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Original Research Article

Study of labetalol vs. methyldopa in treatment of pregnancy induced hypertension

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ABSTRACT

Background: Hypertension is a common medical problem encountered during pregnancy and is associated with increased risk of adverse outcomes. Objective of this study was to compare efficacy and safety of Labetalol and Methyldopa in controlling blood pressure in patients with PIH and pre-eclampsia.
Methods: A comparative, prospective observational, single centre study conducted from November 2015 to November 2017 in women with PIH at Indira Gandhi Government Medical College, Nagpur. Group A included 100 patients treated with Labetalol while Group B included 100 patients who were given Methyldopa. Response in lowering of BP was assessed over a period of 7 days.
Results: Labetalol treated group of patients showed significant fall from 143.50±7.30mmHg/101.30±3.93 (sytolic/diastolic) on 1st day to 126.10±5.49 mmHg/87.40±5.62 mmHg (sytolic/diastolic) on day 7, while systolic/diastolic BP in methyldopa group on 1st day was 145.20±7.17 mmHg/101.60±4.20 mmHg which was reduced to 129.20±4.86 mmHg/90.50±3.30 mmHg on day 7. Author found that MAP in Labetalol group reduced from 115.226±4.17 mmHg to 100.17±4.43 mmHg on day 7 while in Methyldopa group had MAP on admission 115.99±4.38 mmHg and on day 7 it reduced to 103.27±2.99mmHg which is highly significant.
Conclusions: Labetalol controls systolic and diastolic blood pressure more rapidly and effectively than Methyldopa. Safety profile and adverse effects of Labetalol and Methyldopa are similar to each other.

Keywords: Labetalol, Methyldopa, Pregnancy induced hypertension

INTRODUCTION

Hypertension is the most common medical problem encountered during pregnancy.[1] Hypertension complicates up to 10% of all pregnancies and is associated with increased risk of adverse fetal, neonatal and maternal outcomes, including preterm birth, diabetes, chronic hypertension, perinatal death, acute renal or hepatic failure, antepartum haemorrhage, postpartum haemorrhage and maternal death.[2-7] The risk of developing severe hypertension is reduced to half by using antihypertensive medications.[8] Labetalol is widely used nowadays. Methyldopa is centrally acting adrenergic antagonist that acts by stimulating central alpha 2 receptors leading to decrease in sympathetic activity with resultant arterial dilatation and reduction in BP. It has high incidence of side effects because of its central actions.[9] Labetalol is a combined alpha and beta blocker, it has arteriolar vasodilator effect that results in lower peripheral vascular resistance with little or no decrease in cardiac output.

The major goal of antihypertensive medication in PIH is to prevent or treat severe hypertension (generally defined as blood pressure of ≥160/110mmHg) and its associated complications and to prolong pregnancy for as long as possible.[10] Methyldopa has been used for control of blood

pressure since a long time. In the recent times there has been a shift towards the use of Labetalol for same purpose. The purpose of this study is to evaluate the comparative effectiveness of Methyldopa and Labetalol monotherapy in patients with pregnancy-induced hypertension.

The objective of this study was to compare efficacy and safety of Labetalol and Methyldopa in controlling blood pressure in patients with PIH and pre-eclampsia.

METHODS

This study was conducted in pregnant patients with pregnancy induced hypertension admitted in Obstetrics and Gynaecology Department in a tertiary care centre.

It was a comparative, prospective, observational single centre study conducted in women with pregnancy induced hypertension admitted in Obstetrics and Gynaecology Department in a tertiary care centre.

Study was conducted from November 2015 to November 2017.

All the pregnant women attending antenatal clinic were screened for and hypertensive pregnant women were included in the study after obtaining informed consent. It included 200 patients of pregnancy induced hypertension which were divided into two groups i.e. Group A and Group B of 100 patients each. The criteria for diagnosis and classification of the hypertensive disorder of pregnancy were obtained according to National high blood pressure education program working group.

According to this classification patients were divided into four categories

- Gestational hypertension,
- Preeclampsia and eclampsia syndromes
- Chronic hypertension
- Preeclampsia superimposed on chronic hypertension.[11,12]

Inclusion criteria

- The All patients diagnosed PIH as per NHBPEP i.e. BP more than 140/90 mmHg on two separate occasions 6 hours apart, with or without proteinuria (1+ dipstick in two midstream urine samples collected 4 hours apart) and after 20 weeks of pregnancy till term.

Exclusion criteria

- Multifetal pregnancy
- Eclampsia
- Women with pre-existing or concurrent medical disorders like diabetes mellitus, cardiac diseases, renal diseases, thyrotoxicosis, hemophilia and chronic hypertension.
- The patients were clinically examined for systolic and diastolic blood pressure

Technique

- The measurements were taken in the sitting position in a chair after 20 minutes rest
- Inflate the cuff above the systolic pressure as recognized by disappearance of radial pulse. Use korotkoff V (disappearance of the sound) to determine diastolic blood Pressure. If the sound persists when the cuff is deflated use korotkoff IV (muffling of the sound)

Group A of 100 patients were given Labetalol 100mg TDS and if there was no fall in BP within 48 hours i.e. MAP < 106mmHg doses were doubled and were escalated up to 1.2gm/day in divided doses as per required.[13] Group B of another 100 patients were given Methyldopa 250mg QID and if there was no fall in BP within 48 hours i.e. MAP< 106mmHg doses were doubled and increased up to maximum of 3 gm/day in divided doses.[14]

Observations were made as regards in fall of BP with each drug. Monitoring of systolic and diastolic BP was done 6 hourly, comparison of systolic and diastolic BP and mean arterial pressure was done on day 1 of admission and on day 7 after treatment with each drug in respective group.

Ethical clearance was obtained from Obstetrics and Gynaecology, Pathology and Biochemistry departments and the Institutional Ethics Committee.

RESULTS

Table 1 provides the descriptive statistics for patient characteristics in the two treatment groups. In Methyldopa group, there were 52 (52%) patients in the age range of 21-25 years, while in Labetalol group, there were 51 (51%) cases. There were 47 (47%) cases from Methyldopa group in the age range of 26 - 30 years, while 45 in the Labetalol group.

Table 2 provides the mean and standard deviation for systolic and diastolic blood pressure in the two treatment groups before and seven days after starting treatment. The difference between mean systolic and diastolic blood pressure was statistically insignificant on the day of admission for both the groups. Mean systolic blood pressure after treatment for the group treated using Methyldopa was 129.20±4.86mmHg, while it was 126.10±5.49mmHg for the group treated using Labetalol. The difference between the means was statistically highly significant with p-value <0.0001.

Table 1: Descriptive statistics for patient characteristics in two treatment groups.

Patient details	Levels	Groups (Mean±SD)		P-value*
		Drug I: Methyldopa	Drug II: Labetalol	
Age (years)	21 - 25	52	51	0.3959 (NS)**
	26 - 30	47	45	
	> 30	1	4	

Table 2: Mean and standard deviation for systolic and diastolic blood pressure in two treatment groups before and after treatment.

Blood pressure	Levels	Groups (Mean±SD)		P-value*
		Drug I: Methyldopa	Drug II: Labetalol	
Systolic				
	Pre	145.20±7.17	143.50±7.30	0.0983 (NS)
	Post	129.20±4.86	126.10±5.49	< 0.0001 (HS)
P-value**		< 0.0001 (HS)	< 0.0001 (HS)	
Diastolic				
	Pre	101.60±4.20	101.30±3.93	0.6025 (NS)
	Post	90.50±3.30	87.40±5.62	< 0.0001 (HS)
P-value**		< 0.0001 (HS)	< 0.0001 (HS)	

*Obtained using t-test for independent samples; ** Calculated using paired t-test; NS: Not Significant, HS: Highly Significant

Also, the mean diastolic blood pressure seven days after treatment for the group treated using Methyldopa was 90.50±3.30mmHg, while it was 87.40±5.62mmHg for the group treated using Labetalol. The difference between the means was statistically highly significant with p-value <0.0001

For Methyldopa and Labetalol treatment groups, the difference between mean systolic and diastolic blood pressure before and seven days after treatment was statistically highly significant with p-value <0.0001 as obtained using paired t-test.

Table 3: Mean difference in fall of BP.

Blood pressure	Duration	Groups (Mean fall in mmHg±SD)		P value
		Drug I: Methyldopa	Drug II: Labetalol	
Systolic	48 hours	2.1±1.47	5.2±2.99	<0.0001
Diastolic	48 hours	3.8±2.21	7.8±3.48	<0.0001

Table 4: Descriptive statistics for MAP at day 1 and 7 in two groups.

MAP	Groups		P-value*
	Drug I: Methyldopa (n=100)	Drug II: Labetalol (n=100)	
Day 1	115.99±4.38	115.226±4.17	0.2093 (NS)
Day 7	103.27±2.99	100.17±4.43	< 0.0001 (HS)

Table 5: Descriptive statistics for Bishop Score in two treatment groups.

Bishop score	Groups		P-value*
	Drug I: Methyldopa (n=100)	Drug II: Labetalol (n=100)	
Mean ± SD	7.96±1.89	8.23±1.95	0.0232 (S)

Table 3 shows that the fall in systolic BP after 48 hours of starting treatment in Methyldopa group was by 2.1mm Hg whereas in patients treated with Labetalol systolic BP falls by 5.2mmHg. The diastolic BP falls by 3.8mmHg after 48 hours in group treated with Methyldopa and it falls by 7.8mmHg in Labetalol treatment group. Thus systolic and diastolic BP falls more rapidly in patients treated with Labetalol.

Table 4 provides the descriptive statistics for mean arterial pressure (MAP) in two treatment groups. The MAP for patients in Methyldopa group was

115.99±4.38mmHg on day 1, while it was 115.226±4.17mmHg for patients in Labetalol group. The difference between means was statistically insignificant with p-value of 0.2093. However, on day 7, the mean MAP for patients in the group treated with Methyldopa was 103.27±2.99mmHg, while it was 100.17±4.43mmHg for patients treated using Labetalol. Thus the difference was statistically highly significant with p-value <0.0001 as obtained using t-test for independent samples.

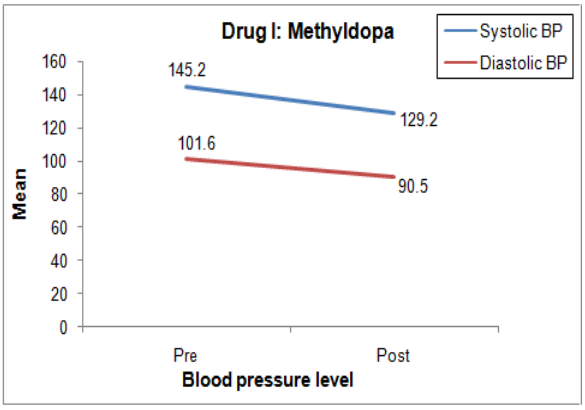

Figure 1: Line plot diagram of pre and post systolic and diastolic blood pressure in patients treated with Methyldopa.

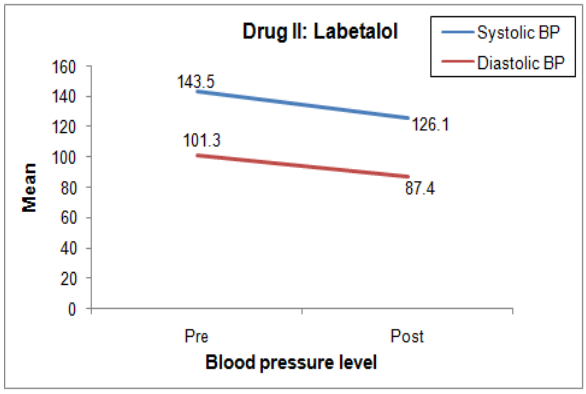

Figure 2: Line plot diagram of pre and post systolic and diastolic blood pressure in patients treated with Labetalol.

Table 5 provides the descriptive statistics for bishop score at the time of spontaneous onset of or induction of labour in the two treatment groups. The difference between means was statistically significant.

Figure 1 shows line plot diagram to compare pre and post treatment systolic and diastolic BP in two treatment groups.

DISCUSSION

In this study, amongst 200 patients maximum number of patients in both the groups i.e. 51 patients receiving Labetalol and 52 patients receiving Methyldopa were in age group of 21-25 years. Both groups were statistically comparable with respect to age distribution. Similarly in the study conducted by Jinturkar A et al, maximum number of patients in group A treated with Methyldopa and group B with Labetalol were in the age group of 15 to 24.[15] In the study conducted by Dharwadkar et al the mean age of patients for Methyldopa group was 25.95±3.94 years and for Labetalol group was 26.65±3.73 years.[16] In a study conducted by Pentareddy et al, the mean age of the patients in the Methyldopa group was 22.3 years while it was 23.23 years in Labetalol group and both groups were statistically comparable.[17]

In Labetalol group systolic/diastolic BP on 1st day was 143.50±7.30mmHg/101.30±3.93 respectively and was controlled to 126.10±5.49mmHg/87.40±5.62mmHg on day 7, while systolic/diastolic BP in methyldopa group on 1st day was 145.20±7.17mmHg/101.60±4.20mmHg which was reduced to 129.20±4.86mmHg/ 90.50±3.30mmHg on day 7. Similar results were shown by study conducted by Qasim et al, in which patients treated with Labetalol systolic/diastolic BP on admission (1st day) was 150±9mmHg/100±8mmHg respectively and was controlled to 123±9mmHg/79±7mmHg on day 7th while systolic/diastolic BP in Methyldopa treated group on the day of admission (1st day) was 148±8mmHg/102±9mmHg which was reduced to 125±10 mmHg/82±6mmHg.[18] Statistically significant reduction in systolic/diastolic BP was observed in case of Labetalol treated group. This is in accordance with the study done by Lamming et al.[10] Study conducted by El Qarmalawi et al says that Labetalol provides more efficient control of BP than Methyldopa in treatment of hypertension in pregnancy.[19] In a study conducted by Wallin JD and Wilson D, Eighty-one severely hypertensive patients were enrolled in a multicenter, double-blind, parallel group study evaluating the efficacy and safety of Labetalol alone or in combination with furosemide versus Methyldopa in combination with furosemide.[20] Moreover, after six months and one year of treatment, respectively, Labetalol caused a significantly ($p<0.05$) greater reduction in the systolic blood pressure than the Methyldopa regimen.

In our study we found that MAP in patients treated with Labetalol on admission was 115.226±4.17mmHg while on day 7 it was reduced to 100.17±4.43mmHg while patients treated with Methyldopa had MAP on admission 115.99±4.38mmHg and on day 7 after treatment it is reduced to 103.27±2.99mmHg. This is highly significant with p value of <0.0001.

In study conducted by Jinturkar A et al MAP in patients treated with Methyldopa on admission was 109.86 mmHg while on day 7 it is reduced to 98.15mmHg with statistically significant p value of <0.05.[15] With Labetalol MAP on admission was 109.48mmHg which reduced to 96.90mmHg on day 7 after treatment and this was statistically significant. This study also quoted that significant fall in Mean Arterial Pressure was seen in

patients treated with Labetalol. Similar results were interpretated in a study conducted by Subhedar et al.[21] In a similar study conducted by El Qarmalawi et al, 81.4% patients receiving Labetalol had significant fall in MAP as against 68.5% in patients taking Methyldopa.[19] Study conducted by Lamming et al, quoted that the average MAP in both groups was same before treatment and there was a highly significant fall in MAP in the group treated with Labetalol ($p<0.001$) but no significant fall in group treated treated with Methyldopa.[10] In our study we found that the fall in systolic BP after 48 hours of starting treatment in Methyldopa group was by 2.1mmHg whereas in patients treated with Labetalol systolic BP falls by 5.2mmHg. The diastolic BP falls by 3.8mmHg after 48 hours in group treated with Methyldopa and it falls by 7.8mmHg in Labetalol treatment group. This shows that systolic and diastolic BP falls more rapidly in patients treated with Labetalol as compared to Methyldopa.

In a study conducted by Lomte D et al, a total of 60 eligible patients were randomized to receive Methyldopa ((n=30), or Labetalol ((n=30).[22] Antihypertensive treatment with Methyldopa was associated with reduction in systolic BP by 50 mmHg and diastolic BP by 30 mmHg at 72 hours. For the same period treatment with Labetalol was associated with reduction in systolic BP by 70mmHg and diastolic BP by 36mmHg at 72 hours. Thus Labetalol is more effective than Methyldopa in controlling blood pressure in patients with pregnancy - induced hypertension. Marked fall of both systolic and diastolic pressure, generally between 24 and 48 hours from the start of using Methyldopa, was noticed by Hans SF.[23] Whereas in a study conducted by Jinturkar A et al, the mean time required to control BP in Methyldopa group was 42.22 hours and in Labetalol group it was 36.97 hours.[15] The difference between the two groups was statistically significant with Labetalol showing earlier control of BP than Methyldopa. Similar results were seen in study conducted by Subhedar et al. It is in accordance with the study conducted by Cruikshank DJ et al which observed that Labetalol had rapid control of BP in 88% of patients.[24] Another study by Lardoux's also showed rapid fall in BP in 82% of patients treated with Labetalol while it was seen in 92% patients treated with Labetalol in study conducted by Michael et al.[25,26]

CONCLUSION

Hypertensive disorders during pregnancy are a major cause of morbidity and mortality worldwide. Antihypertensive medications play an important role in managing maternal blood pressure. In our study we found that Labetalol controls systolic and diastolic blood pressure more rapidly and effectively than Methyldopa. The chances of spontaneous labour and normal vaginal delivery are more in Labetalol, thus Labetalol has ripening effect on cervix.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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