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A randomized trial of intravenous labetalol versus oral nifedipine in acute blood pressure control in hypertensive emergencies of pregnancy

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Abstract
Hypertension (HTN) is a worldwide health problem that affects about 25-40% of individuals. Hypertension in pregnancy is associated with adverse effects for both mother and baby which includes fetal growth restriction, preterm delivery and maternal, fetal, and neonatal morbidity and mortality. These women are at greater risk for the development of cardiovascular risk factors (hypertension, type 2 diabetes, and obesity), chronic kidney disease and premature cardiovascular disease. Severe hypertension in pregnancy is defined by a systolic blood pressure of at least 160 mm Hg or diastolic blood pressure of at least 110 mm Hg. A combined team of obstetricians and cardiologists is an important prerequisite for management of HTN and cardiovascular disease during pregnancy. Labetalol and nifedipine have quickly emerged as alternative drugs for management of gestational hypertension. A Prospective randomized double blind comparative clinical trial was conducted in the Department of Obstetrics & Gynaecology of Darbhanga Medical College & Hospital, Laheriasarai, Bihar which took the study period from April 2019 to December 2020. The present study was executed upon 106 pregnant women with pre-eclampsia with a gestational period of 28 weeks or beyond with blood pressure reading ≥160/110 mmHg. All the patients were randomly divided into two groups Group A and B. Group A patients received intravenous Labetalol and Group B patients received oral Nifedipine as antihypertensive drugs to achieve the target blood pressure reading 150/100.The present study aimed to compare the two most commonly used drugs, oral nifedipine and IV labetalol in terms of time taken to achieve the target blood pressure and number of dosage required.

Keywords: hypertension, gestational hypertension, eclampsia, nifedipine and labetalol

Introduction
Gestational Hypertension is most common medical disorder encountered by a pregnant woman and complicates one in ten pregnancies [1]. A hypertensive disorder of pregnancy is the second leading cause of maternal death worldwide [2]. The disease has a broad spectrum ranging from mild hypertension to preeclampsia and eclampsia. Hypertension in pregnancy is associated with adverse effects for both mother and baby which includes fetal growth restriction, preterm delivery and maternal, fetal, and neonatal morbidity and mortality [1]. These women are at greater risk for the development of cardiovascular risk factors (hypertension, type 2 diabetes, and obesity), chronic kidney disease, premature cardiovascular disease (cardiac, cerebrovascular, and peripheral arterial), and cardiovascular mortality [3, 4]. Severe hypertension in pregnancy is defined by a systolic blood pressure of at least 160 mm Hg or diastolic blood pressure of at least 110 mm Hg and either of these clinical signs is considered to be an obstetric emergency for both mother and fetus; urgent antihypertensive treatment is recommended [5, 6, 7].
The only definite treatment of severe preeclampsia is termination of pregnancy but it also requires immediate antihypertensive management to stabilize the patient and prevent its further complications. Antihypertensive management includes both in form of oral and injectable drugs. Labetalol and hydralazine are intravenous drugs that have been traditionally used as first line drugs in severe hypertension in pregnancy. Oral medication like Nifedipine which is a calcium channel blocker is also considered as latest essential drugs list for treating severe hypertension in pregnancy. Several worldwide studies comparing Nifedipine, hydralazine and labetalol in hypertensive emergency have been done regarding their efficacy in controlling BP and fetal outcome [8, 9]. Recently systematic review has declared all of them to be equally effective in controlling BP in hypertensive emergencies in pregnant women. All three of these are recommended as first line agents [10].

Royal College of Obstetricians and Gynaecologists and American College of Obstetrics and Gynaecology have also recommended labetalol, nifedipine and hydralazine as first-line drugs for gestational Hypertension [11, 12]. But surprisingly World Health Organization (WHO) has included only intravenous hydralazine in its most recent essential drugs list (EDL) for treating severe hypertension in pregnancy [13].

A combined team of obstetricians and cardiologists is an important prerequisite for `management of HTN and cardiovascular disease during pregnancy. Labetalol and nifedipine have quickly emerged as alternative drugs. Though nifedipine is cheap, widely available and easily administered, there is a strong preference for labetalol and there is a trust deficit for oral nifedipine among health care providers. Both drugs have been compared directly with many other antihypertensive agents for treatment of hypertensive crises during pregnancy; however, their direct comparison with each other is limited to a very few trials [8-11]. This study aims to equate to compare the pharmacodynamics of intravenous labetalol and oral nifedipine in patients with severe hypertension.

Materials and Method

Study Design: Prospective randomized double blind comparative clinical trial.

Duration of study: March 2019 to December 2020.

Source of data: Pregnant women with sustained hypertension of 20 weeks pregnancy or more were included in the study.

Place of study: Department of Obstetrics & Gynaecology, Darbhanga Medical College & Hospital, Laheriasarai, Bihar.

Sample size: 106 pregnant women with sustained hypertension of 20 weeks pregnancy or more.

Inclusion criteria: All Singleton pregnant women of 20 weeks gestation or more;
Sustained severe hypertension: Systolic blood pressure≥160 mm Hg; diastolic blood pressure≥110mm Hg; or a mean arterial pressure of >125 mm Hg, lasting for 15 minutes or more in the past 4 hours on at least 2 occasions.

Exclusion criteria: Eclampsia; HELLP syndrome, Bronchial asthma, Cardiac failure, Cardiac rhythm abnormalities, Chronic hypertension, Multiple pregnancy.

Methodology: The present study was done after getting ethical clearance and approval in Darbhanga Medical College, Bihar. Written informed consents were taken from the patients. This study was conducted in the Department of Obstetrics & Gynaecology and it was a prospective randomized double blind comparative clinical trial. The study was done from March 2019 to December 2020. Pregnant women with sustained hypertension of 20 weeks pregnancy or more were enrolled in the study. A total of 106 pregnant women were selected. A thorough detailed history was obtained from the patients regarding age, parity, socio economic status, booking history and gestational age. Their past history for hypertension and other medical disorders were also obtained. A detailed general examination and obstetric examination were done. Blood pressure measurement was done with the mercury blood pressure apparatus. Fetal wellbeing was ascertained with the use of cardiotocograph before and after the usage of anti-hypertensive agents and other drugs.

Investigations done: Urine analysis, Complete blood count including platelet count, Blood grouping and typing, Renal function tests, Liver function tests, Peripheral smear study, Serum lactate dehydrogenase level, Ultrasonogram, Cardiotocograph.

Anti-hypertensive Management: After explaining the condition of the patient and getting prior informed consent, the pregnant women were randomized with computer generated numbers into two groups to receive either oral nifedipine or intermittent intravenous labetalol injections.

Group A: Fifty three patients were selected consecutively according to random numbers to receive the package containing intravenous labetalol injection in escalating doses of 20 mg, 40 mg, 80 mg, 80 mg, 80 mg and a placebo tablet for every fifteen minutes until the target blood pressure of ≤ 150 / ≤ 100 mm Hg was achieved.

Group B: Fifty three patients were randomized to receive the package containing nifedipine 10 mg tablet orally and intravenous placebo saline injections of 4 ml, 8ml, 16 ml, 16 ml, 16 ml up to five doses, every fifteen minutes till the target blood pressure of ≤ 150 / ≤ 100 mm Hg was achieved. Blood pressure was noted every 15 minutes. Once the blood pressure was <150 / 100 mm Hg, no further trial medication was given until two consecutive readings were > 160/ 110 mm Hg. After successful control of blood pressure, further antihypertensive therapy was started two hours after the last trial medication.

Obstetric Management: A careful obstetric examination was carried out. Bishop's score was calculated. Fetal status is ascertained by cardiotocograph. Induction of labour was done with intra-cervical PGE2 gel instillation. Acceleration of labour was done with intravenous oxytocin infusion. Caesarean section was done for obstetric, fetal indications and failed inductions.

Outcome Measures: The primary outcome of this trial was the time taken to achieve a target blood pressure of ≤ 150 mm Hg systolic and ≤ 100 mm Hg diastolic in both the groups. Both had to be achieved. The secondary outcome measures include total number of antihypertensive doses to achieve the target blood pressure, both systolic and diastolic, any cardio-tocographical abnormality, and maternal heart rate profile in the first hour, maternal hypotension, side effect profile.

Statistical Analysis: Data was checked for accuracy and completeness then coded and entered into (Statistical Package for the Social Sciences) version 23.0 for analysis. The results presented in frequency tables, cross tabulations and figures. Categorical data are presented as frequency with percentages. Continuous data with normal distribution are presented as mean with standard deviation. Descriptive and inferential statistics using Chi square test, and Student's *t*-tests were performed. A p value < 0.05 is considered to be level of significance.

Results and Observations

Table 1: Age Distribution

Age Group	Group A Intravenous Labetalol (n=53)		Group B Oral Nefidipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
18-25 years	15	28.3	15	28.3
26-30 years	26	49.1	28	52.8
31-35 years	12	22.6	10	18.9
Total	53	100.0	53	100.0
Mean age:	27.39±4.32		27.30±4.16	
p value	0.669			

Age distribution of the study participants of both the groups (Group A Intravenous Labetalol Group B Oral Nifedipine) is mentioned in Table 1. While analyzing the age distribution we found that majority of patients i.e. 54 (50.9%) belonged to 26-30 years age group among them 26 belonged to Group A and 28 belonged to Group B. The mean age of Group A and B patients were 27.39 ±4.28 and 27.30 ±4.12 years respectively. Above analysis for age distribution in both groups we found no significance (p value= 0.669).

Table 2: Gestational Age

Gestational Age	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
28-33 weeks	14	26.4	11	20.8
34-36 weeks	21	39.6	18	34.0
37-40 weeks	11	20.8	13	24.5
>40 weeks	7	13.2	11	20.8
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 1.646	p Value - 0.648		

Table 2 shows the distribution of study participants according to their gestational age at presentation in each group. Most patients (64%) with pre-eclampsia belonged to 34-36 weeks of gestation in both the groups i.e. 21 (39.6%) patients in Group A and 18 (34%) patients of Group B. While comparing between two groups the data we found was not statistically significant (p value = 0.648).

Table 3: Distribution according to SBP at baseline

SBP (mmHg)	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
160-178 (mmHg)	23	43.4	21	39.6
179-199 (mmHg)	19	35.8	24	45.3
≥200 (mmHg)	11	20.8	8	15.1
Total	53	100.0	53	100.0
Mean SBP:	184.16±15.03		185.35±12.53	
p value	0.121			

Table 3 shows the distribution of study subjects of both groups according to Systolic Blood Pressure at baseline. 23 (43.4%) patients of Group A and 21 (39.6) patients of Group B had a SBP of 160-178 mm of Hg. 160-179 mm of Hg SBP was observed in 19 (35.8%) patients of Group A and 24 patients of Group B. ≥ 200 mm of HG SBP was observed in 11 patients of Group A and 8 patients of Group B. Mean SBP was184.16±14.89mm of Hg in Group A and 185.35±12.42 mm of Hg in Group B, which was statically not significant as 'p' value was 0.121.

Table 4: Distribution according to DBP at baseline

DBP (mmHg)	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
110-119 (mmHg)	25	47.2	24	45.3
≥120 (mmHg)	28	52.8	29	54.7
Total	53	100.0	53	100.0
Mean DBP:	126.09±12.30		128.45±12.63	
p value	0.483			

Table 4 shows the comparison of mean DBP between two groups at baseline. The baseline diastolic blood pressure did not vary significantly in the groups (p value=0.483). The mean of the baseline diastolic blood pressure were 126 mm Hg and 128 mm Hg in Group A and B, respectively. 52.8% and 54.7% in Group A and B had diastolic blood pressure more than 120 mm Hg respectively.

Table 5: Distribution according to Heart Rate at baseline

Heart Rate (bpm)	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
≤90 (bpm)	37	69.8	40	75.5
90-100 (bpm)	13	24.5	12	22.6
≥101 (bpm)	3	5.7	1	1.9
Total	53	100.0	53	100.0
Mean HR:	85.88±8.42		84.56±8.54	
p value	0.964			

Table 5 shows the distribution of study subjects of both groups according to their heart rate at baseline. There was no significant difference in the baseline heart rate between the groups. Majority of the patients in Group A (69.8%) and Group B (75.5%) had heart rate less than 90 per minute during the commencement of the study.

Table 6: Distribution according to the time taken to achieve Target Blood Pressure

Time Taken	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
15 minutes	6	11.3	4	7.5
30 minutes	9	17.0	15	28.3
45 minutes	15	28.3	10	18.9
60 minutes	12	22.6	9	17.0
75 minutes	5	9.4	8	15.1
≥90 minutes	6	11.3	7	13.2
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 4.097 p Value - 0.535			

Distribution of study participants according to the time taken to achieve the target blood pressure of both groups is mentioned in Table 6. In group A, 15 patients, constituting 28.3% of the recruited reached the target blood pressure of less than 150/ 100 mm Hg in 45 minutes. 15 patients, constituting 28.3% of group B achieved the target blood pressure range by 30 minutes. Overall, there is no statistically significant change regarding the time taken to achieve the target blood pressure (p value = 0.535).

Table 7: Distribution according to Number of Doses required achieving Target Blood Pressure

Number of Doses	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
1	11	20.8	17	32.1
2	14	26.4	15	28.3
3	12	22.6	9	17.0
4	9	17.0	8	15.1
5	6	11.3	3	5.7
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 2.807p Value - 0.590			

Table 7 shows comparison of number of doses of drugs required to control BP between two groups. In oral Nefidipine group (Group B) most of the patients i.e. 17 (32.1%) were controlled by 1st dose of drug. In the intravenous Labetalol group (Group A) maximum 14 (26.4%) patients were controlled by 2 doses of drugs. Thereby from the above table we can interpret that oral Nifedipine requires less number of doses to control raised blood pressure in pre-eclampsia compared to intravenous Labetalol. However the difference was not significant (p value = 0.590).

Table 8: Comparison of Mean SBP after anti hypertensive treatment at different time intervals

Time Interval (minutes)	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)		P value
	Mean	±SD	Mean	±SD	
15 minutes	176.96	±13.73	176.77	±11.16	0.029
30 minutes	171.60	±13.40	171.67	±11.15	0.033
45 minutes	170.92	±13.19	166.58	±11.04	0.038
60 minutes	160.94	±11.76	161.39	±11.26	0.494
75 minutes	154.62	±10.69	156.39	±11.26	0.542

Mean SBP levels after anti hypertensive treatment at different time interval is mentioned in Table 8. The difference was statistically significant at 15 minutes, 30 minutes and 45 minutes time interval (p value =<0.05).

Table 9: Comparison of Mean DBP after anti hypertensive treatment at different time intervals.

Time Interval (minutes)	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)		p value
	Mean	±SD	Mean	±SD	
15 minutes	121.09	±12.30	123.45	±12.63	0.483
30 minutes	114.90	±10.94	117.26	±10.31	0.895
45 minutes	108.67	±9.20	112.73	±8.46	0.645
60 minutes	104.66	±6.16	107.73	±8.46	0.001
75 minutes	101.69	±3.79	104.24	±7.16	<0.001

Mean DBP levels after anti hypertensive treatment at different time interval is mentioned in Table 9. The difference was statistically significant only at 75 minutes interval (p value =<0.001).

Discussion

This Prospective randomized double blind comparative clinical trial was conducted in the Department of Obstetrics & Gynaecology of Darbhanga Medical College & Hospital, Laheriasarai, Bihar which took the study period from March 2019 to December 2020. The present study was executed upon 106 pregnant women with pre-eclampsia with a gestational period of 28 weeks or beyond with blood pressure reading ≥160/110 mmHg. All the patients were randomly divided into two groups Group A and B. Group A patients received intravenous Labetalol and Group B patients received oral Nifedipine as antihypertensive drugs to achieve the target blood pressure reading 150/100.

The present study aimed to compare the two most commonly used drugs, oral nifedipine and IV labetalol in terms of time taken to achieve the target blood pressure, number of dosage required.

In the present study we found that majority of patients i.e. 54 (50.9%) belonged to 26-30 years age group among them 26 belonged to Group A and 28 belonged to Group B. The mean age of Group A and B patients were 27.39 ±4.28 and 27.30 ±4.12 years respectively. Regarding age distribution two groups were comparable. Similar findings were observed in a study conducted by Alam *et al*. (2019) where the mean and SD value of IV labetalol and oral Nifedipine group were 25.28±4.87 and 24.68±5.03 respectively. In following studies conducted the maternal mean age in both the group in Shekhar *et al* was 25.9 years, Swapan *et al* was 25.4 years while in Raheem *et al*. was 31.4 years as the distribution of age was from 20 to 40 years [14, 15, 16].

In our study most of the patients (64%) with pre-eclampsia belonged to 34-36 weeks of gestation in both the groups i.e. 21 (39.6%) patients in Group A and 18 (34%) patients of Group B. Similar result was found in other studies conducted by Raheem *et al*, Shekhar *et al*, Swapan *et al* who shows period of gestation in intravenous Labetalol and oral Nifedipine are 36.3-38.6 and 35-38.6, 36-38 and 37-38, 38-40 and 38-40 weeks respectively in their studies [14, 15, 16]. Hence severe pre-eclampsia condition is often seen in late trimester of pregnancy in the study by Sibai and colleagues.

In a randomized control trial conducted by Sibai, Brian, *et al*, on the expectant management of severe preeclampsia, the blood pressure on admission was found to be ≥160/110 mm Hg.

In group A, 15 patients, constituting 28.3% of the recruited reached the target blood pressure of less than 150/ 100 mm Hg in 45 minutes. 15 patients, constituting 28.3% of group B achieved the target blood pressure range by 30 minutes. Overall, there is no statistically significant change regarding the time taken to achieve the target blood pressure (p value = 0.535).

In oral Nifedipine group (Group B) most of the patients i.e. 17 (32.1%) were controlled by 1st dose of drug. In the intravenous Labetalol group (Group A) maximum 14 (26.4%) patients were controlled by 2 doses of drugs. Thereby from the above table we can interpret that oral Nifedipine requires less number of doses to control raised blood pressure in pre-eclampsia compared to intravenous Labetalol. However the difference was not significant (p value = 0.590).

Similar trials conducted by Raheem *et al*. Shekhar *et al*. Anjuman *et al* and Yogita *et al*. showed that BP control was controlled significantly earlier in patients who were given Nifedipine as compared to labetalol and they required less number of doses [14, 17-19]. In their study Sujit *et al* found, the mean time required to achieve target blood pressure is 71.00±66.60 minutes in labetalol group and 25.20±14.03 minutes in the nifedipine group with a significant difference (p value of < 0.01) [21].

Raheem *et al*. showed that the median time taken to achieve target blood pressure was 30 minutes (interquartile range 22.5 to 67.5 minutes) versus 45 mins (interquartile range 30-60 minutes) for nifedipine and labetalol respectively (p=0.59) [14]. Shekhar *et al* study showed that the median time required achieving target blood pressure 40 minutes in nifedipine group and 60 minutes in labetalol group [15].

In a similar study conducted by Swapan *et al* they found the mean time required were 47.2 ± 13.5 mins in the Labetalol groups and 45.6 ± 14.5 minutes in the Nifedipine group. In their study this comparison showed no difference in the two groups with a 'p' value of 0.511 [16].

In the study by Vermillion *et al* mean times needed to achieve target BP were 25 minutes and 43.6 minutes for the nifedipine group and the labetalol group, respectively, compared with median times of 40 minutes and 60 minutes, respectively, in our study.

Gavit Y *et al*. showed that nifedipine took significantly less time in achieving the target BP [20].

In oral Nifedipine group (Group B) most of the patients i.e. 17 (32.1%) were controlled by 1st dose of drug. In the intravenous Labetalol group (Group A) maximum 14 (26.4%) patients were controlled by 2 doses of drugs. Thereby from the above table we can interpret that oral Nifedipine requires less number of doses to control raised blood pressure in pre-eclampsia compared to intravenous Labetalol. Our study showed that oral Nifedipine achieved the target systolic and diastolic blood pressure after treatment with antihypertensive drug in less time compared to intravenous Labetalol. However the difference was not significant (p value = 0.590).

Raheem *et al* showed total antihypertensive doses to achieve target blood pressure were 2(1.5-4.5) in nifedipine group and 3(2-4) in labetalol group with a 'p' value 0.60 [14]. Study conducted by Dhali B *et al* also concluded that oral nifedipine lowers blood pressure in less time and with fewer doses as compared to intravenous labetalol [22].

Sathya Lakshmi *et al* showed out of 100 pre-eclampsia patients 22% patients achieved target BP with a single dose of labetalol whereas only 7% patients achieved target BP with the first oral

dose of nifedipine (p value= 0.002).

Sujit *et al*. in their study, found that nifedipine group had required in average 1.12±.32 doses and the labetalol group 2.04±1.37 doses to achieve the target BP which is statistically highly significant ('P' value <0.01) [23]. Shekhar *et al*, also noted that significantly less number of doses of nifedipine was required to achieve target blood pressure compared to labetalol [15]. Vermillion *et al*. and Gavit Y *et al*. in their studies reported 100% success rate to achieve the target blood pressure with both drugs [20]. Vermillion *et al*. [20] reported 100% success rate in achieving the target BP with both drugs, whereas Raheem *et al*. [14] reported 20% failure rate with both drugs and requiring crossover treatment. In the present study, nifedipine was more successful in achieving the target BP in comparison with the labetalol group.

Conclusion

Hypertensive disorders of pregnancy is one of the most common causes of high maternal death in India and globally as well. Both labetalol and nifedipine are equally effective in controlling acute rise in blood pressure with no serious side effects. However oral nifedipine reduced the blood pressure more rapidly in comparison to intravenous labetalol. Neither of the drugs was associated with any hazardous effect on maternal and perinatal outcomes. Finally, we can conclude; oral Nifedipine and intravenous Labetalol both the drugs can be used as first line antihypertensive agents in acute control of hypertensive emergencies of pregnancy depending upon the clinician's familiarity and choice of the drugs, but oral nifedipine is preferable to intravenous labetalol as its use is more convenient.

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