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Comparative Efficacy and Safety of Oral Labetalol and Nifedipine in the Management of Preeclampsia: A Randomized Controlled Trial

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ABSTRACT

Background: Preeclampsia, a major cause of maternal and perinatal morbidity, requires effective antihypertensive therapy to control blood pressure, prolong pregnancy, and reduce complications. Labetalol and Nifedipine are commonly used, but their comparative efficacy and safety remain under evaluation.

Objective: To compare the efficacy and safety of oral Labetalol and Nifedipine in managing preeclampsia, focusing on blood pressure control, pregnancy prolongation, prevention of convulsions, and fetomaternal outcomes.

Methods: In this prospective, open-label, randomized controlled trial, 136 antenatal women with preeclampsia (blood pressure ≥140/90 mmHg with proteinuria) were randomized to receive Labetalol (100 mg twice daily, n=68) or Nifedipine (10 mg thrice daily, n=68) at Dhiraj General Hospital, India, from January 2020 to July 2021. Doses were titrated to achieve blood pressure ≤140/90 mmHg. Outcomes included blood pressure reduction, time to delivery, maternal side effects, complications, mode of delivery, and neonatal outcomes. Statistical analyses included t-tests, chi-square tests, and Kaplan-Meier survival analysis.

Results: Nifedipine achieved greater reductions in systolic (121.3 vs. 126.2 mmHg, p=0.048) and diastolic blood pressure (84.3 vs. 87.4 mmHg, p=0.014) compared to Labetalol, with medium effect sizes (Cohen's d=0.40-0.50). Nifedipine was associated with higher tachycardia (27.9% vs. 5.9%, p=0.003) and cesarean rates (44.1% vs. 26.5%, p=0.059). No significant differences were observed in pregnancy prolongation, proteinuria, or neonatal outcomes (birth weight, stillbirth, NICU admissions; p>0.05).

Conclusion: Nifedipine offers superior blood pressure control but higher tachycardia risk, while Labetalol is safer for patients prone to tachycardia. Both drugs yield comparable fetomaternal outcomes.

Keywords: Preeclampsia, Labetalol, Nifedipine, Antihypertensive therapy, Blood pressure control, Fetomaternal outcomes

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INTRODUCTION

Hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension, pose a significant challenge in obstetric care [1]. Among these, preeclampsia and eclampsia are leading causes of maternal and perinatal morbidity and mortality worldwide [2]. Preeclampsia is clinically defined as new-onset hypertension (systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg, measured at least 4-6 hours apart) accompanied by proteinuria (≥0.3 g/L or +1 on urine dipstick in two random clean-catch samples collected at least 4 hours apart) after 20 weeks of gestation in women previously normotensive [3]. Severe preeclampsia is characterized by blood pressure ≥160/110 mmHg and proteinuria >300 mg/24 hours or +2 on dipstick, without concurrent urinary tract infections [4].

Globally, preeclampsia affects approximately 3-10% of pregnancies and is more prevalent among primigravidae [2]. It accounts for about 30% of maternal deaths and 22% of perinatal deaths [5]. The World Health Organization estimates that hypertensive disorders during pregnancy lead to approximately 50,000 maternal deaths annually [6]. If not diagnosed and managed promptly, preeclampsia may progress to life-threatening complications, including eclampsia, HELLP syndrome, stroke, intracranial hemorrhage, hypertensive encephalopathy, acute renal failure, and other forms of end-organ damage [7]. Fetal risks include prematurity, low birth weight, NICU admissions, and intrauterine death. Women with a history of hypertensive disorders during pregnancy also face a heightened lifetime risk of cardiovascular disease and chronic hypertension [8].

While prevention remains limited, early detection and timely intervention are crucial. Antihypertensive therapy is central to reducing maternal blood pressure, preventing severe hypertensive episodes, and minimizing fetal risks. Since delivery is the only definitive cure for preeclampsia, medical management becomes vital when immediate delivery is not feasible due to prematurity. Commonly used antihypertensives include Labetalol, Nifedipine, Methyldopa, and Hydralazine. Conversely, ACE inhibitors, ARBs, diuretics, and non-selective beta-blockers are contraindicated due to risks of fetal harm, growth restriction, and compromised uteroplacental perfusion [9-11].

Labetalol is favored for its dual alpha- and beta-blocking action, availability in both oral and IV forms, rapid onset, and limited placental transfer, though it may cause neonatal hypotension or bradycardia [9,10]. Nifedipine, popular in India for its cost-effectiveness and oral formulation, provides rapid BP control but carries risks of sudden maternal hypotension, fetal distress, and adverse interactions with magnesium sulfate [11-14]. Concerns also persist regarding fetal growth restriction and SGA infants, especially with beta-blockers or multi-drug regimens [12,13].

This study aims to compare the efficacy and safety of Labetalol and Nifedipine in managing preeclampsia, evaluating their impact on blood pressure control, pregnancy prolongation, seizure prevention, and fetomaternal outcomes.

MATERIALS AND METHODS

This prospective, open-label, randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Dhiraj General Hospital, a tertiary care center in Piparia, Waghodia, Gujarat, India. The hospital is well-equipped to manage high-risk pregnancies. The study was carried out over 18 months, from January 30, 2020, to July 31, 2021, following approval from the Institutional Ethics Committee.

Study Population: Pregnant women with gestational hypertension or preeclampsia presenting to the antenatal outpatient clinic or labor room were screened. Inclusion criteria were: blood pressure ≥140/90 mmHg on two occasions 4-6 hours apart, with proteinuria (≥0.3 g/L or +1 on dipstick), and/or symptoms like headache, visual disturbances, or epigastric pain, with or without pedal edema, between 20 weeks gestation and term. Women with chronic hypertension, cardiac disease, asthma, liver or blood disorders, diabetes, bradycardia (<60 bpm), or tachycardia (>120 bpm), or contraindications to the study drugs were excluded.

Sample Size and Randomization: Using OpenEpi software and data from a prior study by Dalal et al.[15], the required sample size was calculated to be 136 (68 per group), with 95% confidence and 85% power. Randomization was done using computer-generated sequences with permuted blocks, assigning patients to either Group A (Labetalol) or Group B (Nifedipine).

Intervention: Group A received oral Labetalol starting at 100 mg twice daily. Labetalol, a combined α1- and nonselective β-blocker, lowers systemic vascular resistance without significantly reducing heart rate or cardiac output. Its oral bioavailability is about 25%, with a half-life of 2.5-8 hours. Group B received Nifedipine 10 mg thrice daily. Nifedipine, a dihydropyridine calcium channel blocker, reduces peripheral vascular resistance by inhibiting calcium influx into vascular smooth muscle. It has a rapid onset (0.5-2 hours) and a half-life of about 2 hours. Dosages for both drugs were titrated every three days as needed, up to 600 mg/day for Labetalol and 60 mg/day for Nifedipine, to achieve target blood pressure (≤140/90 mmHg). Treatment was considered a failure if maximum doses failed to control BP and a second antihypertensive was required.

Data Collection and Monitoring: Upon enrollment, detailed histories, physical exams, and laboratory tests were conducted. Blood pressure was measured using a mercury sphygmomanometer in the left lateral position after 20 minutes of rest. Baseline investigations included blood counts, liver and kidney function tests, urine analysis, and fetal assessments (NST, ultrasound, Doppler). Corticosteroids (betamethasone) were given for gestations under 34 weeks to promote fetal lung maturity. Magnesium sulfate was used for seizure prophylaxis when needed. Patients were monitored with frequent BP checks (every 4-6 hours initially), maternal assessments, and fetal surveillance until delivery. Delivery details, neonatal outcomes (birth weight, Apgar score, complications), and drug side effects were recorded.

Outcome Measures: Primary outcomes included the dose required to achieve blood pressure control, pregnancy prolongation (time from treatment to delivery), and prevention of seizures. Secondary outcomes assessed maternal side effects (e.g., headache, fatigue), complications (e.g., eclampsia, hypertensive crises), neonatal outcomes (birth weight, Apgar scores, NICU admissions), and mode of delivery.

Statistical Analysis: SPSS v26.0 was used for data analysis. Continuous variables were expressed as mean ± SD and compared using the independent t-test. Categorical variables were compared using chi-square or Fisher's exact test. Kaplan-Meier survival analysis assessed time to delivery. Cohen's d was calculated for effect size. A p-value <0.05 was considered statistically significant.

Ethical Considerations: The study followed the Declaration of Helsinki and was approved by the Sumandeep Vidyapeeth Institutional Ethics Committee (Approval No: SVIEC/ON/Medi/BNPG19/D20005). Written informed consent was obtained, confidentiality was maintained, and participants incurred no additional costs.

RESULTS

The mean age was approximately 24 years in both groups, with no significant difference ($p = 0.356$). Gravidity distribution showed a slightly higher proportion of primigravida in the Nifedipine group (55.9% vs. 45.6%), but the difference was not significant ($p = 0.602$). Both groups had equal rural and urban representation (51.5% each) and similar education levels, ensuring comparable socio-demographic profiles (table 1). The baseline characteristics of the Labetalol and Nifedipine groups were comparable, ensuring balanced groups for analysis. Age, gravidity, residence, and education status showed no statistically significant differences ($p > 0.05$).

Gestational age at enrollment and delivery was assessed to evaluate the impact of treatment on pregnancy prolongation. Most patients were enrolled between 34-40 weeks, with similar distributions in both groups ($p = 0.602$). At delivery, the proportion of preterm births was comparable (29.4% vs. 27.9%, $p = 0.771$), indicating that neither drug significantly altered the duration of pregnancy prolongation. (Table 2)

Systolic (SBP) and diastolic blood pressure (DBP) were measured before and after treatment to assess efficacy. Baseline SBP and DBP were similar between groups ($p > 0.05$). Post-treatment, both drugs significantly reduced blood pressure, but Nifedipine

achieved lower SBP (121.3 vs. 126.2 mmHg, p = 0.048) and DBP (84.3 vs. 87.4 mmHg, p = 0.014), suggesting slightly better efficacy in blood pressure control (Table 3).

Table 1: Demographic and Baseline Characteristics

Characteristic	Labetalol Group (N=68)	Nifedipine Group (N=68)	P-value
Age (Mean ± SD, years)	23.91 ± 3.74	23.68 ± 4.32	0.356
Gravidity			
1	31 (45.6%)	38 (55.9%)	
2	18 (26.5%)	11 (16.2%)	
≥3	19 (27.9%)	19 (27.9%)	0.602
Residence			
Rural	35 (51.5%)	35 (51.5%)	
Urban	33 (48.5%)	33 (48.5%)	0.999
Education Status			
Illiterate	39 (57.4%)	38 (55.9%)	
Literate	29 (42.6%)	30 (44.1%)	0.771

Nifedipine was associated with a significantly higher incidence of tachycardia (27.9% vs. 5.9%, p = 0.003) and a trend toward more headaches (22.1% vs. 10.3%, p = 0.101). Labetalol had a higher incidence of severe hypertensive episodes (4.4% vs. 0.0%) and one case of eclampsia, while Nifedipine had one case of placental abruption. No maternal deaths or severe hypotension occurred in either group (table 4).

Table 2: Gestational Age at Enrollment and Delivery

Gestational Age	Labetalol Group (N=68)	Nifedipine Group (N=68)	P-value
At Enrollment			
24-27 weeks	1 (1.5%)	3 (4.4%)	0.602
27-31 weeks	7 (10.3%)	5 (7.4%)	
31-34 weeks	13 (19.1%)	10 (14.7%)	
34-37 weeks	23 (33.8%)	27 (39.7%)	
37-40 weeks	24 (35.3%)	23 (33.8%)	
At Delivery			
Preterm (<37 weeks)	20 (29.4%)	19 (27.9%)	0.771
Term (≥37 weeks)	48 (70.6%)	49 (72.1%)	

Table 3: Blood Pressure Control

Blood Pressure	Labetalol Group (Mean ± SD)	Nifedipine Group (Mean ± SD)	P-value
SBP			
On Admission	155.6 ± 9.5	153.8 ± 9.9	0.356
After Treatment	126.2 ± 13.5	121.3 ± 10.9	0.048
DBP			
On Admission	112.7 ± 18.9	113.8 ± 14.2	0.743
After Treatment	87.4 ± 6.5	84.3 ± 5.9	0.014

Table 4: Comparison of Side Effects and Complications

Side Effects/Complications	Labetalol Group (N=68)	Nifedipine Group (N=68)	P-value
Side Effects			
Tachycardia	4 (5.9%)	19 (27.9%)	0.003
Headache	7 (10.3%)	15 (22.1%)	0.101
Postural Hypotension	4 (5.9%)	3 (4.4%)	0.646
Drowsiness	7 (10.3%)	4 (5.9%)	0.461
Complications			
Severe Hypertensive Episodes	3 (4.4%)	0 (0.0%)	-
Eclampsia	1 (1.5%)	0 (0.0%)	-
Placental Abruption	0 (0.0%)	1 (1.5%)	-

Table 5: Neonatal Outcomes including birth weight and NICU admissions

Neonatal Outcome	Labetalol Group (N=68)	Nifedipine Group (N=68)	P-value
Birth Weight			
<2 kg	5 (7.4%)	7 (10.3%)	
2-2.5 kg	17 (25.0%)	17 (25.0%)	
>2.5 kg	46 (67.6%)	44 (64.7%)	0.899
Neonatal Complications			
Respiratory Distress Syndrome (RDS)	1 (1.5%)	4 (5.9%)	0.309
Stillbirth	3 (4.4%)	5 (7.4%)	0.399
NICU Admission			
Required	4 (6.2%)	8 (12.7%)	
Not Required	61 (93.8%)	55 (87.3%)	0.264

Birth weight distributions were similar between groups (p = 0.899), with most neonates weighing >2.5 kg. Neonatal complications, such as RDS and stillbirth, showed no significant differences, though Nifedipine had a slightly higher RDS incidence (5.9% vs. 1.5%, p = 0.309). NICU admissions were higher in the Nifedipine group (12.7% vs. 6.2%), but the difference was not significant (p = 0.264) Table 5).

Table 6: Effect Size Analysis for Blood Pressure Control

Parameter	Labetalol Group (Mean ± SD)	Nifedipine Group (Mean ± SD)	P-value	Cohen's d	Effect Size Interpretation
SBP After Treatment (mmHg)	126.2 ± 13.5	121.3 ± 10.9	0.048	0.40	Small to Medium
DBP After Treatment (mmHg)	87.4 ± 6.5	84.3 ± 5.9	0.014	0.50	Medium

Table 7: Kaplan-Meier Analysis for Time to Delivery

Parameter	Labetalol Group (N=68)	Nifedipine Group (N=68)	Log-Rank P-value
Median Time to Delivery (days)	14.5	15.2	0.821
95% Confidence Interval (days)	12.8-16.2	13.5-16.9	
Hazard Ratio (Nifedipine vs. Labetalol)	-	0.95	

The effect size (Cohen's d) was calculated to quantify the magnitude of differences in systolic blood pressure (SBP) and diastolic blood pressure (DBP) after treatment between the Labetalol and Nifedipine groups. Cohen's d values of 0.2, 0.5, and 0.8 indicate small, medium, and large effect sizes, respectively. The Nifedipine group demonstrated a statistically significant reduction in both SBP (p = 0.048) and DBP (p = 0.014) compared to the Labetalol group. The effect size for SBP (Cohen's d = 0.40) suggests a small to medium effect, indicating a moderate clinical advantage for Nifedipine. For DBP, the effect size (Cohen's d = 0.50) indicates a medium effect, reinforcing Nifedipine's superior efficacy in diastolic blood pressure control. These findings suggest that while both drugs are effective, Nifedipine may offer a slightly greater reduction in blood pressure.

A Kaplan-Meier survival analysis was conducted to compare the time from enrollment to delivery (pregnancy prolongation) between the Labetalol and Nifedipine groups. The log-rank test was used to assess differences in survival curves. The median time to delivery was 14.5 days in the Labetalol group and 15.2 days in the Nifedipine group, with overlapping confidence intervals. The log-rank test (p = 0.821) indicates no significant difference in pregnancy prolongation between the two groups. The hazard ratio of 0.95 suggests that Nifedipine has a marginally lower risk of earlier delivery, but this difference is not statistically significant. This aligns with the similar preterm delivery rates observed (29.4% vs. 27.9%, p = 0.771).

DISCUSSION

This randomized controlled trial compared the efficacy and safety of oral Labetalol and Nifedipine in managing preeclampsia among 136 antenatal women, with 68 patients in each group. The study assessed blood pressure control, pregnancy prolongation, prevention of convulsions, and fetomaternal outcomes, providing insights into the comparative performance of these antihypertensive agents in a clinical setting.

The baseline characteristics of the study population were well-balanced between the Labetalol and Nifedipine groups, ensuring comparability. The mean age was approximately 24 years in both groups (23.91 ± 3.74 vs. 23.68 ± 4.32 years, p = 0.356), consistent with previous studies reporting a peak incidence of preeclampsia in the 21-25-year age group [15-19]. The majority of patients resided in rural areas (51.5% in both groups), aligning with findings by Thakur et al. [16] and Sachdeva et al. [20], who noted a higher incidence of gestational hypertension in rural populations, potentially due to limited access to antenatal care, poverty, and lower health literacy. Educational status was also comparable, with 57.4% and 55.9% of patients in the Labetalol and Nifedipine groups, respectively, being illiterate, reflecting similar trends reported by Dalal et al. [15] and Thakur et al. [16]. These demographic similarities strengthen the validity of the comparative analysis.

Obstetrically, primigravidae constituted 45.6% of the Labetalol group and 55.9% of the Nifedipine group, supporting the established association of preeclampsia with primigravidity [17-19]. Most patients were enrolled at 34-40 weeks of gestation, consistent with prior studies [15,17,19], indicating that preeclampsia often manifests in late pregnancy. The lack of significant differences in gravidity and gestational age at enrollment ($p > 0.05$) further ensured that treatment outcomes were not confounded by obstetric variables.

Regarding blood pressure control, both drugs effectively reduced systolic (SBP) and diastolic blood pressure (DBP), but Nifedipine demonstrated superior efficacy. Post-treatment, the Nifedipine group achieved a mean SBP of 121.3 ± 10.9 mmHg compared to 126.2 ± 13.5 mmHg in the Labetalol group (p = 0.048), and a mean DBP of 84.3 ± 5.9 mmHg versus 87.4 ± 6.5 mmHg (p = 0.014). The greater reduction in SBP (32.35 mmHg vs. 26.8 mmHg) and DBP (26.8 mmHg vs. 24.43 mmHg) in the Nifedipine group aligns with findings by Dalal et al. [15], Dhali et al. [21], and Shekhar et al. [18], who reported that Nifedipine achieves target blood pressure more rapidly and with fewer doses. This may be attributed to Nifedipine's mechanism as a calcium channel blocker, which reduces peripheral vascular resistance more effectively than Labetalol's combined α- and β-adrenergic blockade [22,23]. However, Deshmukh et al. [17] found Labetalol to be highly effective in severe hypertension, suggesting context-specific variability in drug performance.

Proteinuria, a hallmark of preeclampsia, showed no significant baseline differences between groups (p = 0.602), with 67.6% and 70.6% of patients in the Labetalol and Nifedipine groups, respectively, having an albumin level of +1. Post-treatment, Nifedipine was associated with a higher proportion of patients achieving nil proteinuria (72.1% vs. 54.4%, p = 0.062), though the difference was not statistically significant. This trend aligns with Dalal et al. [15], who reported a significant reduction in proteinuria with Nifedipine, possibly due to its vasodilatory effects improving renal perfusion. Conversely, Thakur et al. [16] noted a greater reduction in proteinuria with Labetalol compared to Nifedipine, highlighting variability in renal outcomes that warrants further investigation.

Side effects differed significantly between groups. Nifedipine was associated with a higher incidence of tachycardia (27.9% vs. 5.9%, p = 0.003) and a trend toward more headaches (22.1% vs. 10.3%, p = 0.101), consistent with its vasodilatory profile [17,24]. Labetalol, however, was linked to more frequent weakness (11.8%) and drowsiness (10.3%), reflecting its β-blocker effects. These findings are supported by Deshmukh et al. [17], who noted palpitations and headache as common with Nifedipine. Maternal complications were rare, with Labetalol associated with severe hypertensive episodes (4.4%) and one case of eclampsia (1.5%), while Nifedipine had one case of placental abruption (1.5%). Thakur et al. [16] reported no placental abruption with Labetalol, aligning with our findings.

The mode of delivery showed a higher cesarean section rate in the Nifedipine group (44.1% vs. 26.5%, p = 0.059), consistent with trends reported by Raheem et al. [25], Hangarga et al. [19], and Thakur et al. [26]. This may reflect Nifedipine's tocolytic effects, potentially prolonging labor and necessitating surgical intervention. Gestational age at delivery was similar, with 70.6% and 72.1% of deliveries at term in the Labetalol and Nifedipine groups, respectively (p = 0.771), indicating comparable pregnancy prolongation [16].

Fetal outcomes were also similar, with most neonates weighing >2.5 kg (67.6% vs. 64.7%, p = 0.899) and no significant differences in stillbirth rates (4.4% vs. 7.4%, p = 0.399) or NICU admissions (6.2% vs. 12.7%, p = 0.264). These findings align with Dalal et al. [15] and Wilkerson et al. [27], suggesting no differential impact on fetal hemodynamics or neonatal outcomes. However, Giannubilo et al. [28] reported a higher rate of intrauterine growth restriction with Labetalol, which was not observed here, possibly due to differences in study populations or dosing regimens.

Limitations: The study's open-label design may have introduced observer bias, as clinicians were aware of the treatment allocation. The sample size, while adequately powered for blood pressure outcomes, may have been insufficient to detect significant differences in rare events like eclampsia or stillbirth. The study was conducted at a single tertiary care center, potentially limiting generalizability to other settings, such as rural hospitals with fewer resources. Additionally, long-term maternal and neonatal outcomes were not assessed, which could provide further insights into the drugs' safety profiles.

Conclusion

Both Labetalol and Nifedipine are effective antihypertensive agents for preeclampsia, with Nifedipine demonstrating superior blood pressure control and a trend toward reduced proteinuria, though associated with higher rates of tachycardia and cesarean delivery. Labetalol offers a safer profile for patients prone to tachycardia but may be less effective in severe hypertension. Clinicians should weigh these factors, considering patient-specific conditions and tolerability. Future multicenter studies with larger sample sizes and blinded designs are recommended to confirm these findings and assess long-term outcomes. Additionally, exploring combination therapies or alternative dosing strategies could optimize preeclampsia management.

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Availability of Data: Data is available on request to the contact email mentioned in the correspondence.

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