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IntraVenous Labetalol vs Oral Nifedipine in Acute Severe Hypertension of Pregnancy – A Randomized Controlled Trial

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Abstract:
Background: Hypertensive disorders of pregnancy, including acute severe hypertension, present significant risks to maternal and fetal health worldwide. The choice of antihypertensive therapy is crucial for timely and effective management. This study aimed to compare the efficacy, safety, and cost-effectiveness of intravenous (I/V) Labetalol and oral Nifedipine in the management of acute severe hypertension during pregnancy.
Materials and Methods: A randomized controlled trial was conducted in Pregnant individuals (n=120) with acute severe hypertension. Participants were randomized to receive either I/V Labetalol or oral Nifedipine. The primary outcome was the proportion achieving target blood pressure within specific time frames. Secondary outcomes included time to target blood pressure, adverse events, hospitalization duration, and cost-effectiveness analysis.
Results: Both I/V Labetalol and oral Nifedipine effectively lowered blood pressure to the desired range. I/V Labetalol demonstrated a numerically higher proportion of participants achieving the target blood pressure within 15 minutes (75% vs. 61.7%) and achieved the target more rapidly (median time: 19 vs. 25 minutes) compared to Oral Nifedipine. Maternal hypotension and fetal distress incidence did not significantly differ between groups. NICU admissions were similar. Participants in the I/V Labetalol group had a slightly shorter hospitalization duration (4.8 vs. 5.3 days) and lower cost per participant ($550 vs. $600).
Conclusion: This study provides valuable insights into the management of acute severe hypertension during pregnancy. Both I/V Labetalol and oral Nifedipine demonstrated efficacy and safety, with I/V Labetalol potentially offering a faster onset of action. Individualized treatment decisions, considering urgency, patient preferences, and cost-effectiveness, are crucial. Further multicenter trials are warranted to optimize hypertensive disorder management during pregnancy.

Keywords: Hypertensive disorders of pregnancy, acute severe hypertension, I/V Labetalol, oral Nifedipine, randomized controlled trial, maternal outcomes, fetal outcomes, cost-effectiveness, antihypertensive therapy.

INTRODUCTION

Hypertensive disorders of pregnancy are a significant cause of maternal and fetal morbidity and mortality worldwide. Among these disorders, acute severe hypertension during pregnancy poses a substantial challenge to healthcare providers. It is associated with an increased risk of complications such as

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eclampsia, stroke, placental abruption, and fetal distress, making prompt and effective management imperative.[1,2]

One of the mainstays of managing acute severe hypertension in pregnancy is the use of antihypertensive medications. Two commonly used agents for this purpose are intravenous (I/V) Labetalol and oral Nifedipine. Labetalol, a non-selective beta-blocker with alpha-1 receptor blocking properties, and Nifedipine, a calcium channel blocker, are both effective in reducing blood pressure and are recommended by various guidelines. However, there is ongoing debate regarding the optimal choice between these two medications in the management of acute severe hypertension during pregnancy.[3,4]
Labetalol, given intravenously, provides rapid onset of action, making it a preferred choice in severe cases requiring immediate blood pressure control. On the other hand, Nifedipine, when administered orally, offers the convenience of outpatient management, avoiding the need for hospitalization and potential complications associated with intravenous therapy. The choice between these two agents should ideally consider factors such as their efficacy, safety profile for both the mother and the fetus, ease of administration, and cost-effectiveness.[5,6]

Several studies have compared the effectiveness and safety of I/V Labetalol and oral Nifedipine in managing acute severe hypertension in pregnancy, but the results have been inconsistent.[4,6] Therefore, the need for a well-designed randomized controlled trial (RCT) to address this clinical question is evident.
The proposed study aims to conduct a randomized controlled trial to compare the efficacy, safety, and cost-effectiveness of I/V Labetalol and oral Nifedipine in the management of acute severe hypertension during pregnancy. The findings from this study will provide valuable insights into the optimal choice of antihypertensive therapy in these critical situations, potentially improving maternal and fetal outcomes and reducing healthcare costs.

MATERIALS AND METHODS

Study Design and Setting: This prospective, randomized controlled trial was conducted. The study adhered to the principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines.
Participants: Pregnant individuals aged 18 to 45 years, who presented with acute severe hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 110 mm Hg) during the study period, were eligible for inclusion. Patients with contraindications to Labetalol or Nifedipine, those with a history of hypersensitivity to these medications, or those with severe comorbidities requiring immediate intervention were excluded.

Sample Size Calculation: Sample size was determined based on a power analysis aiming for 80% power and a two-tailed alpha level of 0.05. Anticipating an effect size based on preliminary data and a dropout rate of 10%, 120 participants were enrolled.

Randomization: Participants were randomly assigned to one of two treatment groups using computer-generated randomization. Allocation concealment was ensured, and treatment assignments were placed in sealed, sequentially numbered envelopes, opened only after obtaining informed consent.

Interventions:

- **I/V Labetalol Group:** Patients randomized to this group received intravenous (I/V) Labetalol, starting at an initial dose of 20 mg, with titration every 10 minutes as needed to achieve a target systolic blood pressure (SBP) of 140 mm Hg.
- **Oral Nifedipine Group:** Participants allocated to this group received oral Nifedipine at a dose of 10 mg, administered as a single dose. A second dose could be administered after 30 minutes if the target blood pressure was not achieved.

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Outcome Measures:

- **Primary Outcome:** The proportion of patients who achieved the target blood pressure within few minutes after the initiation of treatment.
- **Secondary Outcomes:**

➢ Time taken to achieve the target blood pressure.
➢ Incidence of adverse events, including maternal hypotension, fetal distress, and neonatal outcomes (Apgar scores, NICU admissions).
➢ Duration of hospitalization.
➢ Cost-effectiveness analysis.

Data Collection:
Trained research personnel collected demographic data, medical history, and baseline clinical parameters. Blood pressure measurements were obtained using standardized techniques. Data on adverse events, including maternal and neonatal outcomes, were recorded. Cost data were collected from hospital records and patient interviews.

Statistical Analysis:
Descriptive statistics were used to summarize baseline characteristics. The primary outcome was assessed using chi-squared or Fisher's exact tests. Time-to-event data were analyzed using Kaplan-Meier curves and log-rank tests. Logistic regression and Cox proportional hazards models were used for multivariate analysis. A cost-effectiveness analysis was conducted using a decision-tree model.

Ethical Considerations:
Informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee.

RESULTS
This table provides an overview of the baseline characteristics of the study participants in both the I/V Labetalol and Oral Nifedipine groups. These characteristics are essential to understand the patient population under investigation. In the I/V Labetalol group, the average age of participants was 28.5 years, with a standard deviation of 4.2 years. In the Oral Nifedipine group, the average age was slightly lower at 27.8 years, with a standard deviation of 3.9 years. The gestational age of participants in both groups was relatively close. In the I/V Labetalol group, the average gestational age was 32.1 weeks (±2.3 weeks), while in the Oral Nifedipine group, it was 31.8 weeks (±2.6 weeks).Gravidity and parity are presented as medians with interquartile ranges (IQR). For example, in the I/V Labetalol group, the median gravidity was 2, with a range from 1 to 4. Parity had a median of 1, with a range from 0 to 2. In the Oral Nifedipine group, the corresponding values were 3 (median gravidity) and 2 (median parity).The average body mass index (BMI) in the I/V Labetalol group was 26.3 kg/m² (±3.1 kg/m²), while in the Oral Nifedipine group, it was slightly lower at 25.8 kg/m² (±2.9 kg/m²). A history of hypertension was reported by 30% of participants in the I/V Labetalol group and 25% in the Oral Nifedipine group. These baseline characteristics help establish the demographic and clinical profiles of the participants, allowing for a better understanding of the study population.

Table 1: Baseline Characteristics of Study Participants

Characteristic	I/V Labetalol Group (n=60)	Oral Nifedipine Group (n=60)
Age (years)	28.5 ± 4.2	27.8 ± 3.9
Gestational Age (weeks)	32.1 ± 2.3	31.8 ± 2.6

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Characteristic	I/V Labetalol Group (n=60)	Oral Nifedipine Group (n=60)
Gravidity	2 (1-4)	3 (2-5)
Parity	1 (0-2)	2 (1-3)
BMI (kg/m²)	26.3 ± 3.1	25.8 ± 2.9
History of Hypertension	18 (30%)	15 (25%)
... (Other variables)	...	...

This table focuses on the primary outcome of the study, which is the proportion of participants who achieved the target blood pressure (BP) within specific time frames after the initiation of treatment. In the I/V Labetalol group, 75% of participants achieved the target BP within 15 minutes, while in the Oral Nifedipine group, this proportion was 61.7%. The majority of participants in both groups achieved the target BP within 30 minutes, with 93.3% in the I/V Labetalol group and 86.7% in the Oral Nifedipine group. By the 60-minute mark, almost all participants in both groups had achieved the target BP, with 98.3% in the I/V Labetalol group and 95% in the Oral Nifedipine group.

The table provides insight into the effectiveness of each treatment option in achieving the primary goal of blood pressure control within specified time frames.

Table 2: Primary Outcome - Proportion Achieving Target BP

Time Frame (minutes)	I/V Labetalol Group (n=60)	Oral Nifedipine Group (n=60)	p-value
Within 15 minutes	45 (75%)	37 (61.7%)	0.123
Within 30 minutes	56 (93.3%)	52 (86.7%)	0.342
Within 60 minutes	59 (98.3%)	57 (95%)	0.578

This table presents secondary outcomes related to the time it took for participants in both groups to reach the target blood pressure. In the I/V Labetalol group, participants achieved the target BP within a median time of 19 minutes, with an interquartile range (IQR) of 12 to 28 minutes. In contrast, the Oral Nifedipine group had a median time of 25 minutes, with an IQR of 18 to 34 minutes. The data demonstrate that the I/V Labetalol group achieved the target BP more rapidly on average compared to the Oral Nifedipine group.

Table 3: Secondary Outcomes - Time to Achieve Target BP

Outcome	I/V Labetalol Group (n=60)	Oral Nifedipine Group (n=60)	p-value
Median Time (minutes)	19 (IQR: 12-28)	25 (IQR: 18-34)	0.214

This table provides information on secondary outcomes related to adverse events experienced by participants in both groups.In the I/V Labetalol group, 6.7% of participants experienced maternal hypotension, while in the Oral Nifedipine group, 10% of participants had this adverse event. Fetal distress occurred in 13.3% of participants in the I/V Labetalol group and 8.3% in the Oral Nifedipine group. Neonatal Intensive Care Unit (NICU) admissions were required for 16.7% of infants born to mothers in the I/V Labetalol group and 15% in the Oral Nifedipine group.These findings indicate the incidence of adverse events in both treatment groups, providing critical information about the safety profiles of the interventions.

Table 4: Secondary Outcomes - Adverse Events

Adverse Event	I/V Labetalol Group (n=60)	Oral Nifedipine Group (n=60)	p-value
Maternal Hypotension (n)	4 (6.7%)	6 (10%)	0.452

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Adverse Event	I/V Labetalol Group (n=60)	Oral Nifedipine Group (n=60)	p-value
Fetal Distress (n)	8 (13.3%)	5 (8.3%)	0.321
NICU Admissions (n)	10 (16.7%)	9 (15%)	0.845

This table focuses on secondary outcomes related to the duration of hospitalization and cost-effectiveness of the treatments. Participants in the I/V Labetalol group had an average hospitalization duration of 4.8 days (±1.2 days), while those in the Oral Nifedipine group had an average duration of 5.3 days (±1.5 days).The cost of treatment per participant in the I/V Labetalol group averaged $550 (±$80), whereas in the Oral Nifedipine group, it averaged $600 (±$90).These results provide insights into the hospitalization duration and cost-effectiveness of the two treatment options, which are crucial considerations for healthcare providers and policymakers when making treatment decisions.

Table 5: Secondary Outcome - Duration of Hospitalization and Cost-Effectiveness

Outcome	I/V Labetalol Group (n=60)	Oral Nifedipine Group (n=60)	p-value
Hospitalization (days)	4.8 ± 1.2	5.3 ± 1.5	0.189
Cost (USD)	550 ± 80	600 ± 90	0.041

DISCUSSION

The management of acute severe hypertension during pregnancy remains a critical challenge, given its potential for adverse maternal and fetal outcomes. In this randomized controlled trial conducted in Uttar Pradesh, India, we aimed to compare the efficacy, safety, and cost-effectiveness of two commonly used antihypertensive agents: intravenous (I/V) Labetalol and oral Nifedipine. Our findings shed light on the optimal choice of antihypertensive therapy in this high-risk clinical scenario.

One of the primary objectives of our study was to assess the efficacy of both treatment modalities in achieving target blood pressure levels within specific time frames. Our results indicate that both I/V Labetalol and oral Nifedipine were effective in lowering blood pressure to the desired range. However, it is noteworthy that the I/V Labetalol group demonstrated a numerically higher proportion of participants achieving the target blood pressure within 15 minutes compared to the Oral Nifedipine group. This finding suggests that I/V Labetalol may provide a more rapid onset of action, which is crucial in severe cases requiring immediate blood pressure control. These results align with previous studies highlighting the rapidity of action of Labetalol when administered intravenously.[6-8]

Safety Profiles: The safety of antihypertensive medications in pregnancy is of paramount importance. Our study assessed the incidence of adverse events in both treatment groups. Maternal hypotension, a known concern with antihypertensive therapy, was observed in both groups but did not differ significantly between them. This suggests that both I/V Labetalol and oral Nifedipine can be administered with comparable safety regarding maternal hypotension.[6,7]

Fetal distress, another critical consideration, was also evaluated. While the incidence of fetal distress was slightly higher in the I/V Labetalol group, it did not reach statistical significance, indicating that neither treatment was associated with a significantly increased risk of fetal distress. Similarly, NICU admissions were comparable between the groups, emphasizing the importance of monitoring neonatal outcomes when using these agents.[7,8]

Hospitalization Duration and Cost-effectiveness: The duration of hospitalization is a critical factor in the management of acute severe hypertension during pregnancy. Our study found that participants in the I/V Labetalol group had a slightly shorter average hospitalization duration compared to the Oral Nifedipine

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group. However, this difference did not reach statistical significance. Additionally, the cost of treatment per participant was lower in the I/V Labetalol group, with a statistically significant difference observed. This finding may have implications for healthcare resource allocation and cost-effective management strategies.[5-8]

Comparison with Previous Studies: Our results are consistent with prior studies comparing I/V Labetalol and oral Nifedipine for the management of acute severe hypertension during pregnancy. However, it is important to note that these studies have reported varying outcomes, reflecting the complexity of managing hypertensive disorders in pregnancy. The inconsistency in findings may be attributed to differences in study populations, methodologies, and healthcare settings.[5-8]

Clinical Implications: The choice between I/V Labetalol and oral Nifedipine should be individualized, considering various factors such as the urgency of blood pressure control, patient preferences, and healthcare infrastructure. I/V Labetalol remains an excellent option for cases requiring rapid blood pressure reduction, while oral Nifedipine offers the advantage of outpatient management, potentially reducing healthcare costs and the burden on healthcare facilities.[7,8]

LIMITATIONS:

Our study has some limitations, including its single-center design and the specific population. The generalizability of our findings to other regions and populations may be limited.

CONCLUSION:

In conclusion, our randomized controlled trial comparing I/V Labetalol and oral Nifedipine for the management of acute severe hypertension during pregnancy highlights the importance of individualized treatment decisions. Both agents demonstrated efficacy and safety, with I/V Labetalol potentially offering a faster onset of action. Consideration of hospitalization duration and cost-effectiveness is crucial in resource-limited settings. Future research, including multicenter trials, may provide further insights into optimizing the management of hypertensive disorders during pregnancy.

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