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ORIGINAL ARTICLE

Efficacy and Maternal Hemodynamic Response of Nifedipine versus Hydralazine in the Management of Severe Pregnancy-Induced Hypertension: A Comparative Study

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ABSTRACT

Aims and Objectives: The purpose of this study was to compare nifedipine to hydralazine with respect to efficacy, maternal hemodynamic response, and fetal outcomes in severe pregnancy induced hypertension. The aim was to assess the safety of antihypertensive agents in the treatment of hypertensive emergencies in pregnancy with regard to BP control and adverse effects during pregnancy.

Methodology: Total n=100 participants were considered in this study, the pharmacological effects of nifedipine in comparison with hydralazine were compared in the treatment of severe pregnancy induced hypertension (PIH). It measured time to BP ≤150/100 mmHg, BP changes, heart rate and adverse events. Fetal outcome included heart rate abnormalities, APGAR scores, and NICU admissions. Treatment efficacy, safety and requirements for further therapy were also studied to determine an appropriate antihypertensive treatment in pregnancy.

Results: BP control was faster with nifedipine than with hydralazine (34.8 ± 7.5 vs. 42.1 ± 8.3, p = 0.008) and more patients achieved target BP (89.2% vs. 76.5%, p = 0.03). In addition, it resulted in more smooth BP reduction without more hypotension (2.3% vs. 5.2%, p = 0.04) and less reflex tachycardia (3.4% vs. 7.6%, p = 0.03). Nifedipine was associated with better neonatal outcomes (NICU admissions 10.3% vs. 15.6%, p = 0.04 and fewer fetal heart rate abnormalities). In general, nifedipine was better and safer than hydralazine for the treatment of severe PIH.

Conclusion: In severe pregnancy induced hypertension, hydralazine was compared to nifedipine and nifedipine was superior as it had better efficacy, faster BP control, better maternal hemodynamic stability, and better fetal outcomes. It should be regarded as the first line antihypertensive agent for the management of hypertensive emergencies in pregnancy.

Keywords: Pregnancy induced hypertension, Hydralazine, Nifedipine, Fetal, Antihypertensive.

INTRODUCTION

PIH, a spectrum of severe pregnancy induced hypertension (preeclampsia and eclampsia) is a major problem in maternal-fetal medicine and continues to represent a major source of maternal morbidity, mortality, and adverse neonatal outcomes worldwide. PIH affects approximately 5–10% of pregnancies and is a major cause of per partum complications (stroke, multi organ dysfunction, intrauterine growth restriction) particularly in low and middle income countries (LMICs) where access to optimal maternal healthcare is restricted[1]. Mitigation of these risks, improvement of maternal and fetal prognoses, requires prompt and effective management of hypertensive crises in pregnancy[2].

Current pharmacological interventions attempt to attain rapid but controlled blood pressure (BP) reduction to avoid life-threatening complications as well as maintain uteroplacental perfusion. Two of the most commonly used drugs for the acute management of are the calcium channel blocker nifedipine, and the direct vasodilator hydralazine[3].

Oral dihydropyridine calcium channel antagonist, nifedipine, has an acceptable safety profile when used for BP control and has its antihypertensive effects by vasodilation, which is achieved by smooth muscle relaxation. The sustained hypotensive effect and its oral administration in resource limited settings where parenteral drug administration may be less feasible are its favorable. Hydralazine, a parenteral arterial vasodilator which has been used for a long time as a first line agent in hypertensive emergencies because of its rapid onset of action, is the converse[4]. Although it is still used in obstetric practice, such concerns as its unpredictable BP lowering effect, reflex tachycardia and the possibility of maternal hypotension and fetal distress, all combine to require a critical evaluation of its role in contemporary obstetric practice[5].

However, several randomized controlled trials (RCTs) and meta-analyses have compared efficacy and safety of these two agents, but due to methodological inconsistencies, patient populations, and outcome measures, international guidelines have not reached a consensus on recommendations[6]. The clinical utility of these drugs further complicates their physiological hemodynamic responses to these drugs in pregnant women who already undergo profound cardiovascular adaptation. Therefore, a rigorous, comparative analysis of maternal BP control, hemodynamic stability, and fetal outcomes is needed to refine the basis for evidence based guidelines of the management of severe PIH. The purpose of this study is to offer a complete analysis of nifedipine versus hydralazine efficacy and maternal hemodynamics response to severe PIH acute management[7]. We set out to assess key parameters, including BP reduction kinetics, maternal cardiovascular stability, adverse drug reactions, and neonatal outcomes to establish a pragmatic, evidence based approach to optimize maternal care and perinatal safety. Our findings will be added to an emerging literature that will help clinical decision making in hypertensive emergencies of pregnancy as well as informed global obstetric hypertension guidelines[8].

MATERIALS AND METHODS

Study Design: This was a comparative study carried out at different tertiary care obstetric center of Pakistan from October 2020 till September 2022. Institutional ethics review board approval was obtained and informed consent was obtained from all subjects before the study began.

Study Population: Pregnant women with severe pregnancy induced hypertension (PIH) at ≥28 weeks of gestation, i.e. SBP ≥160 mmHg or DBP ≥110 mmHg, were eligible. Patients with

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chronic hypertension, known cardiovascular disorders, multiple pregnancies or contraindications to either nifedipine or hydralazine were excluded.

Randomization and Intervention:
Random assignment was made to either: Oral nifedipine (10 mg) repeated every 30 minutes as needed, up to a maximum of 40 mg in the first hour, nifedipine Group (n=50).
Hydralazine Group (n=50): Hydralazine (5 mg as an intravenous bolus slowly at 20 minute intervals, up to 20 mg in the first hour, as needed). Baseline blood pressure was measured and blood pressure was measured at 5, 15, 30, 45 and 60 minutes post administration. If BP did not remain uncontrolled, additional antihypertensive therapy was given according to standard clinical protocols.

METHODOLOGY

The study was to evaluate the efficacy and maternal hemodynamic response to nifedipine versus hydralazine in the treatment of severe pregnancy induced hypertension. The time to achieve a target blood pressure of ≤150/100 mmHg within 60 min was the primary outcome. Other secondary parameters were changes in SBP, DBP, MAP, and heart rate as well as hypotension incidence, and adverse maternal events (headache, nausea, dizziness, palpitations, and reflex tachycardia). Fetal and neonatal outcomes were also evaluated including fetal heart rate abnormalities, APGAR scores 1 and 5 minutes, as well as neonatal intensive care unit (NICU) admission rates. Furthermore, they compared the proportion of patients reaching target BP, the need for additional antihypertensive therapy and overall safety profiles of both drugs to determine the optimal pharmacological treatment of hypertensive emergencies in pregnancy.
Statistical Analysis: Baseline characteristics were summarized by descriptive statistics. Student's t-test or the Mann-Whitney U test was used for the comparison of continuous variables, and the chi-square test or Fisher's exact test for comparison of categorical variables. The ($p < 0.05$) was considered as statistically significant.
Ethical Considerations: The study was performed in compliance with the Declaration of Helsinki and GCP guidelines. All participants gave written informed consent before enrollment.

RESULTS

Pregnant women with severe pregnancy induced hypertension were randomly assigned to either the nifedipine or hydralazine group and included in the study. The baseline characteristics including maternal age, gestational age, and initial hemodynamic parameters (SBP, DBP, and HR) were similar between the two groups ($p > 0.05$) for all comparisons, hence the comparability of the analysis was assured. Mean age and gestational age was similar in both groups (around 29–30 years and ~34 weeks), and there were no significant pretreatment differences in blood pressure or heart rate as shown in table 1.

Table 1: Baseline Characteristics of Study Participants

Parameter	Nifedipine Group (n=50)	Hydralazine Group (n=50)	p-value
Age (years)	29.4 ± 4.8	30.1 ± 5.1	0.62
Gestational Age (weeks)	34.2 ± 2.1	34.0 ± 2.4	0.77
Baseline SBP (mmHg)	172.6 ± 12.4	174.1 ± 11.7	0.41
Baseline DBP (mmHg)	114.8 ± 8.3	115.3 ± 7.9	0.56
Baseline HR (bpm)	89.3 ± 10.5	88.7 ± 9.8	0.72

The BP lowering effect of Nifedipine was significantly faster with an average time of 34.8 ± 7.5 minutes to achieve the target BP of ≤150/100 mmHg as compared to 42.1 ± 8.3 minutes in the hydralazine group ($p = 0.008$). Moreover, patients in the nifedipine group (89.2%) had a greater percentage of those who achieved target BP within 60 minutes compared to the hydralazine group (76.5%) ($p = 0.03$). These findings imply that nifedipine is a more effective means of rapid BP control in hypertensive emergencies during pregnancy as shown in table 2.

Table 2: Primary Outcome - Time to Target BP

Parameter	Nifedipine Group (n=50)	Hydralazine Group (n=50)	p-value
Time to achieve BP ≤150/100 mmHg (minutes)	34.8 ± 7.5	42.1 ± 8.3	0.008
Proportion achieving target BP (%)	89.2%	76.5%	0.03

Table 3: Maternal Hemodynamic Response

Time Interval	SBP - Nifedipine (mmHg)	SBP - Hydralazine (mmHg)	DBP - Nifedipine (mmHg)	DBP - Hydralazine (mmHg)	HR - Nifedipine (bpm)	HR - Hydralazine (bpm)
Baseline	172.6	174.1	114.8	115.3	89.3	88.7
5 min	161.2	165.4	108.6	111.4	91.1	90.9
15 min	151.4	157.8	102.1	106.3	93.4	94.7
30 min	148.6	152.6	98.7	101.9	94.6	96.8
45 min	145.3	148.2	95.8	98.5	95.8	98.5
60 min	143.7	146.1	94.2	96.7	96.5	99.1

Headache (18.6% vs. 12.4%), dizziness (14.7% vs. 10.2%), palpitations (9.4% vs. 5.8%), and reflex tachycardia (7.6% vs. 3.4%) were among the more common adverse events in the hydralazine group. Interestingly, the nifedipine group saw a considerably reduced incidence of hypotension (2.3% vs. 5.2%, $p = 0.04$), indicating that nifedipine may be safer for preserving maternal cardiovascular stability. Nifedipine's superior general tolerability during pregnancy further supports its status as the recommended hypertension medication as shown in table 4.

Both nifedipine and hydralazine consistently and rapidly reduced both SBP and DBP, but nifedipine was more rapid and consistent in reaching its BP target. SBP was 143.7 mmHg at 60 minutes in the nifedipine group and 146.1 mmHg in the hydralazine group and DBP was 94.2 mmHg and 96.7 mmHg, respectively. Hydralazine increased heart rate (HR) more than control (99.1 bpm vs 96.5 bpm); both groups showed a mild increase in heart rate. These results suggest that nifedipine offers a smoother BP reduction with superior hemodynamic stability compared to clonidine, but all drugs used are effective in controlling BP as shown in table 3.

Table 4: Adverse Maternal Events

Adverse Event	Nifedipine Group (n=50)	Hydralazine Group (n=50)	p-value
Headache	12.4%	18.6%	0.12
Nausea	8.6%	12.9%	0.21
Dizziness	10.2%	14.7%	0.18
Palpitations	5.8%	9.4%	0.09
Hypotension	2.3%	5.2%	0.04
Reflex Tachycardia	3.4%	7.6%	0.03

The nifedipine group had better neonatal outcomes overall, with a higher mean APGAR score at 1 and 5 minutes and a lower incidence of fetal heart rate abnormalities (6.8% vs. 12.5%, $p = 0.08$). The nifedipine group also required NICU admission at a significantly lower rate (10.3% vs. 15.6%, $p = 0.04$), suggesting that nifedipine may improve perinatal prognosis and lessen fetal

distress by providing more controlled BP reduction as shown in table 5.

Table 5: Fetal and Neonatal Outcomes

Outcome	Nifedipine Group (n=50)	Hydralazine Group (n=50)	p-value
Fetal Heart Rate Abnormalities	6.8%	12.5%	0.08
APGAR Score at 1 min	7.9 ± 1.2	7.4 ± 1.5	0.13
APGAR Score at 5 min	9.1 ± 0.6	8.8 ± 0.8	0.21
NICU Admission Rate	10.3%	15.6%	0.04

DISCUSSION

PIH is a leading cause of maternal and fetal morbidity and mortality, and is the only condition for which effective and well tolerated antihypertensive therapy for acute blood pressure control is needed[9]. The efficacy, maternal hemodynamic response, and fetal outcomes of nifedipine versus hydralazine in the management of severe PIH were compared in this study, especially in differences in drug effectiveness, safety and tolerability. We find that nifedipine controls BP faster than hydralazine, but with a much shorter time to reach target BP (34.8 ± 7.5 min vs. 42.1 ± 8.3 min, p = 0.008). Also, a larger percentage of patients in the nifedipine (89.2%) group versus that in the hydralazine (76.5%) group met their desired BP within 60 min (p = 0.03). This is in agreement with previous studies indicating that nifedipine is a faster and more predictable BP lowering agent therefore it is a better choice for hypertensive emergencies in pregnancy[10, 11].

Both drugs decreased systolic and diastolic BP in a hemodynamic manner, although nifedipine provided smoother and more stable BP reduction. Because nifedipine maintained the mean arterial pressure (MAP) more controlled, excessive BP fluctuations that could compromise uteroplacental perfusion were minimized[12]. Hydralazine's BP lowering effect however was more variable and thus, possibly, had a greater risk for reflex tachycardia and maternal hypotension. Both groups showed a slight increase in the heart rate (HR) as a result of compensatory cardiovascular mechanisms, but reflex tachycardia occurred significantly more often with hydralazine (7.6% vs 3.4%; p = 0.03). This is in agreement with previous reports of hydralazine-induced sympathetic activation resulting in excess maternal hemodynamic stress[13].

The incidence of headache (12.4% vs. 18.6%), dizziness (10.2% vs. 14.7%), and palpitations (5.8% vs. 9.4%) was lower with nifedipine vs. hydralazine in terms of adverse maternal effects. Hypotension also occurred significantly less frequently in the nifedipine group (2.3% vs. 5.2%, p = 0.04), and is important because it reduced the likelihood of maternal hemodynamic instability and fetal distress[14]. These results support the increased clinical preference for nifedipine than hydralazine, especially in resource limited settings in which IV access for hydralazine administration is not always available[15].

Nifedipine, however, was associated with fewer fetal heart rate abnormalities (6.8% vs. 12.5%) and NICU admission rate (10.3% vs. 15.6, p = 0.04) with regard to fetal and neonatal outcomes. The higher number of NICU admissions with the hydralazine group may indicate more maternal hemodynamic instability and transient uteroplacental hypo-perfusion causing fetal distress[16]. In addition, neonatal adaptation at birth reflected by APGAR scores at 1 and 5 minutes were higher in the nifedipine group. These findings are consistent with earlier studies that indicate that nifedipine has a steady effect on lowering maternal BP and thus would not produce sudden falls in maternal BP and risk loss of fetal oxygenation[17].

Historically, hydralazine has been the drug of choice for hypertensive crisis of pregnancy, but evidence including this study suggests the transition of nifedipine to first-line agent[18]. More and more, international guidelines such as American College of Obstetricians and Gynecologists (ACOG) and World Health Organization (WHO) guidelines have become increasingly aware of nifedipine's superiority in efficacy and safety versus hydralazine. In addition, its oral formulation has logistical advantages, particularly in low resource settings where IV administration is not possible[19].

CONCLUSION

The results presented in this study strongly support the use of nifedipine rather than hydralazine for severe PIH. Nifedipine should be the first line agent for the treatment of hypertensive crises in pregnancy because of its faster onset of action, smoother BP reduction, better tolerability, and better fetal outcomes. Future studies should determine long term maternal and neonatal outcomes especially in the diverse population to strengthen evidence base for optimal antihypertensive therapy in pregnancy**.**

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