	7.01	<0.001	Significant

Table 1. Comparison of MAP on Admission and After Treatment (Observations Made Over a Period of 7 Days)

		Group		Total	p	Significance
		Methyl DOPA	Labetalol			
Time Taken to Control BP	<=48 Hours	17(28.33)	40(66.67)	57(47.5)	<0.001 <=48 Hours	Significant
	>48-96 Hours	17(28.33)	18(30)	35(29.17)		
	>96 Hours	26(43.33)	2(3.33)	28(23.33)		
Total		60(100)	60(100)	120(100)		

Table 2. Comparison for Time Taken to Control BP

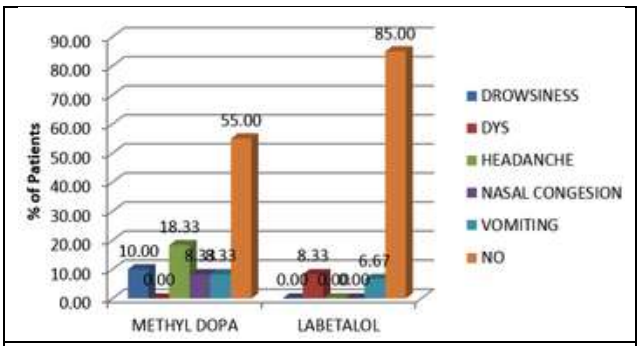

Figure 3. Adverse Drug Reactions in Both Groups

DISCUSSION

Among the total 120 patients in the present study, maximum number of patients in both the groups, group A (Methyldopa) and group B (Labetalol), were in the age group of 18-25 years. Gravidity distribution showed maximum patients of PIH as primigravida in both the groups. There were no significant differences in age and parity distribution in both the groups.

In the present study, the mean arterial pressure in patients treated with methyldopa on admission was 116.78 mmHg while on day 7 it reduced to 105.52 mmHg, with a statistically significant p value <0.05. With labetalol, the mean arterial pressure on admission was 117.99 mmHg which reduced to 95.25 mmHg on day 7. Reduction in MAP was statistically significant. On comparing the two drugs, MAP on admission were comparable but on day 7, significant fall in MAP was seen in patients receiving labetalol.

According to a study conducted by Lamming et al, the average MAP in both groups was same before treatment. There was a highly significant fall in MAP in the group treated with labetalol (p<0.001) but no significant fall was noted in the group tested with methyldopa (p>0.05).[5] In a similar study conducted by El Qarmalawi et al, 81.4% patients in labetalol group had a significant fall in MAP as against 68.5% in patients taking methyldopa.[6]

Table 2 shows time taken to control BP. Here p value is significant (<0.001). Labetalol reduces BP more rapidly (<48 hrs) compared to methyldopa. D.J. Cruickshank, et al[7] observed that Labetalol did control the blood pressure in 45 of the 51 treated women (88%) within 24 hrs. The rapid control of blood pressure with oral labetalol achieving a satisfactory response in 88% (45/51) of cases within 24 h is an obvious advantage. It is interesting that several other workers have found similar response rates - Lardoux's group 82%, CA Michael 92%.[8,9]

Figure 3 shows adverse drug reactions. There were significantly more cases with adverse drug reactions in methyldopa group compared to labetalol group. So more patients will accept labetalol to control BP. The commonest side effects noted in methyldopa group in our study were headache (18.33%) followed by drowsiness (10%) and nasal stuffiness (8.33%). The commonest side effects noted in Labetalol group is dyspnoea (8.33%). Gastrointestinal symptoms in the form of nausea or vomiting were

encountered in about 8.33% in methyldopa group and 6.67% in labetalol group.

Study conducted by Verma et al states that adverse events observed were lower in the labetalol treated group compared to the methyldopa group.[10] In a study by Qarmalawi et al, patients receiving methyldopa complained of side-effects such as drowsiness (22.2%), headache (14.8%), nasal congestion (7.4%), postural hypotension (5.6%).[6] No case of hypersensitivity or major adverse drug effect was encountered in our study. None of the patients in either the treatment groups had any congenital malformation or neonatal hypoglycaemia.

CONCLUSIONS

Present study showed that labetalol is more advantageous than methyldopa in achieving quicker and efficient control of hypertension during pregnancy. Freedom from maternal and foetal side-effects, efficient hypotensive action indicate that labetalol is suitable for treatment of new onset of hypertension during pregnancy. The only limiting factor of its use is high cost among rural population of India.

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