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Comparison of Efficacy of Labetalol Versus Alpha Methyldopa in the Management of Preeclampsia

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ABSTRACT

Background: Preeclampsia is a hypertensive disorder that occurs after 20 weeks of gestation and is known to be one of the major causes of morbidity for mothers and their fetuses. The regulation of blood pressure is important in order to prevent severe consequences for mothers and their fetuses. **Objective:** To compare the efficacy of labetalol and alpha methyldopa in management of preeclampsia. **Study Design:** Randomized controlled trial. **Duration and Place of Study:** This study was conducted from 10 April 2024 to 10 October 2024 in Department of Obstetrics and Gynaecology, Zanana Hospital, Dera Ismail Khan. **Methodology:** A total of 190 women aged 18 to 40 years with singleton pregnancy more than 30 weeks and diagnosed preeclampsia were included. Patients were randomly divided into two equal groups. Group A received labetalol 100 milligram twice daily and Group B received alpha methyldopa 250 milligram three times daily. Efficacy was defined as blood pressure less than 140/90 millimeter of mercury within 48 hours without dose escalation. Data were analyzed using Statistical Package for Social Sciences version 26. **Results:** Mean age was 29.03 ± 6.36 years in labetalol group and 29.37 ± 7.32 years in alpha methyldopa group. Efficacy was achieved in 81 (85.3%) patients receiving labetalol and 67 (70.5%) receiving alpha methyldopa, showing significant difference (p = 0.014). **Conclusion:** Labetalol was more effective than alpha methyldopa for controlling blood pressure in preeclampsia.

INTRODUCTION

Preeclampsia is a pregnancy-associated condition characterized by a hypertensive disorder that manifests after 20 weeks of gestation.[1] It is characterized by the presence of hypertension and proteinuria.[1] It is a significant contributor to maternal and perinatal morbidity and mortality, particularly in developing countries. Although the etiology of preeclampsia is poorly understood, abnormal placentation, endothelial dysfunction, and vasospasm have emerged as key factors.[2] Patients with preeclampsia complain of headaches, blurred vision, epigastric pain, edema, and reduced urinary output.[3] Physical signs include elevated blood pressure >140/90 mmHg, with proteinuria detected by dipstick or 24-hour urine collection.[4] Severe cases can lead to complications such as eclampsia, HELLP syndrome, placental abruption, and fetal growth restriction.[5]

Labetalol is a widely used antihypertensive drug for the treatment of preeclampsia.[6] It works by inhibiting both alpha and beta adrenergic receptors, thereby decreasing systemic vascular resistance without producing a significant decrement in heart rate or cardiac output.[7] It can be administered orally for mild to moderate hypertension and intravenously for severe hypertension.[8] It has a rapid onset and provides effective BP control, making it a popular choice for preeclampsia. It also has a good safety profile for pregnant patients and does not produce a significant reduction in uteroplacental blood flow.[9]

Methyldopa, also known as alpha-methyldopa, is a centrally acting antihypertensive agent that has been used to manage hypertension in pregnant women.[10] Its mechanism of action is the stimulation of central alpha-2 adrenergic receptors, which leads to decreased sympathetic tone and, subsequently, decreased blood pressure.[11] It is given orally and is used to manage mild to moderate hypertension and not severe hypertension because of the slow onset of action, which is less desirable compared to labetalol.[12] Methyldopa is safe in pregnancy and has few adverse effects on the fetus, making it the drug of choice. Its adverse effects include sedation, dry mouth, depression, and increased liver enzymes in some patients.[13]

Preeclampsia is a significant cause of morbidity for mothers as well as for the baby, particularly in the peripheral regions such as Dera Ismail Khan, where there is a lack of proper antenatal monitoring, resulting in uncontrolled hypertension at a late stage. Thus, it is crucial

to manage hypertension to avoid complications such as eclampsia, placental abruption, and fetal mortality. Both labetalol and alpha-methyldopa have been found to be effective in the treatment of hypertension, but there is a lack of data regarding the efficacy of these two medications.

METHODOLOGY

This randomized controlled trial was carried out in the Department of Obstetrics and Gynaecology, Zanana Hospital Dera Ismail Khan from 10th April 2024 to 10th October 2024. Ethical approval was taken from the institutional ethical committee before initiation of study. The approval reference number was No.03/GJMS/ER dated January 13, 2024. The sample size was calculated by using WHO sample size calculator with level of significance 5% and power 80%. Expected efficacy of labetalol was taken as 82% while expected efficacy of alpha methyldopa was 64% in management of preeclampsia.[14] The calculated sample size was 190 patients. Total 190 patients were enrolled, where n1 = 95 patients were allocated in labetalol group (A) and n2 = 95 patients were allocated in alpha methyldopa group (B). Women aged 18 to 40 years having singleton pregnancy confirmed on ultrasound, gestational age > 30 weeks on LMP, any parity and diagnosed cases of preeclampsia were included in the study. Preeclampsia was considered when blood pressure was ≥ 140/90 mmHg measured at 2 occasions at least 4 hours apart along with proteinuria ≥ 300 mg/day on laboratory examination. Patients having history of chronic Hypertension, renal disease, liver disease, bronchial asthma, diabetes or cardiac disease were excluded from the study.

Written informed consent was obtained from each patient after explaining purpose, procedure, possible risks and benefits of the study. Baseline demographic variables were recorded at admission including age, gestational age, parity and BMI, baseline BP. Detailed medical history was taken and general physical examination was performed. Randomization was done by blocked randomization. Allocation concealment was ensured by sealed opaque envelopes which were opened at time of admission. In group A, tablets containing Labetalol 100mg were used. These tablets were given twice daily. In group B, tablets containing Alpha-methyldopa 250mg were used. These tablets were used three times daily. The treatment was continued until delivery, provided adequate blood pressure control was achieved. If blood pressure was not adequately controlled in 48 hours, the dose of each drug was doubled, and response was recorded. The efficacy of each drug was evaluated 48 hours after starting treatment. The efficacy of each drug was defined as the ability of each drug to achieve blood pressure of less than 140/90 mmHg without any need to increase the dose within 48 hours after starting treatment.

All collected data were entered and analyzed using SPSS version 26. Quantitative variables including age, gestational age, parity, BMI and baseline BP were expressed as mean ± standard deviation. Qualitative variables efficacy were presented as frequencies and percentages. Chi-square test was applied to compare efficacy between group A and group B taking $p \leq 0.05$ as statistically significant. Stratification was done with respect to age, gestational age, parity, BMI and residence to observe effect modifiers. Post stratification chi-square test was applied and $p \leq 0.05$ was considered significant.

RESULTS

Total of 190 patients were divided equally into two groups, with labetalol group (n=95) and alpha methyldopa group (n=95). the mean age of patients in labetalol group was 29.03 ± 6.36 years and in alpha methyldopa group it was 29.37 ± 7.32 years. the mean gestational age were 35.27 ± 3.45 weeks and 35.49 ± 3.19 weeks respectively. the parity mean was found to be 2.26 ± 1.51 and 2.66 ± 1.65, while mean BMI was 26.59 ± 2.56 kg/m^2 and 27.04 ± 2.60 kg/m^2 for labetalol and alpha methyldopa groups respectively. the baseline systolic blood pressure (SBP) was 149.81 ± 5.80 mmHg in labetalol group and 150.34 ± 5.77 mmHg in alpha methyldopa group, while baseline diastolic blood pressure (DBP) was 98.97 ± 6.08 mmHg and 101.93 ± 5.89 mmHg respectively. regarding residence, majority of patients in both groups were from rural areas, with 60 (63.2%) in labetalol group and 65 (68.4%) in alpha methyldopa group, while urban residents were 35 (36.8%) and 30 (31.6%) respectively (Table 1).

Table 1

Patients Demographics in Both Groups

Variables	Labetalol (n=95)	Alpha Methyldopa (n=95)
	Mean ± SD	Mean ± SD
Age (years)	29.03 ± 6.36	29.37 ± 7.32
Gestational Age (weeks)	35.27 ± 3.45	35.49 ± 3.19
Parity	2.26 ± 1.51	2.66 ± 1.65
BMI (Kg/m^2)	26.59 ± 2.56	27.04 ± 2.60
Baseline SBP (mmHg)	149.81 ± 5.80	150.34 ± 5.77
Baseline DBP (mmHg)	98.97 ± 6.08	101.93 ± 5.89
Residence	**n (%)**	**n (%)**
Rural	60 (63.2%)	65 (68.4%)
Urban	35 (36.8%)	30 (31.6%)

Regarding the efficacy of treatment, labetalol was found to be more effective as compared to alpha methyldopa. the efficacy was observed in 81 (85.3%) patients in labetalol group and 67 (70.5%) patients in alpha methyldopa group, with a statistically significant difference between both groups (p=0.014) (Table 2).

Table 2

Comparison of Efficacy Between the Two Groups (n=190)

Efficacy	Labetalol Group (A) (n=95) n (%)	Alpha Methyldopa Group (B) (n=95) n (%)	P value
Yes	81 (85.3%)	67 (70.5%)	0.014
No	14 (14.7%)	28 (29.5%)	
Total	95 (100%)	95 (100%)	

In stratified analysis by age subgroup ≤30 years, the efficacy of labetalol was 49 (86.0%) and alpha methyldopa was 36 (72.0%), with p-value of 0.075, and for age >30 years, labetalol showed efficacy in 32 (84.2%) patients while alpha methyldopa in 31 (68.9%) patients with p-value 0.104. when gestational age was ≤36 weeks, labetalol efficacy was 42 (79.2%) versus alpha methyldopa 32 (61.5%) with a statistically significant p-value of 0.047, whereas for gestational age >36 weeks, efficacy was 39

(92.9%) and 35 (81.4%) for labetalol and alpha methyldopa respectively with p-value 0.115. in parity subgroup ≤3, labetalol efficacy was 64 (85.3%) compared to alpha methyldopa 48 (72.7%) with p-value 0.065, and for parity >3, efficacy was 17 (85.0%) and 19 (65.5%) respectively with p-value 0.129. for BMI ≤25 kg/m^2, labetalol efficacy was 30 (85.7%) and alpha methyldopa was 22 (73.3%) with p-value 0.213, while for BMI >25 kg/m^2, a statistically significant difference was found with labetalol 51 (85.0%) versus alpha methyldopa 45 (69.2%) and p-value of 0.037. in rural residents, efficacy of labetalol was 48 (80.0%) and alpha methyldopa 46 (70.8%) with p-value 0.233, while in urban residents, labetalol showed significantly higher efficacy of 33 (94.3%) compared to alpha methyldopa 21 (70.0%) with a statistically significant p-value of 0.009 (Table 3).

Table 3

Association of Efficacy with Demographic Variables

Demographic Variables	Subgroup	Group	Yes (n, %)	No (n, %)	P-value
Age (years)	≤30	A (Labetalol)	49 (86.0%)	8 (14.0%)	0.075
		B (Alpha Methyldopa)	36 (72.0%)	14 (28.0%)	
	>30	A (Labetalol)	32 (84.2%)	6 (15.8%)	0.104
		B (Alpha Methyldopa)	31 (68.9%)	14 (31.1%)	
Gestational Age (weeks)	≤36	A (Labetalol)	42 (79.2%)	11 (20.8%)	0.047
		B (Alpha Methyldopa)	32 (61.5%)	20 (38.5%)	
	>36	A (Labetalol)	39 (92.9%)	3 (7.1%)	0.115
		B (Alpha Methyldopa)	35 (81.4%)	8 (18.6%)	
Parity	≤3	A (Labetalol)	64 (85.3%)	11 (14.7%)	0.065
		B (Alpha Methyldopa)	48 (72.7%)	18 (27.3%)	
	>3	A (Labetalol)	17 (85.0%)	3 (15.0%)	0.129
		B (Alpha Methyldopa)	19 (65.5%)	10 (34.5%)	
BMI (kg/m^2)	≤25	A (Labetalol)	30 (85.7%)	5 (14.3%)	0.213
		B (Alpha Methyldopa)	22 (73.3%)	8 (26.7%)	
	>25	A (Labetalol)	51 (85.0%)	9 (15.0%)	0.037
		B (Alpha Methyldopa)	45 (69.2%)	20 (30.8%)	
Residence	Rural	A (Labetalol)	48 (80.0%)	12 (20.0%)	0.233
		B (Alpha Methyldopa)	46 (70.8%)	19 (29.2%)	
	Urban	A (Labetalol)	33 (94.3%)	2 (5.7%)	0.009
		B (Alpha Methyldopa)	21 (70.0%)	9 (30.0%)	

DISCUSSION

The overall efficacy of labetalol was found to be significantly higher compared to alpha-methyldopa, with 81 (85.3%) responses compared to 67 (70.5%) for alpha-methyldopa, p = 0.014. This may be explained by the effect of labetalol on alpha- and beta-adrenergic receptors, resulting in a more profound decrease in peripheral vascular resistance and cardiac output, leading to a more effective decrease in blood pressure compared to alpha-methyldopa, which acts by central sympatholysis. When gestational age was ≤36 weeks, labetalol was found to be more effective compared to alpha-methyldopa, with 42 (79.2%) responses compared to 32 (61.5%) for alpha-methyldopa, p = 0.047. This may be explained by the increased activity of the renin-angiotensin system and peripheral vascular resistance, which is more pronounced during early gestation, and hence, the dual action of labetalol would be more effective in this subgroup. In patients with a BMI >25 kg/m^2, labetalol was again found to be more effective, with 51 (85.0%) responses compared to 45 (69.2%) for alpha-methyldopa, p = 0.037.

The overall efficacy of labetalol was significantly higher, 81 (85.3%) versus 67 (70.5%) with p=0.014. This finding is in agreement with Khalid *et al.* [15] who also reported significantly higher effectiveness of labetalol 89 (91.8%) versus methyldopa 61 (62.9%) with p=0.0005, and with Qazi *et al.* [16] who found complete response in 86% labetalol versus 74% methyldopa patients. Similarly, Arshad *et al.* [17] and Rekha Kumari *et al.* [18] also demonstrated that labetalol produced greater fall in both systolic and diastolic blood pressure compared to methyldopa with statistically significant difference (p<0.001). The reason for better efficacy of labetalol may be its dual mechanism of action on both alpha and beta adrenergic receptors, which cause more complete reduction in peripheral vascular resistance as well as cardiac output, while methyldopa act only centrally by reducing sympathetic outflow and its effect is relatively slower and less complete. Saad *et al.* [19] further supported this by showing that mean time to control blood pressure was significantly shorter with labetalol 36.97±2.94 hours versus methyldopa 42.22±3.04 hours (p<0.0001), which further confirm the faster onset of action of labetalol.

Regarding stratified analysis by gestational age ≤36 weeks, labetalol showed significantly better efficacy 42 (79.2%) versus alpha methyldopa 32 (61.5%) with p=0.047. This is comparable with findings of Jayanthy *et al.* [20] who reported that majority of patients were between 32–36 weeks gestation and labetalol showed significantly better MAP reduction (p=0.008) in this subgroup. Biswas *et al.* [21] also noted that gestational age at delivery was significantly higher in labetalol group 37.43±0.70 weeks versus 36.54±1.48 weeks in methyldopa group (p<0.001), which suggest that labetalol provide better blood pressure control in preterm gestations and allow pregnancy to continue for longer duration. The possible scientific reason is that in earlier gestational ages, the renin-angiotensin system activity is higher and peripheral vascular resistance is more elevated, so the dual receptor blockade of labetalol become more beneficial in controlling blood pressure effectively. In patients with BMI >25 kg/m^2, labetalol showed significantly better efficacy 51 (85.0%) versus alpha methyldopa 45 (69.2%) with p=0.037. This finding is supported by Khalid *et al.* [15] who also performed BMI stratified analysis and found that labetalol had significantly better MAP control across all BMI subgroups

compared to methyldopa (p<0.0005). Biswas *et al.*[21] reported mean BMI of 25.75±3.32 kg/m^2 in labetalol group and 25.50±3.6 kg/m^2 in methyldopa group, and labetalol still showed better outcomes in terms of blood pressure control and maternal complications. This can be explained by the fact that overweight patients have increased sympathetic nervous system activity and higher cardiac output, so the beta blocking property of labetalol become particularly important and effective in these patients compared to methyldopa which lack this property.

There are limitations to this study that need to be taken into consideration when assessing the findings. This was a single-center study, which might limit the study findings to a wider population. The number of participants was few, which might influence the study power. The study had a short duration, and long-term effects of these two medications on mothers and fetuses were not evaluated. Moreover, blinding was not applied in this study, which might influence the study outcomes. In addition, there were confounding factors such as dietary habits and levels of stress among participants that were not adequately controlled during this study.

CONCLUSION

The present study concludes that labetalol is more effective compared to alpha-methyldopa for the treatment of hypertension that occurs during pregnancy. The efficacy of labetalol is highly significant, particularly for patients with a higher body mass index, gestational age, and those living in urban areas. This is due to the adrenergic blocking action of labetalol, as opposed to the central action of methyldopa.

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