DOI: https://doi.org/10.53350/pjmhs020231712115

ORIGINAL ARTICLE

Efficacy and Safety of Methyldopa and Labetalol in the Treatment of Pre-Eclampsia

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ABSTRACT

Background: Pre-eclampsia, characterized by hypertension and proteinuria in the second half of pregnancy is associated with significant mortality and morbidity throughout the world. Many antihypertensive agents have been used for the management of pre-eclampsia.

Objective: To compare the efficacy and safety of methyldopa and labetalol in the treatment of pre-eclampsia.

Methods: This quasi experimental study was conducted at the Department of Obstetrics & Gynecology, DHQ Nowshehra. The study enrolled 54 pregnant women diagnosed with pre-eclampsia. After obtaining a detailed medical history, participants were non-randomly assigned to receive either labetalol or methyldopa. Baseline systolic blood pressure measurements were recorded for all participants. Treatment efficacy was assessed by measuring the change in SBP 48 hours after the initiation of treatment.

Results: Mean age of study participants was 27.63±4.099 years. The mean baseline SBP was 168.22 ± 6.823 mmHg, which reduced to 142.83 ± 4.801 mmHg after 48 hours of treatment for the entire study population. Stratification by age did not reveal any statistically significant differences in the efficacy or safety of the two drugs ($p > 0.05$). Specifically, for participants aged ≤ 28 years, the SBP decreased from 168.19±7.217 mmHg to 142.96±4.903 mmHg with labetalol, and from 168.26±6.543 mmHg to 142.70±4.786 mmHg with methyldopa.

Conclusion: Labetalol and methyldopa are equally effective in managing pre-eclampsia in terms of blood pressure control. Further research with larger sample sizes is recommended to confirm these findings and evaluate additional outcomes such as maternal and fetal effects.

Keywords: Pre-eclampsia, hypertension, labetalol, safety, efficacy, methyldopa.

INTRODUCTION

About 12–22% of pregnancies are affected by hypertension which poses a serious treatment problem for obstetricians. Seventy percent of these instances are caused by gestational hypertension, which includes diseases like eclampsia pre-eclampsia and pregnancy induced hypertension . Conversely, 30% of hypertensive problems that occur during pregnancy are caused by persistent hypertension[1]

Preeclampsia is defined by the International Society for the Study of Hypertension in Pregnancy as the development of new hypertension proteinuria or other end organ damage indicators after 20 weeks of gestation. The emergence of grand seizures in a woman with preeclampsia is a sign of eclampsia[2]. Visual abnormalities, headache, epigastric discomfort thrombocytopenia, and altered liver function are some of the other symptoms that might appear. Different levels of microangiopathy affecting target organs such the brain liver kidneys and placenta are the cause of these clinical symptoms[3]. Preeclampsia is a multisystem disorder that impairs intervillous blood flow leading to ischemia and inadequate perfusion particularly during the second half of pregnancy. Oxidative stress is thus produced which activates vascular endothelial cells and affects every part of the body (1). Preeclampsia is associated with a high maternal mortality rate of around 15% and can result in severe outcomes for the mother and the fetus including placental abruption organ damage and more. Preterm birth and growth limitation are frequent fetal issues that are typically iatrogenic due to the mother declining health[4]. Additionally women who have had preeclampsia are more likely to develop type 2 diabetes and cardiovascular illnesses in the future[5].

Preeclampsia is a multi-organ system disorder of pregnancy that significantly contributes to maternal morbidity and mortality worldwide. It affects approximately 4.6% of pregnancies globally (2). Around 12% of maternal deaths are directly attributed to preeclampsia. The World Health Organization (WHO) estimates that the occurrence of preeclampsia is seven times higher in developing countries compared to developed countries. In developing nations, the prevalence of preeclampsia ranges from 1.8% to 16.7% (5). Preeclampsia prevalence on the other hand, is 3.4% in the US, 8.9% in Brazil, and 3.3% in Australia[6]. A study in Bangladesh reported a prevalence rate of 14% (5). Additionally, studies in Sweden and China found prevalence rates of 2.8% and 2.2%, respectively (Yingying). In Pakistan, the prevalence of preeclampsia was reported as 14.4%[7]. A 2015 meta-analysis examining data from over 75,000 women who had preeclampsia and became pregnant again revealed that 20% developed hypertension in a subsequent pregnancy, while 16% experienced recurrent preeclampsia[8]. The risk of recurrence is particularly high in women who had early-onset, severe preeclampsia, with recurrence rates ranging from 25% to 65%[9,10].

Medical conditions associated with vascular insufficiency, such as hypertension, diabetes, systemic lupus erythematosus, renal disease, and both acquired and inherited thrombophilia, heighten the risk of abnormal placentation and preeclampsia. Obstetrical conditions that lead to an increased placental mass without a corresponding increase in placental blood flow—such as hydatidiform mole, hydrops fetalis, diabetes mellitus, and twin gestation—result in relative ischemia and are linked with preeclampsia[11]. Additionally, preeclampsia is more prevalent among women living at high altitudes[12]. The risk of preeclampsia is increased more than seven-fold in women who have had preeclampsia in a previous pregnancy. Furthermore, the partners of men who were born from pregnancies complicated by preeclampsia are at a higher risk of developing preeclampsia compared to partners of men without this history. A systematic review and meta-analysis have also shown that the risk of preeclampsia is elevated in pregnant women with urinary tract infections and periodontal disease[13]. Management of preeclampsia involves close surveillance, and immediate delivery is required if the patient exhibits signs and symptoms of severe preeclampsia, such as headache, epigastric pain, visual disturbances, a platelet count < 100 x 10^3, or AST > 50 IU[14]. Commonly used antihypertensive medications include methyldopa, labetalol, nifedipine, and hydralazine[15]. Methyldopa has been reported to prevent the progression to severe hypertension in pregnancy and does not adversely affect utero-placental or fetal hemodynamics.

Labetalol, a β-blocker with arteriolar vasodilator effects, is also frequently used to reduce peripheral resistance[16].

Studies indicate that both drugs are equally effective in lowering blood pressure and improving adverse maternal and neonatal outcomes, while others suggest that labetalol is superior to methyldopa and nifedipine in controlling systolic blood pressure during pregnancy (16). One study found that all three medications were effective in managing hypertension; however, labetalol was noted for its rapid onset and sustained action with a lower incidence of side effects. Post-treatment measurements of systolic blood pressure at 48 hours revealed a mean of 138.39 ± 2.079 mmHg in the labetalol group and 141.56 ± 1.576 mmHg in the methyldopa group, with a p-value of less than 0.001 when compared to baseline levels. Common side effects associated with these antihypertensive drugs include headache, palpitation, insomnia, dizziness, weakness, flushing, and tremors. The safety profile for labetalol regarding these side effects is reported to be 52%, compared to 25% for the methyldopa group[17].

Preeclampsia is a relatively common pregnancy complication in our region, and if not promptly and effectively managed, it can lead to adverse fetal and maternal outcomes. The results will be shared with local obstetricians, and if labetalol is found to be significantly more effective and safer than methyldopa, we will recommend its use as a routine treatment for preeclampsia. The objective of the study is to compare the efficacy and safety of methyldopa and labetalol in managing preeclampsia. We hypothesize that labetalol is more effective and safer than methyldopa for treating preeclampsia.

MATERIAL AND METHODS

This quasi experimental study was conducted at the Obstetrics and Gynaecology Department of DHQ Nowshehra. The research spanned a minimum of six months following the approval of the research synopsis. A non-probability consecutive sampling technique was utilized, with a sample size of 54 participants, determined based on a 52% safety rate for labetalol and a 25% safety rate for methyldopa, and employing a 95% confidence interval with 90% power of the test, according to WHO sample size calculations.

Participants were selected based on specific criteria: inclusion required a blood pressure ≥ 140/90 mmHg, a positive urine albumin test, singleton pregnancy confirmed by ultrasound, and a gestational age between 20 and 37 weeks. Exclusion criteria included essential hypertension recorded in medical history, current use of antihypertensive medication, diabetes mellitus, congestive heart failure, and multiple pregnancies confirmed by ultrasound.

The study was approved by the Institutional Review Committee of the Hospital with Ref No. ERB/04 on dated 09-01-2023. After meeting the inclusion criteria and obtaining informed consent, participants were enrolled in the study. The study's purpose and benefits were explained to all participants or their relatives, ensuring they understood the research was for academic and publication purposes. Written informed consent was obtained from all participants.

Participants were non-randomly assigned to one of two groups: Group-A received labetalol, starting with a dose of 100 mg stat, followed by 100 mg every 12 hours, while Group-B was administered methyldopa, starting with 250 mg stat, followed by 250 mg every 8 hours. Both groups were closely monitored, with routine check-ups conducted by the medical professionals. Systolic blood pressure was recorded at 48 hours to assess the efficacy of the treatment, while participants were observed for a total of 72 hours to detect side effects such as headache, dizziness, and palpitations to evaluate safety. All data were carefully recorded on a pre-designed proforma.

Data analysis was performed using SPSS version 25. Quantitative variables, including age, baseline systolic blood pressure, and follow-up systolic blood pressure, were summarized using mean ± SD. Categorical variables such as headache, dizziness, palpitations, efficacy, and safety were analyzed in terms of frequency and percentages. Comparisons of efficacy and safety between the groups were conducted using the chi-square test, with a p-value of < 0.05 considered significant. To account for effect modifiers such as age stratification was used post stratification p-values < 0.05 were deemed significant.

RESULTS

The study had 54 individuals in total. All participants were between the ages of 21 and 35 with a mean age of 27.63 years (SD = ±4.099). With a mean of 168.22 mmHg (SD = ±6.823), the group's baseline systolic blood pressure (BP) ranged from 155 to 180 mmHg. Following follow up the mean systolic blood pressure was 142.83 mmHg (SD = ±4.801) with a range of 135 to 150 mmHg.

The age range of the 27 individuals in the labetalol group was 21–35 years old with a mean age of 27.48 years and a standard deviation of 4.099. Within this cohort the baseline systolic blood pressure ranged from 156 to 180 mmHg with a mean of 168.19 mmHg and a standard deviation of 7.217. Systolic blood pressure after therapy was 142.96 mmHg with a standard deviation of 4.900 with a range of 135 to 150 mmHg. Conversely the methyldopa group which also included 27 participants had ages ranging from 21 to 35 with a standard deviation of 4.173 and a mean age of 27.78 years. This group initial systolic blood pressure was between 155 and 180 mmHg with a mean of 168.26 mmHg and a standard deviation of 6.543. At follow-up, systolic blood pressure ranged from 135 to 150 mmHg, with a mean of 142.70 mmHg and a standard deviation of 4.786, as shown in Figure 1.

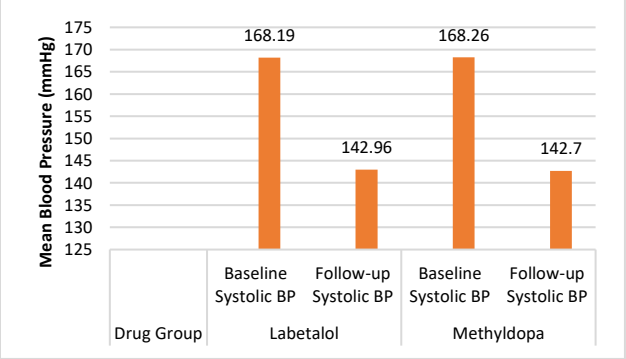

Figure 1: Baseline and Follow-up Systolic BP among the Drug Groups

Side Effects of the Drug among the Participants: All the participants were followed up for side effects such as Headache, dizziness, and palpitation, as presented in Table 1. Among the participants in the study, 29 individuals (53.7%) experienced headaches, while 25 participants (46.3%) did not report this symptom, resulting in a total of 54 participants. When examining the data by drug group, 13 out of 27 participants (48.1%) in the labetalol group reported headaches, compared to 14 participants (51.9%) who did not. In the methyldopa group, 16 out of 27 participants (59.3%) experienced headaches, while 11 participants (40.7%) did not. Among the study participants, 23 individuals (42.6%) reported experiencing palpitations, while 31 participants (57.4%) did not, out of a total of 54 participants. When analyzing by drug group, 11 out of 27 participants (40.7%) in the labetalol group experienced palpitations, whereas 16 participants (59.3%) did not. In the methyldopa group, 12 out of 27 participants (44.4%) reported palpitations, while 15 participants (55.6%) did not.

In the study population, dizziness was reported by 27 participants (50.0%), while an equal number of 27 participants (50.0%) did not experience dizziness, out of a total of 54 participants. When examined by drug group, 15 of the 27 participants (55.6%) in the labetalol group reported dizziness, whereas 12 participants (44.4%) did not. In the methyldopa group, 12 of the 27 participants (44.4%) experienced dizziness, while 15 participants (55.6%) did not.

Table 1: Frequency of Side Effects among the Drug Groups

Drug Group		Headaches	Palpitation	Dizziness
Labetalol	Present	48.1% (n=13)	15% (n=11)	55.6% (n=15)
	Absent	51.9% (n=14)	12% (n=16)	44.4% (n=12)
	Total	100% (n=27)	100% (n=27)	100% (n=27)
Methyldopa	Present	59.3% (n=16)	12% (n=12)	44.4% (n=12)
	Absent	40.7% (n=11)	15% (n=15)	55.6% (n=15)
	Total	100% (n=27)	100% (n=27)	100% (n=27)

Safety of Labetalol and Methyldopa Stratified by Age: The safety and efficacy of both labetalol and methyldopa were stratified by age and analyzed and the results were found to be non-significant ($p > 0.05$), as illustrated in Table 2. For labetalol, among those aged 28 years or younger, 10 participants (71.4%) were classified as having a safe response to the drug, while 4 participants (28.6%) experienced unsafe effects. In contrast, for participants older than 28 years, 5 (38.5%) were deemed safe and 8 (61.5%) were classified as having unsafe effects, yielding a p-value of 0.085. For methyldopa, 9 participants (69.2%) aged 28 years or younger were considered to have a safe response, while 4 participants (30.8%) had unsafe effects. In the group older than 28 years, 8 participants (57.1%) were classified as safe and 6 (42.9%) as unsafe, with a p-value of 0.52. Overall, considering both drug groups, 19 participants (70.4%) aged 28 years or younger were deemed safe compared to 8 (29.6%) who experienced unsafe effects. For participants older than 28 years, 13 (48.1%) were classified as safe, while 14 (51.9%) had unsafe effects, with a p-value of 0.097.

Efficacy of Labetalol and Methyldopa Stratified by Age: The efficacy of labetalol and methyldopa was evaluated based on the participants' age. For labetalol, among those aged 28 years or younger, 3 participants (21.4%) were classified as having an effective response, while 11 participants (78.6%) were considered ineffective. In the group older than 28 years, 5 participants (38.5%) were effective, and 8 participants (61.5%) were ineffective, with a p-value of 0.33, indicating no statistically significant difference. For methyldopa, 5 out of 13 participants (38.5%) aged 28 years or younger were classified as effective, while 8 participants (61.5%) were ineffective. There was no discernible difference in efficacy by age in the older age group with 5 persons (35.7%) being effective and 9 participants (64.3%) being unsuccessful (p-value = 0.88). Overall taking into account both medication groups 19 people (70.4%) had an ineffective reaction whereas 8 out of 27 participants (29.6%) who were 28 years of age or younger had an effective response. A p-value of 0.56 indicates that there is no statistically significant difference in efficacy based on age with 10 people (37.0%) being successful and 17 persons (63.1%) being ineffective for those over 28.

Table 2: Safety and Efficacy of Labetalol and Methyldopa stratified by Age of Participants

Drug Group			Safety of drug			Efficacy of drug		
			Safe	Unsafe	p-value	Effective	Ineffective	p-value
Labetalol	Age	≤ 28 year (n=14)	71.4% (n=10)	28.6% (n=4)	0.085	21.4% (n=3)	78.6% (n=11)	0.330
		> 28 yeas (n=13)	38.5% (n=5)	61.5% (n=8)		38.4% (n=5)	61.6% (n=8)	
	Total (n=27)		55.5% (n=15)	44.5% (n=12)		29.6% (n=8)	70.4% (n=19)	
Methyldopa	Age	≤ 28 years (n=13)	69.3% (n=9)	30.7% (n=4)	0.520	38.5% (n=5)	61.5% (n=8)	0.880
		> 28 years (n=14)	57% (n=8)	43% (n=6)		35.7% (n=5)	64.3% (n=9)	
	Total (n=27)		63% (n=17)	37% (n=10)		37.0% (n=10)	63% (n=17)	

DISCUSSION

The purpose of this study was to examine the safety and effectiveness of methyldopa and labetalol in the treatment of pre-eclampsia with an emphasis on stratifying results according to participant age. The findings showed that when categorised by age neither labetalol nor methyldopa showed statistically significant differences in terms of effectiveness or safety.

According to a recent Indian study labetalol was shown to be both safer and more effective than methyldopa in the treatment of preeclampsia. discovered that both labetalol and methyldopa significantly decreased systolic blood pressure within their respective groups ($p<0.001$) in their randomised controlled study, which included 100 patients. Nevertheless it was shown that labetalol significantly reduced mean arterial blood pressure more than methyldopa ($p<0.001$). Furthermore the labetalol group experienced fewer side symptoms including drowsiness headaches and hypotension[18]. In A recent research conducted in India found that labetalol was both safer and more effective than methyldopa in treating preeclampsia.found that in their randomised controlled research which involved 100 patients both methyldopa and labetalol significantly reduced systolic blood pressure within their respective groups ($p<0.001$). However it was demonstrated that labetalol considerably ($p<0.001$) lowered mean arterial blood pressure more than methyldopa. Additionally the labetalol group had less headaches hypotension and tiredness as adverse effects[19,20].

Furthermore methyldopa and labetalol did not vary statistically significantly in their antihypertensive effectiveness according to a research. This supports the results of our investigation which similarly found no discernible difference in the effectiveness of methyldopa and labetalol[21]. A Pakistani study found that both methyldopa and labetalol significantly reduced diastolic blood pressure throughout the course of a 48 hour intervention. The results of the trial showed that there was no statistically significant difference between the two drugs and that they were equally efficient in reducing diastolic blood pressure[22]. Similarly labetalol was shown to be well tolerated and just as effective as methyldopa in treating new onset hypertension during pregnancy by Pentareddy[21,22]. This findings is consistent with ours which likewise revealed no discernible difference between methyldopa and labetalol effectiveness.

There are many restrictions on this study. First off the study was limited to a single hospital and had a small sample size which would have limited the findings applicability to the larger group of preeclamptic women. Furthermore there is a knowledge gap on the relative efficacy of each medication in terms of the level of blood pressure management because the analysis did not measure the extent of blood pressure decrease attained with each medication. Furthermore neither labetalol nor methyldopa effects on maternal and fetal outcomes which are essential for a thorough assessment of therapy safety and efficacy were evaluated in this study.

In order to improve the findings generalisability future research should overcome the constraints by carrying out bigger multi center investigations. Measures of the amount of blood pressure drop would be helpful in order to compare the effectiveness of methyldopa and labetalol more accurately. A more thorough grasp of the safety and overall effects of these drugs would also be possible with the inclusion of evaluations of maternal and fetal outcomes. By ensuring that efficacy and safety are

carefully assessed such research might aid in improving preeclampsia management techniques and treatment guidelines.

CONCLUSION

Even when results were stratified by participant age our study did not find any statistically significant differences between labetalol and methyldopa in terms of their safety and effectiveness in treating preeclampsia. Both medications were well tolerated and showed comparable efficacy in lowering blood pressure. However the findings applicability to the larger community of pre eclamptic women is limited by the very small sample size.

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This article may be cited as: Khan ZA, Sabah S, Sheikh JS, Ubaid R, Shah R, Karim Z: Efficacy and Safety of Methyldopa and Labetalol in the Treatment of Pre-Eclampsia. Pak J Med Health Sci, 2023; 17(12): 115-118.