Original Article

Labetalol versus Hydralazine in Control of Severe Hypertension in Eclampsia; A Randomized Controlled Trial

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Abstract

Objective: To compare the mean fall in mean arterial pressure between labetalol and hydralazine in patients with severe hypertension in eclampsia.

Methodology: This randomized Controlled Trial study was conducted in the Gynaecology and Obstetrics Department, MTI/Mardan Medical Complex, Mardan Pakistan, from 5th January 2021 5th July 2021.In this study, a total of 150 patients were selected and randomly divided into two groups (A & B) by using random number table generated in SPSS v. 21. Half of the patients were allotted to Group A (Labetalol group) and other half to group B (Hydralazine group). Blood pressure at baseline was recorded and mean arterial pressure (MAP) was calculated. In Group A 20mg labetalol was given slow intravenous while similarly in group B hydralazine 5mg intravenous was given. All patients were observed and followed in the obstetrics ward for 30 minutes with good monitoring facilities. After 30 minutes, blood pressure was noted again, and MAP was calculated and recorded on the proforma. SPSS version 21 was used for data analysis. Age, BMI, gestational age, mean arterial pressure at baseline, and fall in mean arterial pressure were presented in the form of mean ± SD. Parity and booking status was presented in the form of frequency and percentage. Both groups were compared for the mean fall in MAP. The stratification of data was done in both groups and were compared for the mean fall in mean arterial pressure by using an independent samples t-test and level of significance was taken as *p*-value ≤0.05.

Results: Our study showed that in Group A (labetalol) mean age was 27 years, with SD ± 8.10. where in Group B (hydralazine), the mean age was 28 years with SD ± 7.88. In Group A (labetalol) the mean fall in arterial pressure was 30.05 ± 5.32 mmHg while in Group B (hydralazine), the mean fall in arterial pressure was 22.19 ± 8.27 mmHg with, *p*-value 0.0001.

Conclusion: Our study concluded that labetalol was more effective than hydralazine for controlling severe hypertension with eclampsia

Keywords: Eclampsia, Hydralazine, Labetalol, Maternal, Perinatal, Severe hypertension.

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Introduction

Hypertensive disorders of pregnancy occur in 5 to 10% of all pregnancies, with preeclampsia affecting 5 to 8%.[1,2] Estimated prevalence is reported to occur in 3-8% of pregnancies in developed countries.[3,4] The occurrence of hypertensive disorders of pregnancy is 10-30 times higher in women with low socioeconomic status. According to reports, the frequency of hypertensive disorders in pregnancy was 5.34% in Karachi and 3.2% in Lahore.[5] These disorders, along with haemorrhage and infections, form a deadly trio that leads to maternal morbidity and mortality.

Hippocrates observed in the fifth century that symptoms like headaches, convulsions, and drowsiness were warning signs related to pregnancy. In 1619, Varandaeus introduced the term eclampsia in a publication on gynecology.[6] Eclampsia is a complication that is often associated with severe preeclampsia. It is defined as the occurrence of grand mal seizures and/or an unexplained coma during pregnancy or postpartum in a woman showing symptoms or signs of preeclampsia.[7,8] Usually, eclampsia happens between the 20th week of pregnancy and 23 days postpartum, and it is considered

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a complication of severe preeclampsia. However, in the United Kingdom, 38% of reported cases of eclampsia occurred without hypertension and proteinuria.[9] Likewise, a review of cases in the United States found that 16% of cases did not have hypertension.[10]

Except for detecting preeclampsia at an early stage, there are no dependable tests or symptoms that can predict the onset of eclampsia. In developed nations, numerous instances have been labeled as inevitable.[11,12] The cause behind the occurrence of eclampsia is still not clearly understood.[13,14] Various factors have been suggested as the cause of preeclampsia/eclampsia, including genetic predisposition, immunological, endocrinological, and nutritional factors, as well as abnormalities in trophoblastic invasion, coagulation, vascular endothelial damage, cardiovascular maladaptation, dietary imbalances, and infections. Additionally, an imbalance in prostanoid production and an increase in plasma antiphospholipids have also been linked to eclampsia. Some clinical risk factors for preeclampsia have been identified through large-scale epidemiological studies, including being a primigravida, nulliparity, having a teenage or advanced maternal age pregnancy, having a family history of preeclampsia/eclampsia, experiencing poor outcomes in a previous pregnancy such as IUGR, abruptio placenta, or foetal death, and having a lower socioeconomic status.[15,16] Medical conditions that exist prior to pregnancy, such as obesity, chronic hypertension, diabetes, renal diseases, coagulation and connective tissue disorders, are also recognized as risk factors. [17,18,19]

An expecting woman diagnosed with pre-eclampsia or severe hypertension should receive evaluation and treatment at a hospital due to the unpredictable progression of the condition. The level of blood pressure alone is not a sufficient indicator of immediate risk as some women may experience severe maternal end-organ or uteroplacental dysfunction even with only slightly elevated blood pressure levels. The National High Blood Pressure Education Programme suggests that severe hypertension (sBP ≥160mmHg or dBP ≥110mmHg) is the threshold commonly used for treating hypertension during pregnancy.[20] High blood pressure that is serious in nature can indicate negative outcomes for both the mother and the newborn. It is widely agreed upon that this condition should be addressed promptly in a closely supervised environment to ensure that medication designed to lower blood pressure is effective.[21] The drugs typically suggested for managing serious cases of high blood pressure are intravenous labetalol, intravenous hydralazine, and oral nifedipine, either taken alone or in combination.[22] Hydralazine has been the preferred medication for treating high blood pressure in expectant mothers with severe hypertension for a considerable length of time. However, its utilization has been linked to unfavourable consequences. Nowadays, Labetalol is typically the first option for managing sudden high blood pressure during pregnancy. Labetalol has been widely studied, and its safety in pregnancy is well established except for neonatal bradycardia Previous studies showed that similar efficacy and side effects were observed between hydralazine and labetalol in the treatment of severe hypertension in pregnancy, and also have similar side effects.[8,9]

The rationale of this study is to compare the mean fall in MAP between labetalol and hydralazine in patients with eclampsia. It has been reported in literature that the mean reduction in mean arterial pressure was greater with hydralazine. There is only one local study available in this regard. But conflicting results have been noticed in the literature, and that was observed in an international study, where medical compliance is better than our set-ups. So we want to conduct this study to get reliable results and implement the results in a local setting. With the help of this study, we can improve the outcome of pregnancies with severe hypertension.

Methodology

This randomised controlled trial was conducted at Gynaecology and Obstetrics Department of the Mardan Medical Complex, Mardan from 5th January 2021 to 5th July 2021. All patients between the ages of 18-40 with parity <5, gestational age > 32 weeks, and presenting with eclampsia, either booked or unbooked were included in this study The exclusion criteria were: multiple pregnancy, congenital anomalies, chronic hypertension (on anti-hypertensive medicines), bronchial asthma, and diabetics. Patients with placental problems (abruption, previa, accreta, percreta, and increta) were also excluded from this study. The WHO sample size calculator was used to calculate the sample size of 175 patients with 80% power and a 5% level of significance. A non-probability convenience sampling technique was adopted.

The hospital's ethical committee granted approval for the study. All patients were informed about the study's objectives and provided with a written explanation before giving their consent. Patients were recruited from the

outpatient department (OPD) as well as through emergency. A detailed history including patient demographics like name, age, parity, gestational age, BMI, parity, and booking status was noted. Blood pressure at baseline was measured. It was measured in both arms initially, and, thereafter, in the same arm for consistency, choosing the arm with the higher BP. Mean arterial pressure (MAP) was calculated as dBP + 1/3 (sBP-dBP). They were randomly divided into two groups by using a random number table generated in SPSS v. 21. In group A, patients were given 20 mg of labetalol slowly intravenously. Similarly, in group B, 5mg of hydralazine is given intravenously. All females were observed and followed up in obstetrics wards for 30 minutes. After 30 minutes, blood pressure was noted again and means arterial pressure was calculated. The drop in mean arterial pressure was calculated. All this information was recorded on proforma.

Data was collected and analysed by descriptive analysis using computer software (SPSS, version 21; SPSS Inc., Chicago, IL). Variables like age, gestational age, BMI, MAP at baseline, and fall in MAP were described as mean ± SD. Parity and booking status were described as frequency and percentage. Both groups were compared for mean fall in mean arterial pressure. Data was stratified for age, BMI, gestational age, parity, and booking status. Post-stratification, both groups were compared for mean fall in mean arterial pressure by using an independent samples t-test. The statistical significance was defined as p <0.05.

Results

A total of 150 pregnant women were treated in the hospital from 5th January 2021 to 5th July 2021. The age distribution among the two groups was analyzed. In Group A (labetalol), 50 patients (67%) were aged between 18-30 years and 25 patients (33%), were in the age range 31-40 years. The mean age was 27 years with SD ± 8.10. Whereas in Group B (Hydralazine), 48 patients (64%) aged between 18-30 years, and 27 patients (36%), were in the age range of 31-40 years. The mean age was 28 years with SD ± 7.88. BMI distribution of BMI among the two groups was also analyzed as in Group A, 54 patients (72%) had BMI ≤ 27 Kg/m^2 and 21 patients (28%) had BMI > 27 Kg/m^2. Whereas in Group B, 53 patients (70%) had BMI ≤ 27 Kg/m^2 and 22(30%) patients had BMI > 27 Kg/m^2. The mean BMI was 25 Kg/m^2 with SD ± 4.29 in Group A, while in Group B, it was 25 Kg/m^2 with SD ± 3.98, (Table I).

The period of gestation among two groups was analysed as in Group A, 46 patients (61%) had a POG 32-36 weeks and 29 patients (39%) had 37-40 weeks. In Group B, 45 patients (60%) had POG 32-36 weeks and 30 patients (40%) had a POG between 37-40 weeks. Parity distribution among the two groups was also analyzed. Group A had 56 patients (75%) primi para while 19 patients (25%) were multi para. In Group B, 55 patients (73%) were primi para and 20 patients (27%) were multi para. Booking status among two groups showed that in Group A, 23 patients (31%) were booked and 52 patients were (69%) unbooked. Whereas in Group B, 22 patients (30%) were booked and 53 patients (70% were unbooked), (Table II).

The mean fall in mean arterial pressure (MAP) in Group A was 30.05 ± 5.32 mmHg while in Group B, the mean fall in mean arterial pressure was 22.19 ± 8.27 mmHg, p-value 0.0001 (Table III) The stratification of the mean fall in arterial pressure in two groups with respect to age,

Table I: Age and BMI distribution (n=150).

Variables		Group A (n=75)			Group B (n=75)		
		N	%age	Mean ± SD	N	%age	Mean ± SD
Age (years)	**18-30**	50	67	27 ± 8.10	48	64	28 ±7.88
	31-40	25	33		27	36	
BMI (Kg/m^2)	**≤27**	54	72	25±4.29	53	70	25±3.98
	>27	21	28		22	30	

Table II: Distribution according to Gestational age, Parity & Booking status (n=150)

Variables		Group A (n=75)		Group B (n=75)		*P* value
		N	%age	N	%age	
Gestational Age (weeks**)**	**32-36**	46	61	45	60	0.0539
	37-40	29	39	30	40	
Parity	**Primi para**	56	75	55	73	0.8523
	Multi para	19	25	20	27	
Booking Status	**Booked**	23	31	22	30	0.8585
	Un -Booked	52	69	53	70	

BMI, gestational age, parity, and booking status is given in Table IV.

Table III: Mean Arterial Pressure in mmHg (n=150).

Time (hours)	**Group A (n=75)**	**Group B (n=75)**	***P* value**
Baseline	172±3.03	175±4.12	0.0001
Fall (after 30 minutes)	30.05±5.32	22.19±8.27	0.0001

Discussion

Around 5 to 10% of pregnancies are affected by hypertensive disorders, which, along with hemorrhage and infections, contribute to adverse maternal outcomes. Preeclampsia specifically affects approximately 5 to 8% of pregnancies.[1,2] The International Society for the Study of Hypertension in Pregnancy released its updated guidelines for the classification, diagnosis, and treatment of hypertensive disorders in pregnancy in 2021. The recommendations state that expectant mothers with pre-eclampsia or severe hypertension (systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110mmHg or higher) should be evaluated and treated while in a hospital setting. [23]

In the present study, the mean age of females was 27 years with SD ± 8.10 in Group A (Labetalol) where as in Group B (Hydralazine) mean age was 28 years with SD ± 7.88. In labetalol group, the mean fall in mean arterial pressure was 30.05 ± 5.32 mmHg while in hydralazine group it was 22.19 ± 8.27 mmHg. According to a study conducted by Patel et al., a larger proportion of participants (81.5%) were able to attain their target blood pressure with a single dose of labetalol compared to hydralazine (69.5%), indicating a statistically significant difference between the two medications.[24] In comparison to hydralazine, labetalol was able to achieve the target blood pressure more quickly. Furthermore, both medications had similar rates of maternal adverse effects and fetal outcomes. The study's authors concluded that both hydralazine and labetalol were equally effective at reducing high blood pressure in expectant mothers with severe hypertension during pregnancy.

Hydralazine has been used as an antihypertensive medication for more than four decades. The American College of Obstetricians and Gynecologists advises that parenteral hydralazine and labetalol should be the initial drug of choice for managing sudden, severe high blood pressure.[25] Mable et al. conducted a study that revealed that hydralazine was more effective than labetalol in reducing mean arterial pressure, with a difference of 13.3mm Hg versus 11.2mm Hg, respectively.[26] Ashe et al. conducted a study that produced similar findings. [27] A Cochrane review failed to establish whether hydralazine or labetalol is superior in treating high blood pressure. The review concluded that there is insufficient evidence to determine which medication is better. [28] In contrast to the previous studies by Mable and Ashe, our study found that the reduction in blood pressure with labetalol was statistically significant, with a p-value of 0.0001. This finding differs from that of Mable and Ashe. The reason for this difference could be the larger sample size of our study, with n = 75 in each group, which was relatively higher. Additionally, Vigil V Gracia's study did not demonstrate the superiority of hydralazine over labetalol. [29] Magee's meta-analysis suggested that labetalol may be a promising alternative as the initial medication for treating high blood pressure.[30]

Khan et al. conducted a study where they found that the mean age of the participants in the labetalol group was 27.46 (±5.28) years, while it was 26.28 (±5.17) years in the hydralazine group. The study also revealed a statistically significant difference in the mean reduction of mean arterial pressure between the labetalol group (29.10 ± 7.21 mmHg) and the hydralazine group (25.05 ± 10.15 mmHg), with a p-value of 0.046. [31] The researchers concluded that pregnant women with

Table-IV: Stratification of MAP with Age, BMI, Gestational age, Parity & Booking status (n=150)

Variables		**Group A (n=75)** (Mean & SD,mmHg)	**Group B (n=75)** (Mean & SD, mmHg)	***P* value**
Age (years)	**18-30**	29.47 ± 4.56	21.27 ± 7.75	0.0001
	31-40	31.09 ± 5.93	22.34 ± 8.53	0.0001
BMI (Kg/m^2)	**≤ 27**	29.36± 4.30	22.73 ± 7.86	0.0001
	>27	30.55 ± 4.28	22.59 ± 7.91	0.0002
Gestational Age (weeks**)**	**32-36**	30.77 ± 5.42	23.11 ± 8.10	0.0001
	37-40	31.63 ± 4.41	22.46 ± 7.62	0.0001
Parity	**Primi para**	30.21± 5.23	21.66 ± 8.10	0.0001
	Multi para	30.37 ± 5.21	21.72 ± 7.95	0.0003
Booking Status	**Booked**	29.87± 4.15	21.39 ± 7.13	0.0001
	Un -Booked	31.76 ± 5.43	23.41 ± 8.44	0.0001

severe hypertension due to pre-eclampsia or pregnancy-induced hypertension experienced a greater reduction in mean arterial pressure (MAP) when treated with intravenous labetalol compared to hydralazine.

A study conducted by Gaur N et al found that the median time to achieve target blood pressure was similar for both drugs, with a value of 22.4 minutes in each group. During the study, it was observed that 46.66% of the participants in the labetalol group did not require repeat doses, while 50% of the participants in the hydralazine group did not require repeat doses. No significant maternal or foetal side effects were observed in either group. [32]

Conclusion

Our study concluded that labetalol is a more effective drug than hydralazine in managing severe hypertension in patients with eclampsia. Additionally, both groups had similar rates of maternal adverse effects and fetal outcomes.

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