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The safety and efficacy of labetalol vs. methyldopa in treatment of pregnancy induced hypertension

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Abstract
Background: Hypertensive disorder of human pregnancy is one of the common and serious complication of pregnancy that affects both mother and baby. It is not only common and dangerous but also unpredictable in onset and progression and incurable except by termination of pregnancy. Fetus and neonates also are at increases risk from complication such as poor placental transfer of oxygen, fetal growth restriction, preterm birth, placental abruption, still birth and neonatal death.
Objective: To compare the efficacy of two drugs, labetalol and methyldopa as an antihypertensive to control of blood pressure.
Methodology: A randomized controlled trial carried among 100 pregnant women pregnancy induced hypertension (PIH) attending Obstetrics & Gynaecology, General Hospital Barisal, Bangladesh from January to June 2023. Total 100 patients includedin our study. 50 patients treated with tab. Labetalol (Group A) and 50 treated with tab. Methyldopa (Group B).
Results: Total 100 patients included in our study. Finding of the study showed mean age, gestational age and occupation did no differ significantly variation between Labetalol (group A) and Methyldopa (group B). Majority of the patients in group A and group B around 20-25 years. Mean age of patients in group B 25.42±3.92 years and 26.50±4.87 years in group A. Among 36% had gestational HTN, 62% had preeclampsia and 2% had eclampsia in group A. 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: It concluded that labetalol is more advantageous than methyldopa in terms of better and quicker control of blood pressure. The chances of normal vaginal delivery were greater in the labetalol group than in the methyldopa group. Safety profile and adverse effects of Labetalol and Methyldopa are similar to each other.

Keywords: Labetalol, methyldopa, pregnancy induced hypertension

Introduction
Hypertensive disorder of human pregnancy is one of the common and serious complication of pregnancy that affects both mother and baby. It is not only common and dangerous but also unpredictable in oaznset and progression and incurable except by termination of pregnancy [1]. Hypertension is the most common medical problem encountered during pregnancy. Hypertension complicates up to 10% of all pregnancies and is associated with increased risk of adverse fetal, neonatal and maternal outcomes. Pregnancy induced hypertension is associated with 5-fold increase in perinatal mortality and its socioeconomic impact on developing countries is immense. In pregnancy induced hypertension as well as preeclampsia oxidative, coagulative and vasomotor balance is altered by increase sensitivity to angiotensin II associated with reduced synthesis of vasodilator, prostaglandin, sympathetic nervous system, hyperactivity and incomplete implant of cytotrophoblast in maternal spiral arteries. 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 [2].

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 [3]. 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. General vasoconstriction could be a consequence with related uteroplacental ischemia and endothelial damage. These features are clinically characterized by hypertension, proteinuria and sodium retention [4]. Pregnancy induced hypertension is a significant management problem for every Obstetrician. Pregnancy Induced Hypertension as well as Preeclampsia is major cause of maternal and perinatal morbidity and mortality. Hypertension is defined as a sustained blood pressure higher than 140/90mm of Hg [5]. Pregnancy induced hypertension (PIH), includes gestational hypertension. preeclampsia, eclampsia [7]. Gestational hypertension, which develops after 20 wks of gestation & complicates 5-10% of pregnancies [6]. Hypertension associated with proteinuria, greater than 0.3g/L in a 24-hour urine collection or 1+ by qualitative urine examination, after 20wks of gestation called preeclampsia. Convulsions occurring in a patient with preeclampsia are known as eclampsia [8]. Diagnosis of pregnancy induced hypertension (PIH) depends on presence of hypertension after 20wks of gestation and were normotensive before 20wks of gestation, oedema, headache, blurring of vision, epigastric pain, disturbed sleep, proteinuria etc. [6]. Regular antenatal checkup is the key point to diagnose pregnancy induced hypertensive patient. This study was carried out to find the result in treatment of pregnancy induced hypertension. Findings of this study may help to control of blood pressure, prevent any complication and thus help to improve both maternal and foetal outcome.

Methods & Materials

A randomized controlled trial carried among 100 pregnant women pregnancy induced hypertension (PIH) attending Obstetrics & Gynaecology, General Hospital Barisal, Bangladesh from January to June 2023. Total 100 patients includedin our study. 50 patients treated with tab. Labetalol (Group A) and 50 treated with tab. Methyldopa (Group B).

Grouping of the sample

Group A= 50 patients who were treated with tab. Labetalol.
Group B= 50 patients who were treated with tab. Methyldopa.

Inclusion criteria

- Patients who diagnosed as a case of PIH 2.8.

Exclusion criteria

- Patients who were not give consent.
- Subjects who has diabetes, heart disease or any contraindication of beta adrenoceptor blocker and unconscious 19.

Study procedure

100 patients with pregnancy induced hypertension will be studied. All patients in the study was less than 40 wks pregnant and were normotensive before 20wks allocated to either of the treatment groups who satisfied the eligibility criteria were recruited. Patients were given either labetalol 200-400mg twice daily or methyldopa 750-2000mg/day according to the patient's response to maintain a mean arterial pressure ≤130 mmHg. Venous blood were taken for biochemical analysis. Urine R/M/E were done to detect albumin.

Operational Definition

Gestational hypertension: Hypertension without proteinuria developing after 20 wks of gestation during labour, or the puerperium in a previously normotensive nonproteinuric women.

Preeclampsia

Hypertension associated with proteinuria, greater than 0.3 gm/L in a 24 hrs urine collection or 1+ by qualitative urine examination after 20 wks of gestation.

Eclampsia

Convulsion occurring in a pt with preeclampsia.

Procedure of data analysis of interpretation

All data were entered, checked, rechecked & scrutinized by the principal investigator following standard procedure & were analyzed by SPSS program. Chi-square test were done as a significance level.

Results

Total 100 patients included in our study. Maximum 44% were age between 20-25 years followed by 40% were 26-30 years and 12% were 31-35 years in group A. On the other hand, in group B maximum 46% were age between 20-25 years followed by 42% was 26- 30 years age group and 4% were age group 31-35 years. The average age was 26.50 years in group A and 25.42 years in group B. The difference was statistically not significant between two groups (P>0.05) (Table-1). Table-1 shows multigravida were more in group A than group B which was 38% vs 34% respectively. On the other hand, in primigravida were more in group B than group A which was 66% vs 62% respectively. The difference was statistically not significant between two groups (P>0.05). Table shows maximum patients were 34-37 weeks of gestational age between two groups group A (54%) and group B (46%). The difference was statistically not significant between two groups (p>0.05).

Table-1: Distribution of age and gravidity

Age	Group A (n=50)		Group B (n=50)		p-value
	No	%	No	%	
<20	2	4	4	8	
20-25	22	44	23	46	
26-30	20	40	21	42	
31-35	6	12	2	4	0.225
Total	50	100	50	100	
Mean±SD	26.50±4.87		25.42±3.92		
Gravida					
Primi	31	62	33	66	
Multi	19	38	17	34	0.677
Total	50	100	50	100	

Table 2: Distribution of pregnancy induced hypertension between two groups

PIH	Group A (n=50)		Group B (n=50)		p-value
	No	%	No	%	
Gestational HTN	18	36	16	32	0.792
Preclampsia	31	62	32	64	
Eclampsia	1	2	2	4	
Total	50	100	50	100	

Table-2 shows 36% had gestational HTN, 62% had preeclampsia and 2% had eclampsia in group A. On the other hand in group B 32% had gestational HTN, 64% had preeclampsia and 4% had eclampsia.

Table 3: 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)	

Table-3 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. 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 4: Mean difference in fall of BP

Blood pressure	Duration	Groups (Mean fall in mm Hg±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 5: 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 6: 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-4 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-5 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. Table-6 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. To compare pre and post treatment systolic and diastolic BP in two treatment groups.

Discussion

The most frequent medical disease in pregnancy is hypertension, which contributes considerably to maternal and perinatal mortality and morbidity [7]. It is estimated that hypertension complicates around 6-10% pregnancies [8]. Pregnancy induced hypertension is a disease with worldwide significance to mothers and infants. Its greatest impact is in developing countries where it accounts for 20-40% of the strikingly increased maternal mortality. If it remains uncontrolled, it can lead to complications like pre-eclampsia, eclampsia, fetal growth retardation, abruptio placentae, premature delivery and fetal mortality as well as maternal morbidity and the mortality. Preeclampsia and eclampsia cause a woman's mortality every three minutes around the world [5, 6]. However, even in developed countries there is a major effect, primarily on the fetus. In developed countries perinatal mortality of infants of preeclamptic mothers is 5 fold greater than for non-preeclamptic women and indicated preterm deliveries for preeclampsia accounts for 15% of preterm birt [9]. Despite extensive search for years, the exact aetiology is unknown. It is likely to be multifactorial and may result from the deficient placental implantation during 1st half of pregnancy. In this study statistically there was no significant age difference between group A and group B. The mean age of patients was 26.50±4.87 years in control group and 25.42±3.92 years in case group ranging from 18-40 years. The difference was statistically not significant (P>0.05). Maximum 46% patients were age group 20-25 years in group A. This finding is consistent with the study of Duckitt and Harrington in which they have found young maternal age did not seem to affect the risk of developing pregnancy induced hypertension [10]. About the gravidity, the study revealed primigravida were more in group B than that of group A which was 66% vs 62% respectively but multigravida were more in group A than group B which was 38% vs 34% respectively. The difference was statistically significant between two group (P<0.05). So primgravida more significantly higher in group B than group A women. This finding is consistent with the findings Dutta [11] in which he has found the incidence of PIH in primigravida is about 10% and multigravdia 5%. 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 [12]. 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 [13]. 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 [14]. 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. [15] 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 [16]. 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 [17]. In our study we found that the fall in systolic BP after 48 the study conducted by Cruikshank DJ et al. which observed that Labetalol had rapid control of BP in 88% of patients [10]. 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. [11, 18].

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. The development of pregnancy induced hypertension is high in developing countries like Bangladesh where antenatal care is inadequate. Since this complication may be preventable in large number of cases if detected and treated at an early stage, it is essential to detect the condition at an early stage and to provide adequate antenatal care in due time.

Conflict of Interest: Not available

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