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Research Article

A comparative randomized controlled parallel group study of efficacy and tolerability of labetalol versus methyldopa in the treatment of mild preeclampsia

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ABSTRACT

Background: The objective of the current study was to compare the efficacy and tolerability of labetalol versus methyldopa in the treatment of mild preeclampsia.
Methods: We carried out a prospective randomized controlled parallel group study on 100 outpatients of Obstetrics and Gynaecology Department of Government Medical College, Patiala, a tertiary care teaching hospital. Pregnant patients (20-40 weeks gestational age) newly diagnosed with blood pressure (BP) of ≥140/90 mm Hg were included in the study. All patients with systolic BP (SBP) ≥160 mm Hg and diastolic BP (DBP) ≥110 mm Hg after 20 weeks of gestation, history of hypertension, renal diseases, diabetes mellitus, epilepsy, and thyroid diseases were excluded from the study. After taking the informed consent, 50 patients each were randomized to either of the two treatment arm-oral labetalol or oral methyldopa. Difference in the BP measurements at the time of admission and at the time of delivery were analyzed by applying paired t-test. For intergroup analysis, we applied independent t-test using SPSS version 16. A $p<0.05$ was regarded as significant.
Results: Both methyldopa and labetalol cause significant fall in SBP, DBP and mean arterial pressure (MAP) in their groups ($p<0.001$). However, when we compared both groups it was labetalol, which causes significant fall in MAP as compared to methyldopa ($p<0.001$). The incidence of adverse effects like hypotension, headache, and sedation were also less in labetalol group.
Conclusion: Labetalol has an upper edge over methyldopa in control of BP during pregnancy with minimal adverse effects.

Keywords: Preeclampsia, Methyldopa, Labetalol

INTRODUCTION

Maternal mortality represents one of the starkest disparities in health outcomes between developing and developed countries, the rich and the poor. An estimated 358,000 maternal deaths occurred worldwide in 2008 and over 8 million women suffer from illness, infection or injury as a consequence of pregnancy or childbirth. These estimates are likely to be underreported. With 99% of deaths occurring in the developing world it comes as no surprise that the majority of these deaths are preventable and that progress toward Millennium Development Goal 5 "the reduction of maternal mortality by 75% by 2015" is stalling.[1]

Hypertension is the most common problem encountered during pregnancy. It is estimated that globally 6-8% of pregnancies are complicated by hypertension. It is said that preeclampsia and eclampsia contribute to death of a woman every 3 mins worldwide.[2] The incidence of preeclampsia is 7 times higher in developing countries (2.8% of live births) as compare to the developed countries (0.4%) Moreover, it is thought that preeclampsia and eclampsia are also associated with one-quarter of stillbirths and neonatal deaths in developing nations.[1,3,4] Mild hypertension, which is defined as systolic blood pressure (SBP) of 140-159 mm Hg or diastolic BP (DBP) of 90-109 mm Hg or both, is common during pregnancy.

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,[5] so more research is needed. Methyldopa, labetalol and long-acting nifedipine are acceptable oral antihypertensive agents if drug therapy is required in pregnant women with mild to moderate hypertension.[2]

The current study was planned to assess and compare efficacy and tolerability of labetalol and methyldopa in controlling BP in patients with mild preeclampsia.

METHODS

We carried out a prospective randomized controlled parallel group study on 100 outpatients of obstetrics and gynecology department of tertiary care teaching hospital. Ethical clearance for the study was obtained from the Institutional Ethics Committee. Patients were enrolled after informed consent was taken. A total of 100 patients were enrolled in the study as per selection criteria.

Inclusion criteria

Pregnant patients (20-40 weeks gestational age) newly diagnosed with BP of ≥140/90 mm Hg were included in the study.

Exclusion criteria

All pregnant patients with SBP ≥160 mm Hg and DBP ≥110 mm Hg after 20 weeks of gestation, history of pre-existing hypertension/renal diseases/immunological disorders/liver diseases/diabetes mellitus/epilepsy/thyroid diseases were excluded from the study. Patients present with eclampsia, unwilling or unable to comply with the study proceedings were also excluded from the study.

After taking a thorough history and clinical examination patients were randomly divided into two groups of 50 cases each. After randomization Group I patients received labetalol 100 mg twice a day and subsequent titration carried out up to maximum recommended dose of 800 mg daily depending on therapeutic response. Group II patients received methyldopa 250 mg thrice a day and subsequent titration carried out up to maximum dose of 3 g depending on therapeutic response.

BP was recorded by using mercury sphygmomanometer. During the process of BP measurement, the woman was at rest. The BP cuff of 12 cm was firmly applied over the right arm 2.5 cm above the elbow. 2-3 readings were taken at the interval of 5 mins to confirm the readings. SBP corresponded at appearance of the Korotkoff's sound I whereas DBP corresponded at the disappearance of Korotkoff's sound V. The mean of three recordings was taken as the value of BP. BP was measured on every fortnightly till 28 weeks, then weekly till term.

Adverse effects as reported by patients was recorded and compared.

Statistical analysis was done by applying paired t-test for the difference in pre- and post-treatment values. For intergroup analysis, we applied independent t-test, using SPSS version 16. A $p<0.05$ was regarded as significant whereas <0.001 was regarded as highly significant.

RESULTS

In the labetalol treated group (Group I), the mean SBP, mean DBP, and mean arterial pressure (MAP) at time of admission was 138.16±3.07 mm Hg; 92.72±4.38 mm Hg and 107.87±3.31 mm Hg, respectively. With treatment, at the time of delivery mean SBP was 121.76±3.99 mm Hg; mean DBP was 80.06±1.79 mm Hg; and a mean MAP was 93.96±1.96 mm Hg. Reduction in SBP, DBP, and mean MAP was statistically highly significant ($p<0.001$), compared to pre-treatment value (Table 1).

In the methyldopa treated group (Group II), the mean SBP, mean DBP, and mean MAP at the time of admission was 137.56±4.06 mm Hg; 93.28±4.57 mm Hg; and 108.04±3.37 mm Hg respectively. With treatment, at the time of delivery mean SBP was 123.52±3.69 mm Hg; mean DBP was 82.00±3.07 mm Hg and mean MAP was 95.84±2.71 mm Hg. Reduction in SBP, DBP, and mean MAP was statistically highly significant ($p<0.001$), compared to pre-treatment value (Table 2).

The baseline value of mean SBP, mean DBP, and mean MAP in Group I (labetalol) and Group II (methyldopa) are statistically non-significant ($p>0.05$) (Table 3).

On comparing both the group, significant fall in SBP ($p<0.05$), DBP ($p<0.001$), and MAP ($p<0.001$), was observed in labetalol group (Table 4).

On comparison, the incidence of adverse effects between the two group was statistically non-significant ($p>0.05$) (Table 5).

DISCUSSION

Preeclampsia is a major contributor to the maternal and neonatal mortality and morbidity. It is the 2nd largest cause of maternal mortality worldwide and affects 5-7% of pregnant women worldwide. This disease is a great challenge for obstetricians because there are no effective interventions to treat or prevent it, and antenatal care involves a difficult balance between the risks for women to continue pregnancy and the risks for the baby's early birth.

Early diagnosis, close medical supervision and timely delivery are the cardinal requirements of the management of preeclampsia. However, there is no clear consensus on the management of mild to moderate hypertension in pregnancy to optimize pregnancy outcomes. Antihypertensive drug therapy in mild to moderate hypertension lowers the rates of progression to severe disease, although there is no evidence of difference in outcome of preeclampsia, neonatal death, preterm birth, and small for gestational age babies with treatment.

Table 1: Mean SBP, mean DBP and mean MAP at the time of admission and at the time of delivery in Group I (labetalol).

Parameter (mmHg)	At time of admission	At time of delivery	% age fall in BP	t value	p value
Mean SBP	138.16±3.07	121.76±3.99	11.87	22.48	<0.001
Mean DBP	92.72±4.38	80.06±1.79	13.65	21.32	<0.001
Mean MAP	107.87±3.31	93.96±1.96	12.89	26.53	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Table 2: Mean SBP, mean DBP and mean MAP at the time of admission and at the time of delivery in Group II (methyldopa).

Parameters (mmHg)	At time of admission	At time of delivery	% age fall in BP	t value	p value
Mean SBP	137.56±4.06	123.52±3.69	10.2	23.589	<0.001
Mean DBP	93.28±4.57	82.00±3.07	12.09	18.508	<0.001
Mean MAP	108.04±3.37	95.84±2.71	11.29	27.255	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Table 3: Comparison of mean SBP, mean DBP, and mean MAP at the time of admission in the Group I (labetalol) and Group II (methyldopa).

Parameters (mmHg)	Group I (labetalol)	Group II (methyldopa)	t value	p value	S
Mean SBP	138.16±3.07	137.56±4.03	0.838	>0.05	NS
Mean DBP	92.72±4.38	93.28±4.57	0.625	>0.05	NS
Mean MAP	107.87±3.31	108.04±3.37	0.26	>0.05	NS

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Table 4: Comparison of mean SBP, mean DBP, and mean MAP at the time of delivery in the Group I (labetalol) and Group II (methyldopa).

Parameters (mmHg)	Group I (labetalol)	Group II (methyldopa)	t value	p value	S
Mean SBP	121.76±3.99	123.52±3.69	2.288	<0.05	S
Mean DBP	80.06±1.79	82.00±3.07	3.854	<0.001	HS
Mean MAP	93.96±1.96	95.84±2.71	3.974	<0.001	HS

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Table 5: Comparison of adverse effects in Group I (labetalol) and Group II (methyldopa).

Adverse effects	Group I	Group II	p value
Hypotension	3	6	p<0.601
Headache	3	5	p<0.629
Sedation	3	4	p<0.867
Nausea	1	2	p<0.659
Vomiting	1	1	p<0.909
Myalgia	1	1	p<0.909
Arthalgia	1	1	p<0.909
Paraesthesia	1	1	p<0.909
Weakness	5	1	p<0.066
Diarrhea	2	2	p<0.872

Methyldopa, labetalol, and long-acting nifedipine are acceptable oral antihypertensive agents if drug therapy is required in pregnant women with mild to moderate hypertension.

The present study was conducted with the aim to evaluate and compare efficacy and safety of labetalol versus methyldopa in patients of pregnancy induced hypertension.

In the present study, both labetalol and methyldopa cause significant fall in SBP, DBP, and MAP in their respective groups. In the labetalol treated group, the mean SBP, mean DBP, and average MAP at the time of admission was 138.16±3.07 mm Hg; 92.72±4.38 mm Hg; and 107.87±3.31 mm Hg. After treatment, at the time of delivery mean SBP reduced to 121.76±3.99 mm Hg; mean DBP reduced to 80.06±1.79 mm Hg; and average MAP reduced to 93.96±1.96 mm Hg. Reduction in SBP, DBP, and MAP was statistically significant (p<0.001), compared to pre-treatment value. These finding of significant fall in BP with labetalol are supported by other studies also.[6-10]

Similarly in the methyldopa treated group, the mean SBP, mean DBP, and average MAP at the time of admission was 137.56±4.06 mm Hg; 93.28±4.57 mm Hg; and

108.04±3.37 mm Hg. After treatment, at the time of delivery mean SBP reduced to 123.52±3.69 mm Hg; mean DBP reduced to 82.00±3.07 mm Hg; and average MAP reduced to 95.84±2.71 mm Hg. Reduction in SBP, DBP and MAP was statistically highly significant ($p<0.001$), compared to pre-treatment value. These findings are similar to other studies observations.[10-12]

On comparing the two drugs, SBP, DBP; and MAP on admission was comparable, but at the time of delivery significant fall in SBP, DBP, and MAP was seen in patients receiving labetalol ($p<0.001$).

According to a study conducted by Lamming and Symonds 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 treated with methyldopa ($p>0.05$).[13] 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.[14] Present study findings are also supported by the study conducted by Subhedar et al. which shows significant fall of MAP in labetalol group.[2] However, present study findings are in contrast to the studies conducted by Plouin et al., and Verma et al. which shows that both labetalol and methyldopa have equal efficacy in reducing MAP.[15,16]

Adverse effects were lower in the labetalol treated group as compared to the methyldopa group. The most common adverse effect in labetalol group was weakness (10%) whereas in methyldopa group the most common adverse effect was hypotension (12%) followed by headache (10%). The incidence of adverse effects such as vomiting, myalgia, arthalgia, paresthesia was similar in both the groups.

CONCLUSION

Present study showed that both labetalol and methyldopa caused significant fall in BP. However, labetalol is more efficacious than methyldopa in terms of reducing SBP, DBP and MAP. The incidences of adverse events were also less in labetalol group.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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