

# Comparison of Role of Hydralazine Vs Labetalol in Mean Reduction of Mean Arterial Pressure in patients with Severe Preeclampsia

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## ABSTRACT

**Aim:** To compare the mean reduction in mean arterial pressure with the use of Hydralazine versus Labetalol in females presenting with severe preeclampsia.

**Study Design:** Randomized Controlled Trial

**Setting:** Unit I, Department of Obstetrics & Gynaecology, PGMI/Lahore General Hospital, Lahore.

**Duration of study:** Six months after the approval of synopsis (July 26, 2016 till January 26, 2017)

**Methods:** 80 females who will fulfil the selection criteria were randomly divided into two equal groups by using lottery method, baseline MAP were recorded. In group A, females were given intravenous injection of Hydralazine 5mg bolus (slowly over 2 minutes) and after 15 minutes BP was recorded, if BP  $\geq$  160/110 then second bolus of 5mg Hydralazine was given till maximum 4 boluses after every 15 minutes or attainment of BP 140/100. In group B, females was given intravenous injection Labetalol 20 mg at presentation, 40 mg after 10 minutes and 3 doses of 80 mg every 10 minutes (each bolus slowly over 2 minutes) till maximum 5 doses or attainment of BP 140/100. Females were followed-up in Labour room for 70 minutes and BP was recorded after every 10 minutes. Mean reduction in MAP was calculated (as per operational definition).

**Results:** The mean age in Hydralazine and Labetalol groups were  $30.62 \pm 6.22$  years and  $28.55 \pm 5.72$  years. The mean gestational age in Hydralazine was  $27.25 \pm 4.06$  weeks and in Labetalol was  $27.35 \pm 4.05$  weeks. The mean number of doses in Hydralazine was  $2.40 \pm 1.10$  and in Labetalol was  $2.42 \pm 0.96$ . The mean reduction in MAP in Hydralazine and Labetalol groups was  $36.40 \pm 5.63$  and  $21.40 \pm 6.40$ . The mean reduction in MAP was significantly higher in hydralazine group, p-value  $< 0.001$ .

**Conclusion:** Through the findings of this study we conclude that the mean reduction in MAP was significantly higher in Hydralazine than Labetalol groups. The reduction in MAP was not affected by age, parity, gestational age and number of doses when stratified for these variables.

**Keywords:** Pregnancy induced hypertension, preeclampsia, Hydralazine, Labetalol, Mean arterial pressure.

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## INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are one of the most common medical complications of pregnancy and according to multiple reports affect 10–15% of all pregnancies and a major cause of maternal, fetal and neonatal morbidity and mortality<sup>1,2</sup>. Hypertensive disorders in pregnancy deserve special attention in the setting of global public health. Pre-eclampsia remains a syndrome that leads to serious repercussions on maternal and fetal mortality and its etiology is not well known<sup>3</sup>. Pre-eclampsia is primarily a disorder of placental dysfunction leading to a syndrome of endothelial dysfunction and vasospasm. The wide spread endothelial damage may manifest as a maternal syndrome, fetal syndrome or both. Considering the pathophysiology, anticipation of delivery is the best treatment for pre-eclampsia. The use of Magnesium sulfate is recommended in all cases of severe pre-eclampsia and eclampsia for prevention and treatment of seizures. Likewise, Hydralazine, Nifedipine and Labetalol have been the most commonly used drugs for treatment of severe pre-eclampsia, but their use depends on the familiarity of the treating physician<sup>3-5</sup>.

In some meta-analysis of clinical randomized trials that compared Hydralazine and Labetalol for the treatment of severe hypertensive disorder of pregnancy, they reported that the use of Hydralazine was associated with

less persistent hypertension than other antihypertensive agents for the control of hypertensive crisis. However, the use of Hydralazine in continuous infusion was associated with more episodes of hypotension than Labetalol and was associated with higher maternal adverse effects (headache, palpitations, tachycardia and flushing<sup>6,7</sup>).

In a randomized trial, it was stated that Hydralazine lowered the mean arterial pressure (MAP) more than did Labetalol ( $33.3 \pm 13.2$  mmHg versus  $25.5 \pm 11.2$  mmHg;  $p < 0.05$ ), but Labetalol had a more rapid effect<sup>8</sup>. In another randomized trial, equal reduction in Mean Arterial Pressure was found with Hydralazine and with Labetalol ( $19 \pm 1.4$  mmHg versus  $20 \pm 1.0$  mmHg;  $p < 0.05$ ) and author concluded that Hydralazine and Labetalol for intravenous use are equally effective in the management of hypertensive crisis in pregnant patients (24 weeks or more) with severe hypertensive disorders of pregnancy, showing a similar frequency of adverse effects in both groups<sup>9</sup>.

Rationale of this study is to compare the mean reduction in MAP with Hydralazine versus Labetalol in females presenting with severe preeclampsia. Literature has shown that Hydralazine is more effective in reducing MAP in pregnant females as compared to Labetalol. But the Labetalol has faster effect on lowering BP as compared to Hydralazine. Moreover, Labetalol has fewer side effects as compared to Hydralazine. There is controversy reported in literature as well as there is no local evidence found in this regard. So I want to conduct this study to find more appropriate and local evidence which was applicable in

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future. It will help the patients to prevent from severe sequel of preeclampsia and bad obstetrical outcome and to counsel the females to present for proper antenatal checkup during pregnancy to avoid such complications.

**Epidemiology:** Up to 10% of women have elevated blood pressure during pregnancy<sup>10</sup>. Three percent to 8% of women in developed countries develop pre-eclampsia and 0.56 per 1000 births are complicated by eclampsia<sup>11</sup>. However, eclampsia affects almost 10–30 times as many women in low-income countries<sup>10</sup>. The incidence of pre-eclampsia is rising in the United States and may be attributable to the rising prevalence of risk factors including advanced maternal age, obesity, diabetes and preexisting hypertension<sup>12</sup>.

The objective of the study was to compare the mean reduction in mean arterial pressure with the use of Hydralazine versus Labetalol in females presenting with severe preeclampsia

**OPERATIONAL DEFINITION**

**Severe Preeclampsia:** It is defined as BP≥ 160/110 mmHg with proteinuria ≥+1 on urine dipstick method after 20 weeks of gestation.

**Mean arterial pressure:** It is defined as “Average arterial pressure during a single cardiac cycle”, and calculated as; MAP = diastolic blood pressure + 1/3 of pulse pressure (systolic BP – diastolic BP)

**Reduction in MAP:** It was measured as Reduction in MAP = Baseline MAP – Post treatment MAP (One hour + 10 minutes post treatment)

**Hypothesis:** There is a difference in mean reduction in MAP with Hydralazine versus Labetalol in females presenting with severe preeclampsia.

**MATERIAL AND METHODS**

This randomized controlled trial was conducted in the Department of Obstetrics & Gynaecology, PGMI/Lahore General Hospital, Lahore for a period of six months (July 26, 2016 till January 26, 2017). Sample size of 80 cases; 40 cases in each group is calculated with 80% power of test, 95% confidence level and taking magnitude of mean reduction in MAP i.e. 33.3±13.2mmHg<sup>8</sup> with Hydralazine versus 25.5±11.2mmHg<sup>8</sup> with Labetalol in females presenting with pre-eclampsia. Non-Probability, Convenient Sampling technique was used. All females of age 20-40 years, parity<5 presenting with singleton pregnancy after 20 weeks of gestation with severe pre-eclampsia (as per operational definition) were included in the study.

**Exclusion criteria:**

- High risk females i.e., gestational diabetes (BSR≥200mg/dl) or eclampsia, pre-eclampsia with convulsions) or HELLP syndrome.
- Females with chronic hypertension (BP≥140/90mmHg) on medical record.
- Female with systemic problems i.e., asthma, deranged LFTs (ALT>40IU, AST>40IU), deranged RFTs (serum creatinine>1.2mg/dl) or cardiac problem.

**Data collection procedure:** 80 females who will fulfil the selection criteria were enrolled in the study from Emergency Department of Obstetrics & Gynaecology, PGMI/ Lahore General Hospital, Lahore after approval from hospital ethical committee. Informed consent was obtained

from all females. Their demographic information (name, age, parity, gestational age) was noted. Then females were randomly divided into two equal groups by using lottery method, baseline MAP was recorded. In group A, females were given intravenous injection of Hydralazine 5mg bolus ( slowly over 2 minutes) and after 15 minutes BP was recorded, if BP ≥160/110 then second bolus of 5mg Hydralazine was given till maximum 4 boluses after every 15 minutes or attainment of BP 140/100. In group B, females was given intravenous injection Labetalol 20 mg at presentation, 40 mg after 10 minutes and 3 doses of 80 mg every 10 minutes (each bolus slowly over 2 minutes) till maximum 5 doses or attainment of BP 140/100. Females were followed-up in Labour room for 70 minutes and BP was recorded after every 10 minutes. Mean reduction in MAP was calculated (as per operational definition). All this information was recorded on a proforma.

**Data analysis procedure:** The collected data was analysed statistically by using SPSS version 21. Quantitative variables like age, gestational age, number of doses, parity, MAP (pre, post treatment and reduction at 70 minutes) was presented in form of mean ± S.D. In both groups, post-treatment MAP was subtracted from baseline MAP and reduction in MAP was calculated and reduction in MAP was presented as mean±SD. Both groups were compared for mean reduction in MAP by using independent sample t-test taking p-value ≤0.05 as significant. Data was stratified for age, gestational age, BMI, parity and no of doses. Post-stratification, independent sample t-test was applied with p-value ≤0.05 as significant.

**RESULTS**

The mean age in Hydralazine and Labetalol groups were 30.62 ± 6.22 years and 28.55 ± 5.72 years (Table 1). The mean gestational age in Hydralazine was 27.25 ± 4.06 weeks and in Labetalol was 27.35 ± 4.05 weeks (Table 2). The mean parity in Hydralazine and Labetalol groups was 2.55 ± 1.06 and 2.50 ± 0.88 (Table 3). The mean number of doses in Hydralazine was 2.40 ± 1.10 and in Labetalol was 2.42 ± 0.96 (Table 4). The mean MAP before treatment in Hydralazine and Labetalol groups was 141.55 ± 11.97 and 140.80 ± 12.92 (Table 5). The mean MAP after treatment in Hydralazine was 94.08 ± 9.34 and in Labetalol was 96.08 ± 9.92 (Table 6). The mean reduction in MAP in Hydralazine and Labetalol groups was 36.40 ± 5.63 and 21.40 ± 6.40. The mean reduction in MAP was significantly higher in hydralazine group, p-value < 0.001 (Table 7). When data was stratified for age, gestational age, parity, obesity and number of doses we found higher mean reduction in MAP was significantly higher in hydralazine group, p-value < 0.001 (Table 8 to 12).

Table 1: Comparison of age (years) in both groups

Study Groups	Mean	S.D
Hydralazine(n=40)	30.62	6.22
Labetalol(n=40)	28.55	5.72

Table 2: Comparison of gestational age (weeks) in both groups

Study Groups	Mean	S.D
Hydralazine(n=40)	27.25	4.06
Labetalol(n=40)	27.35	4.05

Table 3: Comparison of Parity in both groups

Study Groups	Mean	S.D
Hydralazine(n=40)	2.55	1.06
Labetalol(n=40)	2.50	0.88

Table-4: Comparison of number of doses in both groups

Study Groups	Mean	S.D
Hydralazine(n=40)	2.40	1.10
Labetalol(n=40)	2.42	0.96

Table 5: Comparison of MAP before medication in both groups

Study Groups	Mean	S.D
Hydralazine(n=40)	141.55	11.97
Labetalol(n=40)	140.80	12.92

Table 8: Comparison of Reduction in MAP in both groups with respect to age groups

Age groups (years)	Reduction in MAP	Mean	S.D	t-test	p-value
20-30 (years)	Hydralazine	37.88	6.06	9.604	<0.001
	Labetalol	21.97	6.24		
31-40 (years)	Hydralazine	33.93	3.84	6.618	<0.001
	Labetalol	19.44	6.95		

Table 9: Comparison of Reduction in MAP in both groups with respect to gestational age (weeks)

Gestational Age (weeks)	Reduction in MAP	Mean	S.D	t-test	p-value
21-27 (weeks)	Hydralazine	36.00	5.23	7.411	<0.001
	Labetalol	22.71	6.60		
28-34 (weeks)	Hydralazine	36.84	6.15	8.591	<0.001
	Labetalol	19.44	5.75		

Table 10: Comparison of Reduction in MAP in both groups with respect to parity

Parity	Reduction in MAP(mmHg)	Mean	S.D	t-test	p-value
< 3	Hydralazine	36.71	5.63	8.456	<0.001
	Labetalol	20.50	6.85		
3 or more	Hydralazine	36.05	5.76	7.122	<0.001
	Labetalol	22.50	5.81		

Table 11: Comparison of Reduction in MAP in both groups with respect to BMI

BMI	Reduction in MAP(mmHg)	Mean	S.D	t-test	p-value
Obese	Hydralazine	36.12	6.01	4.964	<0.001
	Labetalol	22.75	5.83		
Non-obese	Hydralazine	36.47	5.63	9.872	<0.001
	Labetalol	20.82	6.65		

Table 12: Comparison of Reduction in MAP in both groups with respect to number of doses

Number of doses	Reduction in MAP(mmHg)	Mean	S.D	t-test	p-value
1-2	Hydralazine	35.05	4.33	8.020	<0.001
	Labetalol	22.05	6.11		
>2	Hydralazine	37.89	6.58	7.831	<0.001
	Labetalol	20.61	6.84		

## DISCUSSION

In current study the mean age in Hydralazine and Labetalol groups were  $30.62 \pm 6.22$  years and  $28.55 \pm 5.72$  years..A study reported that mean ( $\pm$ SD) age of the labetalol group was  $27.46 (\pm 5.28)$  years while that in the hydralazine group was  $26.28 (\pm 5.17)$  years. The mean age in current study relatively higher than the above study.

Some clinical trials showed that hydralazine is more effective but it is associated with more maternal hypotension as compared to labetalol (66.67% vs. 16.67%,  $p=0.007$ ) with RR 3.29; however, these results conflict with some studies that showed insignificant difference between both drugs as hydralazine showed maternal hypotension in 2% cases and labetalol showed in 0 cases,  $p$ -value>0.05.

Table-6: Comparison of MAP after medication in both groups

Study Groups	Mean	S.D
Hydralazine(n=40)	94.08	9.34
Labetalol(n=40)	96.08	9.92

Table-7: Comparison of Reduction in MAP in both groups

Study Groups	Mean	S.D
Hydralazine(n=40)	36.40	5.63
Labetalol(n=40)	21.40	6.40

t-test: 11.127 P-value < 0.001

In a randomized trial, it was stated that Hydralazine lowered the mean arterial pressure (MAP) more than did Labetalol ( $33.3 \pm 13.2$  mmHg versus  $25.5 \pm 11.2$  mmHg;  $p < 0.05$ ), but Labetalol had a more rapid effect.<sup>8</sup> Our findings are consistent with above study<sup>8</sup>.

A study reported that the mean fall in MAP observed in the labetalol group was  $29.10 \pm 7.21$  mmHg and that in the hydralazine group was  $25.05 \pm 10.15$  mmHg which was statistically significant with the  $p$  value being 0.046. The study has conclude that intra Venous labetalol lowered MAP more than hydralazine, when administered to pregnant females with severe Pregnancy induced hypertension and pre eclampsia in pregnancy. These findings are not in agreement to our study.

In another randomized trial, equal reduction in Mean Arterial Pressure was found with Hydralazine and with

Labetalol (19±1.4mmHg versus 20±1.0mmHg; p<0.05) and author concluded that Hydralazine and Labetalol for intravenous use are equally effective was found in pregnant patients (24 weeks or more) with severe hypertensive disorders of pregnancy, showing a similar frequency of adverse effects in both groups<sup>9</sup>. In 2016, a study was done in which women divided in 2 groups (113 each) divided randomly: Labetalol (Group-A), Hydralazine (Group-B) measured the difference between pretreatment and after treatment mean arterial blood pressure. Pretreatment mean arterial blood pressure was 127.40±40 and 126.61±6.475 mmHg in labetalol and Hydralazine group respectively. After treatment mean arterial blood pressure was 112.25±5.821 and 109.27±14.30 mmHg in labetalol and Hydralazine group respectively. Mean arterial blood pressure change was 15.14± 8.02 mmHg in labetalol group and 17.34±13.42mmHg in hydralazine group. (p=0.136, Not significant).

Furthermore, 2003, a Meta-analysis is conducted to review the outcomes in randomized controlled trials comparing hydralazine against other antihypertensives for severe hypertension in pregnancy. The study has concluded that the results are not robust enough to guide clinical practice, but they do not support use of hydralazine as first line for treatment of severe hypertension in pregnancy. Adequately powered clinical trials are needed, with a comparison of labetalol and nifedipine showing the most promise.

## CONCLUSION

Through the findings of this study we conclude that the mean reduction in MAP was significantly higher in Hydralazine than Labetalol groups. The reduction in MAP was not affected by age, parity, gestational age, and number of doses when stratified for these variables.

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