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Original Research Article

A Randomized Comparative Assessment of the Maternal and Fetal Outcomes and Adverse Effects of both Intravenous Labetalol and Oral Nifedipine

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Abstract

Aim: To compare the two most commonly used drugs, oral nifedipine and IV labetalol in terms of their adverse effects, maternal and perinatal outcomes.

Material & Methods: The present study was a prospective randomized double blind comparative clinical trial conducted in the Department of Obstetrics & Gynecology, Patna Medical College & Hospital, Patna, Bihar, India**.** The study was done over a period of four months in which a total of 100 women with sustained hypertension of 20 weeks pregnancy or more were enrolled in the study.

Results: In our study we observed there is a higher incidence of preeclampsia in the first pregnancy. No notable adverse effects were reported in the majority of the recruited patients. The commonest adverse effect was nausea in both groups.

Conclusion: Both intravenous Labetalol and oral Nifedipine are efficacious having minimal side effects; however oral Nifedipine controls hypertension more rapidly compared to intravenous Labetalol.

Keywords: Hypertension**,** Pregnancy**,** Pre-eclampsia**,** Labetalol and nifedipine

Introduction

Hypertensive disorders of pregnancy accounts for 5% to 10% of all pregnancies, and together they are one member of the deadly triad - along with hemorrhage and infection. [1] According to World Health Organization at least a woman dies every seven minutes from complications of hypertensive disorders of pregnancy. [2] Prevalence of hypertensive disorders of pregnancy was 7.8% with preeclampsia in 5.4% of the study population in India. [3] In several worldwide studies reviewed by Staff and co-workers (2015), the incidence of preeclampsia in a nulliparous woman ranges from 3 to 10 percent while in multiparous it ranges from 1.4 to 4 percent. [4]

Intravenous hydralazine has been the drug of choice since the 1970s but a recent meta-analysis cautions against its use as the drug of first choice due to severe hypotension and other maternal and fetal complications. [5] Similarly, the use of sublingual nifedipine and oral nifedipine

has been criticized because of an unpredictable decrease in blood pressure (BP) and major cardiac events leading to maternal death and fetal distress. A recent review advised against their use for hypertensive crisis, although a randomized double blind trial of oral nifedipine and intravenous labetalol did not report any adverse outcome with oral nifedipine. [6]In this context more randomized trials are required.

In 2017, it was the 120th most commonly prescribed medication in the United States, with more than six million prescriptions. [7]It may be used to treat severe high blood pressure in pregnancy with safety. Its use in preterm labor may allow more time for steroids to improve the baby's lung function and provide time for transfer of the mother to a well-qualified medical facility before delivery. Common side effects include light-headedness, headache, feeling tired, leg swelling, cough, and shortness of breath. Serious side effects may include low blood pressure and heart failure. Nifedipine has now been used safely in a number of obstetric trials for the treatment of hypertensive emergencies. It is orally effective, cheap, easy to administer and store as well. Intravenous labetalol is equally effective in controlling severe hypertension in pregnancy and has the advantage of using in unconscious patient. Labetalol is effective in the management of pregnancy-induced hypertension, hypertensive emergencies, postoperative hypertension, pheochromocytoma-associated hypertension, and rebound hypertension.[8]Common Side effects includes headache (2%), dizziness (11%) nausea (6%), dyspepsia (3%) nasal congestion (3%), ejaculation failure (2 %) dyspnea (2%) fatigue (5%), vertigo (2%) and orthostatic hypotension.[9]

Thus, the present study aimed to compare the two most commonly used drugs, oral nifedipine and IV labetalol in terms of their adverse effects, maternal and perinatal outcomes.

Material & Methods:

The present study was a prospective randomized double blind comparative clinical trial conducted in the Department of Obstetrics & Gynecology, Patna Medical College & Hospital, Patna, Bihar, India. The study was done over a period of four months in which a total of 100 women with sustained hypertension of 20 weeks pregnancy or more were enrolled in the study.

Methodology

A thorough history was taken from the patients regarding age, parity, socio economic status, booking history and their past history. A thorough general examination and obstetric examination were carried out. Mercury sphygmomanometer apparatus was used for blood pressure measurement with the patient lying at an angle of 45 degrees. Fetal wellbeing was ascertained before and after the usage of anti-hypertensive agents and other drugs with the use of cardiotocograph. The pregnant women were randomized into two groups- Group A & Group B: to receive either oral nifedipine or intermittent intravenous labetalol injections with computer generated numbers.

Group A: 50 patients received the package containing intravenous labetalol injection in escalating doses of 20 mg, 40 mg, 80 mg, 80 mg, 80 mg and a placebo tablet was given every fifteen minutes until the target blood pressure of ≤ 150 / ≤ 100 mm Hg was obtained.

Group B: 50 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..

Obstetric management: A careful obstetric examination was carried out. Bishop's score was calculated. Fetal status is ascertained by cardiotocograph. According to individual condition of the patients, delivery of the fetus and placenta was expedited. Induction of labor was done with intra-cervical PGE2 gel. Acceleration of labor was done with intravenous oxytocin infusion. LSCS was done for obstetric, fetal indications and failed inductions. Maternal side effect profile was recorded. Neonatal outcome monitoring included number of admissions in the neonatal intensive care unit, occurrences of hypotension and hypoglycaemia. During the course of trial, maternal heart rate and fetal heart rate was monitored every 15 minutes. The trial was abandoned when there was non-reassuring fetal status and if maternal complications like hypotension, chest pain occurred.

Outcome measures: The primary outcome of this trial was cardio-tocographical abnormality and maternal heart rate profile in the first hour, maternal hypotension, side effect profile and perinatal outcomes. After completion of the trial protocol, patients were asked to complete a questionnaire with yes or no answers on the symptoms of nausea, palpitation, flushing, dizziness, headache, and shortness of breath experienced.

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 test were performed. A p value< 0.05 is considered to be level of significance.

Results:

Age distribution of the study participants of both the groups (Group A -Intravenous Labetalol, Group B - Oral Nifedipine) is mentioned in figure 1.

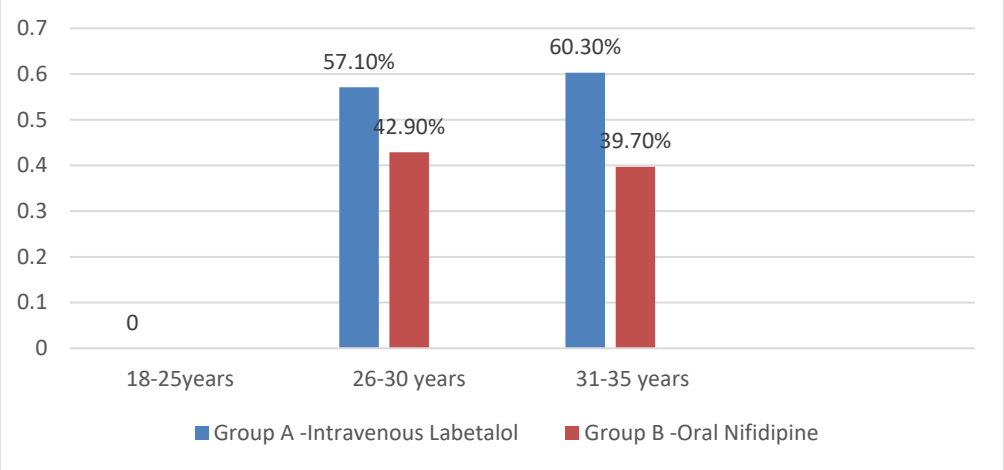

Fig. 1: Age distribution

While analyzing the age distribution we found that majority of patients belonged to 26-30 years age group among them 57.1% belonged to Group A and 60.3% belonged to Group B. The mean age of Group A and B patients were 28.9 ± 5.8 and 28.4 ± 5.2 years respectively. Above analysis for age distribution in both groups we found no significance (p value= 0.551).

Group A and Group B. Majority of the patients constituting 54% of Group A and 50% of Group B were primigravida. In our

study we observed there is a higher incidence of preeclampsia in the first pregnancy. Data is tabulated in Table 1.

Table 1: Distribution according to gravida

Gravidity	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)	
	Frequency	Percentage	Frequency	Percentage
Primi	27	54	25	50
G2	10	20	11	22
G3	8	16	10	20
G4	5	10	4	8
Total	50	100.0	50	100.0
Chi- Square p Value	Chi- Square- 0.382 p Value - 0.641			

Table 2: Gestational age

Gestational Age	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)	
	Frequency	Percentage	Frequency	Percentage
28-33 weeks	12	24	11	22
34-36 weeks	20	40	17	34
37-40 weeks	11	22	12	24
>40 weeks	7	14	10	20
Total	50	100.0	50	100.0
Chi- Square p Value	Chi- Square- 1.430 p Value - 0.333			

Table 2 shows the distribution of study participants according to their gestational age at presentation in each group. Most patients with pre-eclampsia belonged to 34-36 weeks of gestation in both the groups i.e. 21 (40%) 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 = 0.420).

Distribution of study subjects according to their BMI status of both the Groups is mentioned in Table 3.

Table 3: Distribution according to BMI

BMI (kg/m^2)	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)	
	Frequency	Percentage	Frequency	Percentage
25.0-29.99 (kg/m^2)	23	46	24	48
≥30 (kg/m^2)	27	54	26	52
Total	50	100.0	50	100.0
Mean BMI	31.62 ± 3.20		31.78 ± 3.28	
p value	0.402			

Patients with a BMI of 25.99-29.99 kg/m^2 that belonged to Group A were 46% and 48% belonged to Group B. Remaining 54% patients had a BMI of ≥30kg/m^2 belonged to Group A and 52% belonged to Group B. The mean BMI of Group A and Group B patients were 31.62 ± 3.20 and 31.78 ± 3.28 respectively. Above analysis for BMI distribution in both groups we

found no statistical significance (p value = 0.402).

Table 4: Distribution according to degree of proteinuria

Degree of Proteinuria	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)	
	Frequency	Percentage	Frequency	Percentage
1+	17	34	20	40
2+	12	24	13	26
3+	15	30	12	24
4+	6	12	5	10
Total	50	100.0	50	100.0
Chi- Square p Value	Chi- Square- 0.842 p Value - 0.761			

Table 4 shows the distribution of the study participants according to degree of proteinuria irrespective of groups. We observed there was no significant difference between two groups regarding the degree of proteinuria by dipstick estimation (p value =0.761).

Table 5: Distribution according to mode of delivery

Mode of Delivery	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)	
	Frequency	Percentage	Frequency	Percentage
Labour Naturale	34	68	37	74
LSCS	16	32	13	26
Total	50	100.0	50	100.0
Chi- Square p Value	Chi- Square- 0.528 p Value - 0.296			

Table 5 shows the mode of delivery of the two groups. Vaginal delivery rate in the intravenous Labetalol group (Group A) was 68% while in oral Nifedipine group (Group B) it was 74%. Caesareans section rate was 32% and 26% in the intravenous Labetalol and oral Nifedipine group respectively. While comparing we found no statistical significant difference as the p value was 0.296.

Distribution of the newborns according to NICU admission of both groups is mentioned in Table 6.

Table 6: Distribution of the newborns according to NICU admission

NICU Admission	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)	
	Frequency	Percentage	Frequency	Percentage
No	40	80	36	72
Yes	10	20	14	28
Total	50	100.0	50	100.0
Chi- Square p Value	Chi- Square- 0.765 p Value - 0.790			

Total 24 newborns of both groups had an admission in NICU among them 10 belonged to Group A and 14 belonged to Group B. Above analysis over NICU admission of newborns of both groups we found no significant difference as the p value was 0.790.

Neonatal outcome is mentioned in Table 7.

Table 7: Distribution according to neonatal outcome neonatal outcome

Neonatal Outcome	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)	
	Frequency	Percentage	Frequency	Percentage
Alive	47	94	46	92
Dead	3	6	4	8
Total	50	100.0	50	100.0
Chi- Square p Value	Chi- Square- 0.464 p Value - 0.785			

Neonatal outcome was accounted on discharge of the mother. 6% babies of Group A and 8% of babies in Group B died. The major cause was from neonatal respiratory distress syndrome arising out of prematurity. There was no significant change in terms of perinatal death in both the groups (p value= 0.785).

Table 8: Incidence of adverse effects

Adverse Effects	Group A Intravenous Labetalol (n=50)		Group B Oral Nifedipine (n=50)		p Value
	Frequency	Percentage	Frequency	Percentage	
No Notable adverse events	34	68	32	64	0.528
Nausea	7	14	6	12	0.437
Vomiting	0	0	3	6	0.732
Palpitation	4	8	4	8	0.271
Headache	3	6	5	10	0.183
Chest pain	0	0	0	0	-
Shortness of breathing	2	4	0	0	0.538
Tingling of scalp	0	0.0	0	0	-
Flushing of face	0	0.0	1	2	0.182

Table 8 shows the incidence of adverse effects in both groups. No notable adverse effects were reported in the majority of the recruited patients. The commonest adverse effect was nausea in both groups.

Discussion:

Oral nifedipine achieved target BP (≤150/100 mmHg) more rapidly in 26.25±12.60 minutes (Mean±SD), in comparison to 32.62±12.19 minutes (Mean±SD) with IV labetalol, (p=0.024). Study conducted by Vermillion et al. [6] found that nifedipine took significantly less time (mean±SD, 25±13.6 minutes) in comparison to labetalol group (43.6±25.4 minutes; P = 0.002) in achieving the target BP. In many other studies like that conducted by Sujit et al, Shekhar et al, Gavit Y et al, showed that nifedipine took significantly less time in achieving the target BP. [10-12]

Previous study have demonstrated that nifedipine effectively lowers blood pressure without any apparent reduction in uteroplacental blood flow [13-14] & without any significant heart rate abnormalities. [15-16]

The number of doses required to control the BP indirectly reflects the time required to reach the desired BP, the probability of persistent severe hypertension and the side-effects, all increasing with increasing dose requirements. As 44% of patients in the labetalol group required a single dose compared with 14% in the nifedipine group to reach the target BP, it is evident that intravenous labetalol is more effective than oral nifedipine in reducing the BP to target levels. Seventy percent of patients required only 1–2 doses of labetalol to reach target MAP similar to the success rate obtained in the study by Vigil-de Gracia et al. [17]

All the patients responded to antihypertensive agents except for a single patient who did not respond to the maximum dose in the labetalol group. The failure rate with labetalol is similar to that in other studies. [17-18] Further, there were no cases of overshoot hypotension, cerebrovascular accidents, eclampsia or abruption after initiation of antihypertensive treatment. There were no cases of maternal mortality. Though efficacy has been demonstrated with sublingual administration of nifedipine, it is not recommended due to the risk of sudden hypotension. [19]

In a study by Satyalakshmi et al [20] they found vaginal delivery rate was in 28% Labetalol group and 36% in Nefidipine group with no significant difference (p value=0.22). In the study by Hangarga et al [21] showed the mode of delivery in nifedipine group out of 50 patients 25 (50%) had a LSCS and another 25 patient had a normal delivery.

Adverse effects profile of the present study was comparable with the study conducted by Raheem IA et al. [22] In our present study the results indicate that both intravenous Labetalol and oral Nifedipine are efficacious having minimal side effects; however oral Nifedipine controls hypertension more rapidly compared to intravenous Labetalol. [23]

Conclusion:

Both intravenous Labetalol and oral Nifedipine are efficacious having minimal side effects; however oral Nifedipine controls hypertension more rapidly compared to intravenous Labetalol

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