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Original Research Article

A Comparison of Oral Nifedipine and Intravenous Labetalol for Severe Pregnancy Induced Hypertension

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Abstract

Goal: To evaluate the effectiveness of oral nifedipine and intravenous labetalol in the management of severe pregnancy induced hypertension.

Materials and Methods: Pregnant women with blood pressure ≥160/110 mm Hg participated in this double-blind, randomised, controlled trial. Between 01-01-2021 and 31-12-2021, a total of 75 patients were enrolled. Nifedipine (10 mg tablet orally up to five doses), an intravenous placebo saline injection, or an intravenous labetalol injection in doses of 20mg, 40mg, 80mg and 80mg together with a placebo tablet every 20 minutes were given to patients according to their assigned treatment groups. The study's main finding was the amount of time needed to reach the desired blood pressure. Secondary outcomes were the number of doses needed, the start of labour, the method of delivery, any negative effects on the mother or the baby, side effects and perinatal outcome.

Results: Nifedipine considerably shortened the time needed to reach the target blood pressure. In comparison to labetalol the nifedipine group needed considerably fewer doses. When compared to the labetalol group, the amount of urine produced by the nifedipine group was substantially higher and remained significantly higher 24 hours after first treatment. Nobody needed crossover treatment. The negative consequences weren't common. Maternal age, gestational age, and blood pressure did not significantly differ across the groups.

Conclusion: Both oral nifedipine and intravenous labetalol are effective in treating severe pregnancy induced hypertension; however, nifedipine works faster and requires fewer doses while also significantly increasing urine output.

Keywords: Pregnancy Induced Hypertension, Nifedipine, Labetalol, Pre-eclampsia, Pregnancy.

Introduction

Pregnancy induced hypertension is a frequent medical condition. In India, it is the third most frequent cause of maternal death and morbidity after haemorrhage and infections and complicates 6–10% of pregnancies. [1] Because there is a danger of cardiovascular accident, intracerebral haemorrhage, hypertensive

encephalopathy, and other target organ damage, severe pregnancy induced hypertension (PIH) has to be treated very away. [2] Additionally, it puts the foetus at a higher risk for complications including preterm, low birth weight, admission to the neonatal intensive care unit, and even foetal death. [3]

The most effective treatment for PIH is debatable. For the treatment of severe PIH, the majority of guidelines suggest labetalol, hydralazine, and nifedipine as first-line choices.2 Hydralazine was once the medicine of choice, however it has a greater rate of "overshoot" hypotension. [4,5] Labetalol and nifedipine, however, have quickly become popular medications.

Both oral nifedipine and intravenous labetalol are beneficial in the therapy of severe hypertensive crises of pregnancy, as shown by Vermilion and Shekhar et al. [6,7] However, nifedipine reduces hypertension more quickly and is linked to a large increase in urine output. Shekhar et al meta-analysis [8] for severe PIH revealed that oral nifedipine is just as effective and secure as intravenous labetalol and is linked with a lower incidence of persistent hypertension. But Raheem's study [9] found that intravenous and oral nifedipine regimens were equally efficacious in the immediate management of severe hypertension in pregnancy. Although both oral nifedipine and intravenous labetalol are effective in treating hypertensive crises during pregnancy, Lakshmi and Chawla D et al [10,11] discovered that intravenous labetalol may have advantages because it is more effective in lowering the BP to target levels with a smaller number of doses. Due to disagreements about the therapy, the current study was designed to assess and compare oral nifedipine and intravenous labetalol in patients with severe PIH.

Materials and Methods

At SNMMC, Dhanbad, Jharkhand individuals with severe pregnancy-induced hypertension (PIH) participated in this double-blind, randomised clinical investigation.

Inclusion standards

Pregnant women between the ages of 20 and 45 with a gestational age of at least 34 weeks, blood pressure of at least 160/110 mmHg, and proteinuria (defined as greater than or equal to 1+ or 300 mg in a 24-hour urine sample) were enrolled in the trial.

Exclusion standards

Patients with absolute contraindications to labetalol and nifedipine as well as chronic hypertension, asthma, cardiogenic shock, cardiac failure, pulmonary oedema, chronic obstructive pulmonary disease, bradycardia, and exposure to medication within the previous 24 hours were excluded from the study.

Calculating the sample size and using randomization

According to a prior research, which was used to determine the sample size, patients who took oral nifedipine reached their goal blood pressure in 25.0 minutes (mean SD) as opposed to 43.6 minutes (mean SD) for patients in the labetalol group.[6] The needed sample size, determined using the Open epi CDC tool, was computed using these results as guideline data, an alpha value of 0.05, and a power of 90%. The required sample size was 40 patients in each arm. In order to account for participant dropouts and the potential for non-parametric outcome statistics, we grew our sample size by 10% for each presumption. There were 40 individuals in each arm of the final sample, which was computed.

A and B were produced as separate bundles. Package A contained either 60 ml of sodium chloride solution (0.9 percent) in a syringe and 10 mg of nifedipine tablets, or 60 ml of injectable labetalol (5 mg/ml) and placebo pills that were the

same as oral nifedipine tablets. For crossover, package B included the opposing regimen. Both the gynaecologist and the patients were blindfolded, and the study team member who worked as a ward sister read the envelopes. Magnesium sulphate was administered to all patients as a seizure prevention measure. (4g IV and 10g IM for loading dosages, 5g IM every four hours for maintenance doses)

Patients were positioned on beds in a semi recumbent position. As the first course of therapy, the sister was directed to give the patient one pill to consume and 4 ml of syringe A intravenously. After 20 minutes, a second pill and 8 cc from syringe A were given (if the patient's blood pressure was greater than 150/100 mmHg). If the goal blood pressure was still not reached after another 20 minutes, a third pill and 16 cc from syringe A were administered. If necessary, this can be done again for additional two cycles. Crossover to regimen B was done if the goal blood pressure was not reached after five cycles of regimen A. Regimen B was carried out in the exact same way as regimen A was. All patients had thorough examinations and histories. Hematological, biochemical, and urine tests were performed routinely. Vital signs and urine production were observed. The fundus was examined. A foetal well-being ultrasound and cardiotocography were performed.

The study's main finding was the amount of time needed to reach the goal blood pressure (140/90 mm Hg). Patients were followed up on for 6 weeks after delivery and monitored up to delivery or 48 hours after blood pressure control. Secondary outcomes were the number of doses needed, the start of labour, the method of delivery, any negative effects on the mother or the baby, side effects, and perinatal outcome.

Results:

In this trial, a total of 75 concordant individuals were included. According to Table 1, two groups were comparable in terms of mother age, parity, and gestational duration. High systolic or diastolic blood pressure on their own, or combined, were equivalent across the two groups. The study's age distribution revealed that the mean age of the nifedipine group was 23.33 ± 4.48years old and the mean age of the labetalol group was 21.50 ± 4.13years old (p = 0.66).

Most patients in both groups were primigravida. Furthermore, 15 patients in the labetalol group and 17 patients in the nifedipine group were multigravida. (p= 0.75) The majority of the patients in our research were, in the groups receiving nifedipine and labetalol, respectively, at mean gestational ages of 36.2 ± 1.99and 36.5 ± 2.63weeks. (p=0.58) The mean systolic blood pressure was 181.40 ± 15.84mmHg in the nifedipine group and 185.7 ± 14.62mmHg in the labetalol group. (p= 0.62) In the groups receiving nifedipine and labetalol, the mean diastolic blood pressure was 115.07 ± 8.43mmHg and 114.57 ± 6.34mmHg, respectively. (p=0.51)

In the nifedipine group, the mean arterial blood pressure was 138.78 ± 8.16mmHg, while in the labetalol group, it was 146.11 ± 30.83mmHg. (p=0.13) In the nifedipine group, 37 patients and in the labetalol group, 38 patients had proteinuria. (p=0.97)

Women who got nifedipine required an average of 33.45 ± 21.71minutes to reach their goal blood pressure, whereas women who received intravenous labetalol required an average of 51.70 ± 26.54 minutes. (Table 2) Compared to labetalol, patients taking oral nifedipine more quickly reached their goal blood pressure. It was statistically significant to find that. (p =0.01) In the nifedipine group, the mean dose needed to reach the goal blood pressure was 1.63 ± 1.15, but in the labetalol group, it was 2.64 ± 1.53. Less medication was needed in the nifedipine

group. Statistics showed that the difference was significant (p=0.017). The mean urine output during a 24-hour period for the labetalol and nifedipine groups, respectively, was 1375.00 ml and 2287.15ml, both of which were statistically significant. (p< 0.00) There was no difference in the method of birth between the two groups.

The two medications had no statistically significant difference in the adverse effects of nausea, dizziness, palpitations, headache, flushing, and exhaustion. In neither of the research groups, maternal hypotension or foetal tachycardia was seen.

The mean birth weight of infants in the labetalol and nifedipine groups was 2.66 kg and 2.63 kg, respectively. Statistical significance could not be determined based on the p value of 0.99. 10 percent of the nifedipine group and 16.66 percent of the labetalol group had an APGAR score of 7 at 5 minutes. At 5 minutes, 90% of the nifedipine group and 83.3% of the labetalol group displayed APGAR scores of 7. (p< 0.48) Prematurity, newborn ICU hospitalizations and IUGR were comparable across the two groups as no statistically significant difference was seen in these outcomes. (Table 2)

Table 1: Characteristics of pregnancy in both the groups

Characteristics	Nifedipine	Labetalol	P value
Age in years, (mean ±SD)	23.33 ± 4.48	21.50 ± 4.13	0.66
Parity:			
Primigravida	25	18	0.75
Multigravida	15	17	
Booked /Un-booked			
Booked	16	15	0.57
Un-booked	24	20	
Gestational age in weeks (mean ±SD)	36.2 ± 1.99	36.5 ± 2.63	0.58
Systolic Blood Pressure (mmHg) (mean ±SD)	181.40 ± 15.84	185.7 ± 14.62	0.62
Diastolic Blood Pressure (mmHg) (mean ±SD)	115.07 ± 8.43	114.57 ± 6.34	0.51
Mean arterial Blood pressure (mean ±SD)	138.78 ± 8.16	146.11 ± 30.83	0.13
Proteinuria	37	38	0.97

Table 2: Outcomes

Characteristics	Nifedipine n=40	Labetalol N=35	P value
Primary outcome			
Mean time taken to achieve blood pressure< 160/110mg	33.45 ± 21.71	51.70 ± 26.54	0.01
Secondary Outcomes			
Mean dosages to achieve blood pressure <160/100 mmHg	1.63 ± 1.15	2.64 ± 1.53	0.01
Urine output in 24 hours(ml)	2287.15 ± 211.43	1375.00 ± 154.78	0.00
Onset of Labour			
Spontaneous	15	17	0.67
Induced	25	18	0.87

Mode of delivery			
Caesarean	15	17	0.89
Vaginal (Including instrumental)	25	18	0.87
Birth weight (kg)	2.63	2.66	0.95
Side Effects			
Nausea	8	11	0.52
Dizziness	6	9	0.17
Headache	25	3	0.01
Flushing	1	8	0.68
Fatigue	00	4	0.03
Hypotension	00	00	-
Shortness of breath	00	00	-
Chest Pain	00	00	-
Perinatal Outcome			
Birth weight (kg)	2.66 ± 0.37	2.63 ± 0.11	0.99
APGAR Score (5 minutes)			
< 7	10	10	0.48
>7	30	25	
Prematurity	5	3	0.49
IUGR	2	4	0.89
Neonatal intensive care admission	3	5	0.48

Discussion

The most frequent medical issue among expectant mothers is still hypertension. Several etiological hypotheses have been put out for the pregnancy-induced hypertension. The imbalance between the vasoconstrictor thromboxane A2 and the vasodilator prostacyclin, which results in global vasospasm, is a frequent pathophysiological alteration. As a result, endothelial damage occurs and vasoactive chemicals are released. As a result, the extravascular volume increases and the intravascular volume decrease. Placental insufficiency has the consequence of causing issues. [12]

In order to prevent unfavourable consequences for both the mother and the foetus, blood pressure lowering is the major therapy method for severe preeclampsia. Oral nifedipine, intravenous labetalol, and hydralazine are the medications advised for the treatment of hypertensive crises. [13] numerous randomised control studies have been carried out with these medications. It has been discovered that nifedipine offers the advantages of an oral route, a quick start, and a longer duration of action. It has a diuretic effect because it preferentially raises renal perfusion. [14] A fast-acting antihypertensive with little side effects on the mother and foetus is intravenous labetalol. [15,6] Additionally, it may lower cerebral perfusion pressure, reducing the risk of eclampsia. [16]

Both nifedipine and labetalol were shown to be beneficial in the current study's treatment of hypertensive crisis, which is in line with the findings of the earlier research. [17,16,15,11,6] when compared to pregnant women receiving intravenous labetalol, those assigned to oral nifedipine attained goal blood pressure much faster and with fewer doses.

Vermillion et al. [6] show that for the nifedipine and labetalol groups, respectively, the mean periods required to

attain target blood pressure were 25 minutes and 43.6 minutes. In the groups receiving nifedipine and labetalol, we discovered mean times of 34.67 (20.297) and 52.00 (29.054) minutes, respectively. (p <.017) However, a flat dosage of nifedipine (10 mg) employed in our trial may be to blame for the extended time needed to reach target blood pressure. Although Shekhar et al. [7] reported longer periods needed to obtain the target BP than our trial, they saw a comparable impact.

However, the research by Raheem et al. [9] indicates that both nifedipine and labetalol are equally effective since the median periods required to reach the goal blood pressure were 30 minutes and 45 minutes, respectively, in the nifedipine and labetalol groups (P= 0.59).

According to Shi etalresearch's on the treatment of severe PIH with nifedipine and labetalol, oral nifedipine was more efficient in safely lowering blood pressure to goal values and required fewer doses than intravenous labetalol. [18] Because of this, oral nifedipine may be used instead of intravenous labetalol to reduce blood pressure during hypertensive situations in pregnancy. Because it is simple to administer orally, is inexpensive, and has a consistent dose schedule, oral nifedipine may also be preferred. Results from Shridhran et al [19] meta-analysis and trial sequence analysis of randomised clinical trials were comparable.

The number of doses needed to manage blood pressure is inversely related to the amount of time needed to achieve the target BP, the likelihood of long-term, severe hypertension, and the adverse effects, all of which increase as dosage needs rise. Our findings show that, compared to the labetalol group, the nifedipine group was able to attain the therapeutic target of blood pressure with fewer dosages. Similar results were shown by Dhali et al [20]. Because nifedipine has a quick onset, oral bioavailability, and a longer duration of action, it requires less time and dosage. Furthermore, nifedipine is mostly processed in the liver and eliminated through the urine, and it seldom causes adverse effects. Additionally, studies have shown that nifedipine decreases blood pressure while maintaining normal heart rate and uteroplacental blood flow. [21,7,6]

Patients with PIH frequently experience decreased renal perfusion and urine production as a result of intravenous volume depletion. Randomized controlled trials show that patients using nifedipine had significantly higher urine output than those on labetalol. [22,6] after selective renal arteriolar vasodilation, nifedipine enhances urine production. [23,24,6]

In several randomised clinical studies, nifedipine has been used safely to treat hypertensive situations and as a tocolytic drug. [25,23,6] Due to the lower concentration of nifedipine, it was not possible to assess the tocolytic impact in our patients after 1 to 2 doses of nifedipine, who then obtained the desired blood pressure.

Magnesium sulphate is frequently used in severe preeclampsia for seizure prevention. [26,27,28] Therefore, it is important to take into account any potential interactions between magnesium sulphate and antihypertensive medications. When nifedipine and magnesium-sulphate were administered together in hypertensive pregnancies, certain incidences of severe hypotension, neuromuscular blockade, and symptomatic hypocalcaemia [29] were observed. Nifedipine and magnesium sulphate usage, however, appears to be well tolerated and does not appear to raise the risk of major magnesium-related side effects. [30,26] None of the patients in either group who received magnesium sulphate as prophylaxis experienced a serious adverse event.

In our study, neither group's mother health nor the health of the foetus had any substantial negative consequences. Minor

adverse effects, such as tiredness, nausea, headaches, dizziness, and cutaneous flushing, were nonetheless recorded. These symptoms were uncommon, brief, and did not call for stopping the medicine in either group. No major maternal side effects were found in any of the randomised investigations. Fetal side effects were uncommon and occurred in both groups at comparable rates [10,9,8,7,6]. In earlier research, comparable results were obtained [30,14,13] According to S Shekhar's meta-analysis, nifedipine considerably lowers the likelihood of adverse maternal consequences.

Nifedipine also decreases blood pressure without appearing to reduce uteroplacental blood flow [14,12], or to significantly alter foetal heart rate. [6] The maternal and perinatal outcomes did not differ significantly, making nifedipine a superior or optimal substitute for labetalol. [31]

In our investigation, all patients responded to antihypertensive medications. Furthermore, after the start of antihypertensive therapy, no occurrences of overshoot hypotension, cerebrovascular accidents, eclampsia, or abruption were documented. Maternal mortality was non-existent.

Conclusion

Both oral nifedipine and intravenous labetalol are efficient at lowering blood pressure. Nifedipine had a positive impact on urine production and decreased blood pressure more quickly. No notable side effects on the mother or the foetus were observed with either medication. Nifedipine taken orally has a flat dose schedule and is easier to administer than other options.

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