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Comparison of methyldopa and labetalol in control of blood pressure in preeclampsia

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Abstract
Background: Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality in developing world.
Materials and Methods: 188 eligible patients were randomly assigned to receive treatment with either labetalol or methyldopa.
Observation and Results: Proteinuria was drop down to 8.51 % after treatment with labetalol. There were 14 cases of IUGR in methyldopa group as compared to 4 cases in labetalol group. Patients with labetalol group delivered at term were 82.97 % whereas in methyldopa group 76.59%. There was no significant difference in Apgar score between two groups. Need of nicu in labetalol group was 6% as compared to 7% in methyldopa group. Drowsiness was the most common side effect observed in methyldopa group while very few cases of adverse effects in labetalol group.
Conclusion: Our study suggests that labetalol is better than methyldopa in treatment of hypertension in pregnancy and has good perinatal and maternal outcome.

Keywords: Preeclampsia, labetalol, methyldopa, maternal and perinatal outcome

Introduction
The hypertensive disorders of pregnancy are common medical complications of gestation and continue to be responsible for the high maternal and perinatal mortality and morbidity [1]. good prenatal supervision following appropriate treatment will ameliorate many cases sufficiently, so that outcome for the baby and the mother is satisfactory. This disorder affects approximately 5-10% of pregnancies and is significant in causing maternal and fetal morbidity and mortality [2].
The first choice medication for the treatment of hypertension in pregnancy patients has been methyldopa. This was the only antihypertensive medication that has been submitted to large number of clinical trials during pregnancy. But, in recent day's nifedipine and labetalol is being used more frequently. Acog currently recommends labetalol as one of the first line antihypertensive medication in preeclampsia [3].
The combined alpha and beta adrenergic blocking action of labetalol is pharmacological advance that provides a new conceptional approach for managing the patient with hypertension. Labetalol decreases peripheral resistance without significantly lowering maternal cardiac output. This may be an additional factor in maintaining the placental perfusion and therefore fetal oxygenation.
The present study aims at comparison between centrally acting methyldopa and alpha-beta blocker labetalol with respect to the following:
1. Effective blood pressure control
2. Occurrence of proteinuria
3. Apgar score of the newborn
4. Birth weight of newborn

Objectives
To assess control of blood pressure, the adverse effects of drugs and to assess the maternal and perinatal outcome in preeclampsia

Material and Method
The study was carried out in a tertiary care hospital from July 2018-june 2019.approval of institutional ethical committee taken.

Study design: prospective interventional
Study type: randomised controlled trial
Sample size: 94 cases in each group

Inclusion criteria
Patient with preeclampsia bp≥ 140/90 mm of mercury at or more than 28 weeks of gestational age
Urine albumin 1+ by dip stick method

Exclusion criteria
Patient with severe preeclampsia i.e. Diastolic bp≥ 110 mmof mercury
Patient with previous anti-hypertensive treatment in this pregnancy
Less than 28 weeks of pregnancy and more than 37 weeks of pregnancy
Eclampsia
Asthma, diabetes mellitus, heart disease
Severe bradycardia
Hypoglycaemia
Allergic disorder

Randomisation
All hypertensive pregnant women examined in the antenatal outpatient department from july2018-june 2019 were screened for inclusion and exclusion criteria. After giving their informed oral consent, 188 eligible patients were randomly assigned to receive treatment with either labetalol or methyldopa in 2 groups.94 patients received labetalol and 94 patients received methyldopa.
Total 188 patients were randomly allocated into two groups i.e. 94 in each group.
We prepared a randomised block of 10 patients each, of which 5 patients were randomly allocated to one of the 2 groups, hence total 19 blocks were prepared. Each block was randomly selected with the help of random sampling method. Last block was of only 8 patients. Briefly pregnant women who met eligibility criteria at 2 baseline examination were assigned at random to open treatment with either labetalol or methyldopa.
Patients were managed as only inpatients. The timing and management of delivery varied to meet the needs of the individual patients. Mother and their babies were followed at least to the fifth day of delivery.
Information obtained at entry included basic demographic data, medical, personal, family history blood pressure recording and biochemical tests.
As recommended by the drug manufacturers, starting dosage were 100mg for labetalol twice daily and 250 mg thrice daily for methyldopa. Dosage were increased as needed to maintain diastolic blood pressure around 84 mm of mercury or lower.
Daily follow up examination of the patient was done. Blood pressure was recorded twice a day and daily estimation of urine proteins (albumin) was done.
Neonatal assessment included estimation of apgar score at 1 and 5 minutes. Birth weight was also taken into account. Newborn babies requiring intensive and careful monitoring were transferred to the neonatal intensive care unit (nicu). neonate were followed till fifth day after delivery.
Since the trial was open, prenatal and neonatal care received in both treatment groups was carefully checked, in order to detect any bias in medical attitudes in connection with a particular treatment.

Statistical analysis
Continuous variable (blood pressure, pulse rate) were presented as mean ±sd.
Continuous variable were compared between two groups by performing unpaired "t" test. Categorical variable (parity, preterm babies) were compared by "chi square test".
For small numbers 'fischer extract test 'was applied whenever necessary. P value of less than 0.05 was considered as statistically significant.
Statistical software stata version 10.0 was used for data analysis.

Observations and Results
Out of the 188 eligible patients, 94 patients were allocated to the labetalol group and 94 to the methyldopa group.
Thus the records of total 188 patients who received labetalol and methyldopa at random were analysed.
Treatment groups with labetalol and methyldopa were comparable at entry for age, obstetrics history, gestational age, blood pressure and proteinuria.

Table 1: Distribution of patients according to age

Age (Years)	Number of patients	
	Labetalol group	Methyldopa group
Less than 20	02 (2.12%)	01(1.06%)
20-25	60(63.82)	05(57.44%)
26-30	23(24.44%)	30(31.91%)
More than 30	09(9.57%)	09(9.57%)

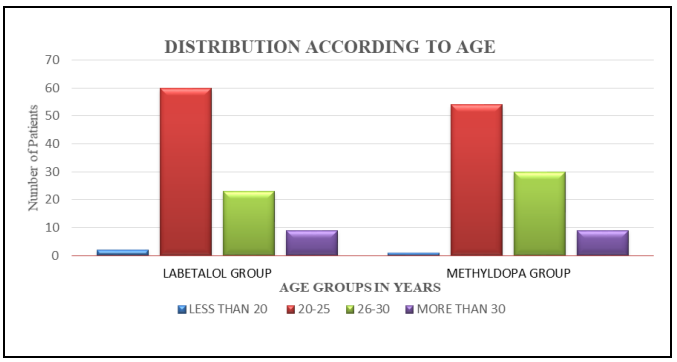

Chart 1: Distribution of patients according to age group

About 60 percent of the patients belonged to the 20-25 years of age group, whereas about 30percent of the patients belonged to the 26-30 year age group and only 9 percent of the patients contributed to above 30 years age group.
So the patients age was comparable in both labetalol and methyldopa groups.

Table 2: Distribution of patient according to parity

Parity	Number of patients	
	Labetalol group	Methyldopa group
Primigravidae	46 (48.93%)	48(51.06%)
Multigravidae	48(51.06%)	46 (48.93%)

The percentage of primigravidae and multigravidae patients included in the study is almost same in both the treatment groups.

Table 3: Distribution of patients according to gestational age at entry

Gestational age (weeks)	Number of patients	
	Labetalol group	Methyldopa group
28	15 (15.95%)	13 (13.82%)
29	04 (4.25%)	02 (02.12%)
30	26 (27.65%)	23 (24.46%)
31	12 (12.76%)	12 (12.76 %)
32	28 (29.78%)	30 (31.91%)
33	09 (9.57%)	14 (14.89%)

About 30 percentage of the patient belonged to the 32 weeks gestational age group and about 25% and 15 % belonged to the 30 and 28 weeks group respectively.
So the patients gestational age at entry was comparable in both labetalol and methyldopa groups.

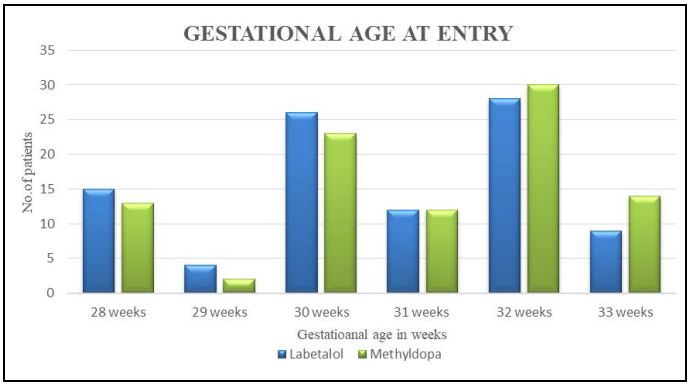

Chart 2: Distribution according to gestaional age at entry

Table 4: Distribution of patients according to severity of hypertensive disorder at entry

Diastolic blood pressure (mm of mercury)	Number of patients	
	Labetalol group	Methyldopa group
90-100	88 (93.61%)	88 (93.61%)
101-109	06(06.38%)	06(06.38%)

In each group 93.61 percentages of the patients had diastolic blood pressure between 90 and 100 mm of mercury at the start of treatment while 6.38 percentage of the patients in each group had diastolic blood pressure more than 100 mm of mercury.

Table 5: Distribution of patients according to significant protienuria at entry and after treatment

Significant proteinuria	Number of patients	
	Labetalol group	Methyldopa group
At entry	36(38.29%)	39(41.48%)
After treatment	08(08.51%)	49 (52.12%)
Reduction (%)	83.30 %	-25.64%

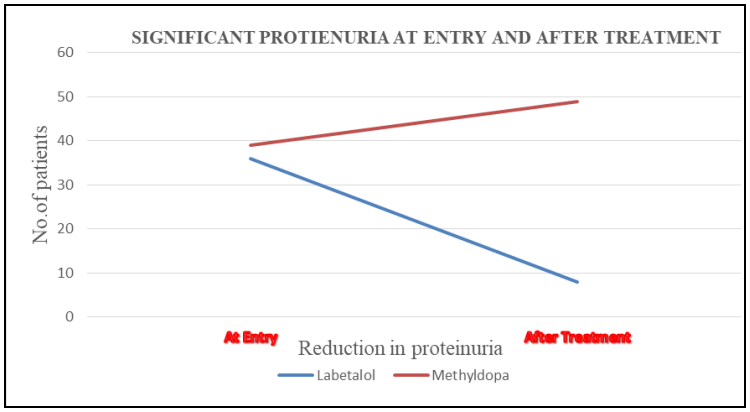

Chart 3: Reduction of significant protienuria at entry and after treatment

Significant proteinuria defined as dip test of more than or equal to 2+ on at least 2 occasions
The above table shows that 38.29% of the patients allocated to treatment with labetalol showed significant proteinuria on admission and the percentage drop down to 8.51% after treatment with labetalol while in the methyldopa group, percentage rose to 52.12% from 41.48 %.

From the above we can see that reduction in significant proteinuria in labetalol group was 83.3% as compared to the -25.64% in the methyldopa group with p value of 0.00which is highly significant. So it is clear that labetalol helps in preventing occurrence of proteinuria when used in the treatment of hypertension in pregnancy.

Table 6: overall maternal outcome

Patient characteristics	Number of patients		P value
	Labetalol group	Methyldopa group	
Increase in dosage	08(08.51%)	58 (61.70%)	0.00hs
Supplementary therapy given	02 (2.12%)	26(27.65%)	0.00 hs
Significant proteinuria	08(08.51%)	49(52.12%)	0.00 hs

Hs-highly significant

In the labetalol group 08.51% patients and 61.70% in the methyldopa group required increase in the dose. 2.12 % of patients in the labetalol group and 27.65% in the methyldopa group required supplementary therapy in the form of nifedipine

to achieve a satisfactory blood pressure control. As evident from observation table no 5 and table no 6 there was diminution in the incidence of proteinuria in patients treated with labetalol.
When we analysed these values statistically we came to know that methyldopa treated patients required increase in dosage and additional antihypertensive therapy much more as compared to the labetalol treated group and these values are statistically significant as p value comes to be 0.00.

Table 7: Assessment of patients at 35-37 weeks

Patient characteristics	Number of patients		P value	Inference
	Labetalol group (92)	Methyldopa group (91)		
Mean systolic blood pressure (mm of mercury)	123.86±5.59	129.75±8.31	0.00	Highly significant
Mean diastolic blood pressure (mm of mercury)	78.78± 2.93	83.94± 4.98	0.00	Highly significant
Mean pulse rate (beats per min)	82.69±1.83	86.95 ±5.50	0.00	Highly significant

Two patients from the labetalol group and three patients from methyldopa group went into premature labour. The mean systolic blood pressure in the labetalol and methyldopa group was found out to be 123.86±5.59 mm of mercury and 129.75±8.31mm of mercury respectively.
The difference in mean systolic blood pressure between 35-37 weeks was significant with p value of 0.00. The mean diastolic blood pressure in the labetalol and methyldopa groups was found out be 78.78± 2.93 mm of mercury and 83.94± 4.98 mm of mercury respectively.
The difference in mean diastolic blood pressure between 35-37 weeks was significant with p value of 0.00. From this we can conclude that blood pressure control was significant better in the labetalol group during 35-37 weeks of gestation.
The mean heart rate was 82.69±1.83 and 86.95 ± 5.50 in the labetalol and methyldopa group respectively with p value of 0.00. This suggests that labetalol has protective against tachycardia as compared to the methyldopa.

Table 8: Onset of labour

Onset of labour	Number of patients		P value	Inference
	Labetalol group	Methyldopa group		
Spontaneous	48(51.06%)	16(17.02%)	0.00	Highly significant
Preterm	10(20.83%)	6(37.50%)	0.182	Not significant
Term	38(79.16%)	10(62.50%)	0.182	Not significant
Induced	35(37.23%)	67(71.27%)	0.00	Highly significant

In the labetalol treated group, more patients went into spontaneous labour near term with higher bishop score.51.06% of the patients from labetalol group went in spontaneous labour as compared to the 17.02 % from the methyldopa group, with p value of 0.00 which is highly significant. There was no significant difference observed in patients who went into spontaneous labour in relation to the prematurity in labetalol and methyldopa group. Patient treated with methyldopa required induction more frequently as compared to the patients of labetalol group i.e. 71.27 % vs. 37.23 % with p value of 0.00 which is highly significant.

Table 9: Mode of delivery

Mode of delivery	Number of patients	
	Labetalol group	Methyldopa group
Vaginal	55 (58.51%)	55 (58.51%)
Caesarean section	39(41.48%)	39(41.48%)
Elective	11 (28.20%)	09 (23%)
Emergency	28 (71.79%)	30 (76.92%)

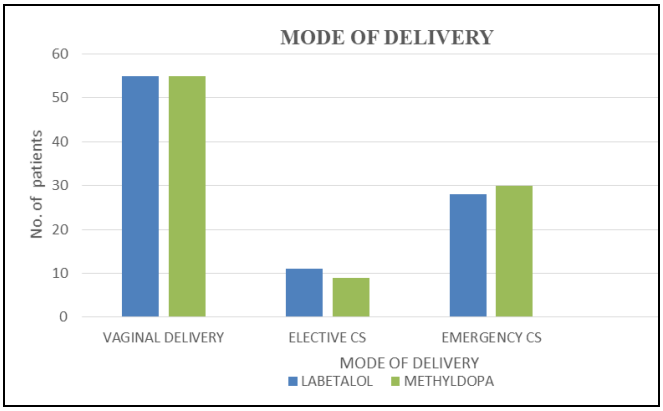

Chart 4: Mode of delivery in labetalol and methyldopa

Number of patients delivered by vaginal and caesarean route were same in both groups each contributing to 58.51% and 41.48% respectively. Among the patients who required caesarean section, emergency caesarean section was marginally more in methyldopa group (76.93 %) as compared to the labetalol group (71.79%).

Table 10: Gestational age at delivery

Gestational age (weeks)	Number of patients	
	Labetalol group	Methyldopa group
28 -34 weeks	02(02.12%)	0
34 weeks 1 day to 37 weeks	14 (14.89 %)	22 (23.40%)
More than 37 weeks	78(82.97%)	72 (76.59%)

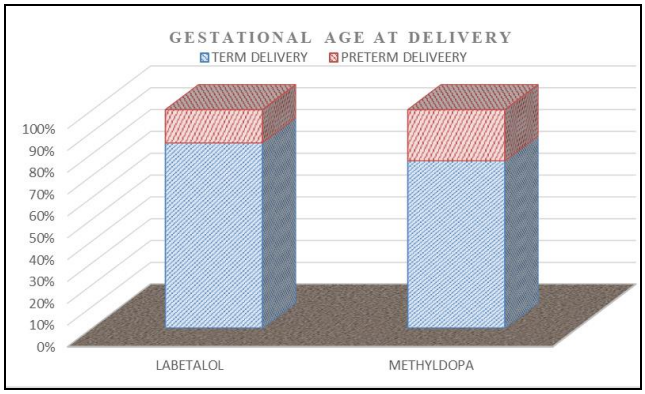

Chart 5: Gestational age at delivery in labatealol and methyldopa group

Table shows that 82.97% of patients in the labetalol group were delivered at term which were more as compared to the methyldopa group (76.59%). chi^2 =4.0178 with p value of 0.134 which is not significant.

Table 11: Birth weight

Weight (kg)	Number of patients	
	Labetalol group(97)	Methyldopa group (98)
< 1.5	05(05.15%)	03(03.06%)
1.5-<2.0	19 (19.58 %)	19 (19.58 %)
2- < 2.5	28(28.86%)	26(26.53%)
>2.5	45 (46.39%)	50 (51.02%)

In the methyldopa group 51.02% of babies had birth weight greater than or equal to 2.5 kg which is more as compared to the labetalol group (46.39%).but this difference is not statistically significant.

Table 12: Apgar score at 5 minute

Apgar score	Number of babies	
	Labetalol group(97)	Methyldopa group (98)
< 4	0	1
4-6	0	0
7-8	0	1
9-10	97	96

All babies in the labetalol group had apgar score at 5 minutes of 9 or 10 while in methyldopa group one baby had apgar score of less than 4 and one baby had apgar score of 8 at 5 minutes.

Table 13: Babies requring admission to NICU

	Labetalol group	Methyldopa group
Number of babies	97	98
Nicu admission	6	7

Six babies from labetalol group required intensive care while seven babies in the methyldopa required intensive care. P value of 0.789 which is not significant.

Table 14: Maternal and fetal complication

Complication	Labetalol group	Methyldopa group	P value	Inference
Aph	1	2	1.00	Not significant
IUGR	4	14	0.013	Significant
Oligohydraminos	2	4	0.407	Not significant
Eclampsia	0	5	0.023	Significant

There were 14 cases of IUGR in methyldopa group as compared to 4 cases in labetalol group. This difference was significant with p value of 0.013 which suggests that labetalol treatment decreases the IUGR cases.

There were 5 cases of eclampsia in methyldopa group as compared to the nil in labetalol group, this difference was significant with p value of 0.023, which suggest that after treatment with labetalol there are less chances that patient will progress to eclampsia.

With regard to antepartum haemorrhage and oligohydraminos numbers of cases were not significantly different in methyldopa and labetalol group.

Table 15: Side effects

Side effects	Labetalol group	Methyldopa group	P value	Inference
Headache	1	1	1.00	Not significant
Drowsiness	1	20	0.000	Highly Significant
Lethargy	1	0	0.500	Not significant
Depression	0	5	0.023	Significant
Drowsy + depression	0	2	0.497	Not significant

In methyldopa group, the most common side effect was drowsiness seen in 20 patients, 5 patients had depression, 2 patients had both drowsy and depression, one patient had headache.

In the labetalol group only 3 patients' experienced side effects. One patient had headache, 2nd patient had lethargy while 3rd patient had drowsiness.

Discussion

Although antihypertensive treatment has not been shown to decrease perinatal mortality in pregnancies complicated by hypertensive disorder, the administration of antihypertensive drugs is becoming increasingly a matter of routine. The antihypertensive drug methyldopa is safe for the fetus and is considered the reference drug for treating hypertensive disorder

in pregnancy.

Since there is only limited evidence for the usefulness of the blood pressure reduction per se in mild hypertensive disorder of pregnancy, alternative antihypertensive drugs must be carefully compared with methyldopa, especially in terms of perinatal safety. Particularly in case of beta adrenergic blockers special attention to be paid to the potential effects of beta blockade on the fetus particularly with regard to the risks of impaired fetal growth and of impaired neonatal defence against hypotension, hypoglycaemia and asphyxia.

Labetalol was compared with methyldopa in three randomized trails

Lamming *et al* (1980) [4]

Plouin *et al* (1988) [5]

Reena verma *et al* (2012) [6]

In present study of 188 patients with preeclampsia we compared effect of oral labetalol with oral methyldopa.

Age distribution

In patients with labetalol group 63 percent and in methyldopa group 57 percent women belong to 20-25 years of age group.

Blood pressure control

In accordance with the trial of lamming *et al*. In the present study, we found blood pressure control to be smoother and comparatively better in patients treated with labetalol [4].

Study	Number of patients studied	Number of patients with diastolic blood pressure more than 85 mm of mercury at 35-37 weeks	
		Labetalol group (%)	Methyldopa group (%)
Plouin *et al*. [5]	176	22(28)	24(33)
Present study	188	0(0)	29 (31.86)

Supplementary drug therapy

The following table shows the number of patients requiring additional drug therapy for satisfactory blood pressure control, between the two studies.

Methyldopa group required supplementary drug therapy for effective blood pressure control (27.65% vs. 2.12 %) (Plouin *et al*. 13 % vs. 26 %) [4].

Study	Total number of patients	Number of patients requiring supplementary drug therapy	
		Labetalol group (%)	Methyldopa group (%)
Plouin *et al*. [5]	176	12(13)	22(26)
Present study	188	02(2.12)	26 (27.65)

Reduction of proteinuria

In the labetalol treated group, incidence of proteinuria was found to be less as compared to the methyldopa group. This finding was also noted by lamming *et al*. In their trial [4].

Study	No of patients studied	No of patient with significant proteinuria			
		On admission		After treatment	
		Labetalol group (%)	Methyldopa group (%)	Labetalol group (%)	Methyldopa group (%)
Plouin *et al*.[5]	176(91+85)	3 (3.2)	7(8.2)	8 (8.7)	8(9.4)
Lamming *et al*.[4]	26 14+12)	1(7)	-	5(41)	-
Present study	188 94+94)	36(38.29)	39(41.48)	8 (8.51)	49(52.14)

Gestational age at delivery

In present study 82 percent of the patients had term delivery in labetalol group whereas in methyldopa group 76 percent had term deliveries. A study conducted by a.m. El-qarmalawi *et al*. Reported that prolongation of pregnancy was more common in labetalol group than methyldopa group [7]. The present study correlates with author's study. This finding is explained by mild tocolytic effect on myometrium [8].

Onset of labor

In present study 51 percent had spontaneous onset of labor in the labetalol group where as in patient with methyldopa group 17 percent had spontaneous onset of labor. Need for induction is less in patient of labetalol group compared to methyldopa group, as labetalol reduces induction of labor due to its ripening effect on cervix which is supported by study sibai *et al* [9].

Study	No of patients studied	No of patients with			
		Spontaneous labour		Induced labour	
		Labetalol group	Methyldopa group	Labetalol group	Methyldopa group
Plouin *et al*. [5]	176	40	35	23	27
Lamming *et al* [4]	26	6	2	5	6
Present study	188	48	16	35	67

Mode of delivery

The mode of delivery (vaginal or abdominal) was almost similar in both the treatment groups. However in accordance with lamming trial, more and more patients from the labetalol group went in spontaneous labour near term (40 % vs. 10%) [4].

Study	No of patients studied	No of patients delivered			
		Vaginal delivery		Cesarean delivery	
		Labetalol group	Methyldopa group	Labetalol group	Methyldopa group
Plouin *et al*. [5]	176	60	59	31	26
Lamming *et al*. [4]	26	10	7	4	5

Present study	188	55	55	39	39

Incidence of IUGR

In present study, 4 percent had IUGR fetuses in labetalol group where as 14 percent had IUGR in methyldopa group.

Redman *et al*. Compared labetalol and methyldopa in severe pregnancy induced hypertension. He found higher incidence of IUGR in methyldopa group and less perinatal mortality in labetalol group [10].

Mean birth weight

Study	Number of patients	Mean birth weight (kg)	
		Labetalol group	Methyldopa group
Plouin *et al*. [5]	176	2.86	2.89
Lamming *et al*. [4]	26	2.56	2.47
Present study	188	2.34	2.34

In the present study, for live born babies, mean birth weight and gestational age at delivery were quite similar in both the groups'. Accordance with plouin *et al*. We found no significant difference between the two groups [5].

Nicu admission

Study	Number of patients	Number of babies requiring nicu	
		Labetalol group	Methyldopa group
Plouin *et al*. [5]	176	2o	18
Present study	188	6	7

In present study need of nicu admission in labetalol group, was 6 percent compared to 7 percent in methyldopa group.

Michael *et al* reported that labetalol has a direct action on the fetal lung maturation, thereby significantly reducing respiratory distress syndrome [11].

Apgar score at 5 minutes

In present study, number of babies with apgar score less than or equal to 8 at 5 minutes were 2 in methyldopa group but there was not a single baby in labetalol group. In study by reena v *et al*. There were 7 and 6 babies each in the labetalol and methyldopa treated group with apgar score of less than or equal to 8 at 5 minutes [6].

Study	Number of patients	Number of babies apgar score ≤ 8 at 5 minutes	
		Labetalol group	Methyldopa group
Reena v *et al*. [6]	90	7	6
Present study	188	0	2

Adverse effects

In the methyldopa group, 20 patients had drowsiness, 5 patients had depression, 2 patients had both drowsiness and depression, and one patient had headache. Thus most common side effect of methyldopa was drowsiness. This finding is similar to that of el-qarmalawi *et al* [7].

In the labetalol group only three patients experienced the side effects. One patient had headache, 2nd had lethargy and 3rd had drowsiness.

Study	Headache		Drowsiness		Depression	
	Labetalol group	Methyldopa group	Labetalol group	Methyldopa group	Labetalol group	Methyldopa group
Nita patel *et al*. [12]	4 %	4%	-	-	2%	7%
Shaba molvi *et al*. [13]	10 %	10 %	6 %	6 %	-	-
El qarmalawi *et al*. [7]	0 %	14.8%	0 %	22.2%	-	-
Present study	1 %	1 %	1 %	21 %	0 %	5 %

Labetalol is a beta blocker with alpha adrenoreceptor blocking properties which limit the bradycardia induced by beta blockade and may cause peripheral vasodilatation.

Indeed we show no difference in maternal heart rate between the two groups.

Conclusion

Hypertensive disorder in pregnancy is one of the major causes of maternal and fetal mortality and morbidity.

This study showed that labetalol is more advantageous than methyldopa in terms of better control of blood pressure, fewer side effects and decrease in severity of proteinuria.

The chances of spontaneous onset of labour were greater in labetalol group than methyldopa group. Patients in labetalol group who had induction of labour were noted to have good bishop score. Labetalol group had lesser number of IUGR and no case landed in eclampsia

Thus we can say that there was decrease in maternal morbidity in the form of proteinuria, eclampsia, IUGR and side effects of drug in patients treated with labetalol. But the perinatal outcome in patient treated with labetalol was comparable with methyldopa group.

For the reason detailed above, the maternal outcome was better in labetalol group than methyldopa group.

However this being pilot study, of only 188 patients, long term study with larger number of patients is needed to get better understanding of the efficacy of the drug and its safety.

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