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A randomized trial to compare the maternal and fetal outcomes and adverse effects of both intravenous labetalol and oral nifedipine

Pratibha Kumari[1,*], Onam Kumari[2], Sangeeta Pankaj[3], Kumudini Jha[2]

[1]*Dept. of Gynaecological Oncology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India*
[2]*Dept. Obstetrics & Gynaecology, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India*
[3]*Dept. of Gynecological Oncology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India*

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ABSTRACT

Hypertensive disorders of pregnancy is one of the most common causes of high maternal mortality in India and globally as well. Hypertension in pregnancy is associated with many adverse effects for both mother and baby. Blood pressure reading ≥160/110 mmHg is often associated with increased risk of complications like placental abruption, pulmonary edema, hypertensive encephalopathy, intracranial hemorrhage, eclampsia and other end organ damage with poor perinatal outcome. 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. Both intravenous labetalol and nifedipine have been compared directly with many other antihypertensive agents; however, literature on their direct comparison with each other for adverse effect is very limited.

1. Introduction

Hypertension is one of the most common medical disorders in pregnancy, and this condition complicates every one in ten pregnancies.[1] Hypertension in pregnancy is associated with many adverse effects for both mother and baby which includes fetal growth restriction, preterm delivery, and maternal, fetal, and neonatal morbidity and mortality.[1] A hospital survey done on maternal and neonatal health by international agency like WHO in 2013 found an prevalence of pre-eclampsia of 2·5% and an incidence of eclampsia of 0·3% in 314 623 women from Asia, Africa, and Latin America.[2] A 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 is found in women with hypertensive disorders of pregnancy.[3] National institute for health and clinical excellence has defined severe hypertension in pregnancy as diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater.[4–6] Blood pressure reading ≥160/110 mmHg is often associated with increased risk of complications like placental abruption, pulmonary edema, hypertensive encephalopathy, intracranial hemorrhage, eclampsia and other end organ damage with poor perinatal outcome. This necessitates reduction of blood pressure to levels ≤150/100 mmHg to reduce these complications. Various drugs have been used to control raised blood pressure during hypertensive emergencies in pregnancy. The three most frequently employed drugs are hydralazine, labetalol and nifedipine. All of these are recommended as first line agents.[7] Many Clinical trials have typically evaluated medications that are administered intravenously (such as hydralazine or labetalol).[8] Though these regimens

* *Corresponding author*.
E-mail address: pratibhabseb@gmail.com (P. Kumari).

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are effective in controlling raised blood pressure acutely, they require intravenous access and careful fetal monitoring. However, oral medications do not require cold storage, special equipment and a provider trained in intravenous drug administration, and are easily available in most low-income and middle-income countries.[9] In 1967, Nifedipine was patented and in 1981, got approval for use in the United States. It is on the World Health Organization's List of essential Medicines.[10] It is available as a generic medication. In 2017, it was the 120th most commonly prescribed medication in the United States, with more than six million prescriptions.[11] 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 lightheadedness, 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.[12] 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.[4,13]

Women with hypertensive disorders of pregnancy should have a comprehensive plan of care, which includes prenatal counseling, frequent checkups during antenatal period, timely delivery, appropriate intrapartum monitoring and care, and postpartum follow up. These patients requires counseling at every step of the pregnancy to ensure that the woman is aware of the risks to her and her fetus such that she can make informed decisions. Both intravenous labetalol and nifedipine have been compared directly with many other antihypertensive agents for management of hypertensive crises during pregnancy; however, their direct comparison with each other is limited to a very few randomized trials. 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.

2. Materials and Methods

The present study was a prospective randomized double blind comparative clinical trial conducted in the Department of Obstetrics & Gynaecology, Darbhanga Medical College, Bihar after obtaining clearance and approval from the Institutional Ethics Committee. Written informed consents were taken from the participants. The study was done from April 2019 to December 2020 in which a total of 106 women with sustained hypertension of 20 weeks pregnancy or more were enrolled in the study. 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: Fifty three 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: 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..

2.1. 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 labour was done with intra-cervical PGE2 gel. Acceleration of labour 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.

2.2. 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.

2.3. 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.

3. Results and Observation

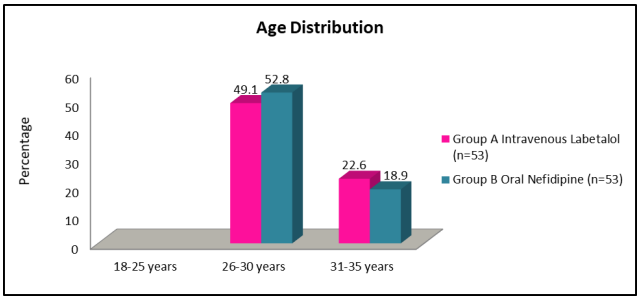

Fig. 1: Age distribution

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

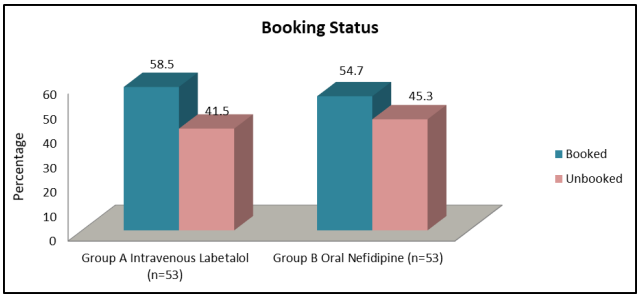

Fig. 2: Booking status

A booked pregnant woman is one who attends at least three antenatal clinic session by trained personnel, an unbooked pregnant woman is one has not attended any antenatal clinic session with a trained personnel before presentation in labour. Distribution of the subjects studied according to their booking status is mentioned in figure 3. 60 (56.6%) patients were in a booked status position among them 31 belonged to Group A and 29 belonged to Group B. 46 (43.4%) patients were in an unbooked status position among them 22 belonged to Group A and 24 belonged to Group B. Above analysis the booked and unbooked status of both groups we found the p value (0.695) was not statistically significant.

Regarding gravidity we found it was comparable in Group A and Group B. Majority of the patients constituting 54.7% of Group A and 49.1% of Group B were primi gravida. 51.9% patients enrolled in the study 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 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).

Distribution of study subjects according to their BMI status of both the Groups is mentioned in Table 3. 47.2% (50) patients had a BMI of 25.99-29.99 kg/m^2 among them 29 belonged to Group A and 27 belonged to Group B. Remaining 56 (52.8%) patients had a BMI of ≥30kg/m^2 among them 29 belonged to Group A and 27 belonged to Group B. The mean BMI of Group A and Group B patients were 30.73 ±2.98 and 30.82 ±3.11 respectively. Above analysis for BMI distribution in both groups we found no statistical significance (p value = 0.437).

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 =0.862).

Table 5 shows the mode of delivery of the two groups. Vaginal delivery rate in the intravenous Labetalol group (Group A) was 66% while in oral Nifedipine group (Group B) it was 73.6%. Caesareans section rate was 34% and 26.4% in the intravenous Labetalol and oral Nifedipine group respectively. While comparing we found no statistical significant difference as the p value was 0.397.

Distribution of the newborns according to NICU admission of both groups is mentioned in Table 6. Total 26 newborns of both groups had an admission in NICU among them 11 belonged to Group A and 15 belonged to Group B. Above analysis over NICU admission of newborns of both groups we found no significant difference as the p value was 0.366.

Table 1: Distribution according to Gravida

Gravidity	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
Primi	29	54.7	26	49.1
G2	11	20.7	12	22.6
G3	9	17.0	11	20.8
G4	4	7.5	4	7.5
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 0.407 p Value - 0.938			

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 3: Distribution according to BMI

BMI (kg/m^2)	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
25.0-29.99 (kg/m^2)	24	45.3	26	49.1
≥30 (kg/m^2)	29	54.7	27	50.9
Total	53	100.0	53	100.0
Mean BMI	30.73±3.01		30.82±3.14	
p value	0.437			

Table 4: Distribution according to degree of proteinuria

Degree of Proteinuria	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
1+	18	34.0	21	39.6
2+	13	24.5	14	26.4
3+	15	28.3	13	24.5
4+	7	13.2	5	9.4
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 0.743 p Value - 0.862			

Table 5: Distribution according to mode of delivery

Mode of Delivery	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
Labour Naturale	35	66.0	39	73.6
LSCS	18	34.0	14	26.4
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 0.716 p Value - 0.397			

Table 6: Distribution of the newborns according to NICU admission

NICU Admission	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
No	42	79.2	38	71.7
Yes	11	20.8	15	28.3
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 0.815 p Value - 0.366			

Table 7: Distribution according to neonatal outcome

Neonatal Outcome	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)	
	Frequency	Percentage	Frequency	Percentage
Alive	50	94.3	48	90.6
Dead	3	5.7	5	9.4
Total	53	100.0	53	100.0
Chi- Square p Value	Chi- Square- 0.540 p Value - 0.462			

Neonatal outcome is mentioned in Table 7. Neonatal outcome was accounted on discharge of the mother. 5.7% babies of Group A and 9.4% 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= 0.462).

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.

4. Discussion

Hypertension is one of the most common medical disorders encountered during pregnancy. Hypertensive disorders of pregnancy accounts for 5% to 10% of all pregnancies, and together they contribute one member of the deadly triad - along with hemorrhage and infection.[14] According to World Health Organization at least a woman dies every seven minutes from complications of hypertensive disorders of pregnancy. Prevalence of hypertensive disorders of pregnancy was 7.8% with preeclampsia in 5.4% of the study population in India.[15] In several studies reviewed by Staff and co-workers (2015), the incidence of preeclampsia ranges from 3 to 10 percent in a nulliparous woman while in multiparous it ranges from 1.4 to 4 percent.[16] The three most commonly employed medications are hydralazine, labetalol and nifedipine. All three of these are recommended as first line agents.[4] 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.[17–19] Maximum patients of severe pre-eclampsia were primigravida i.e. 29 (54.7%) and 26 (49.1%) patients of Group A and B respectively were primi gravida in our study. According to the study by Duckitt et al, primiparity is one of the risk factors for preeclampsia. Raheem et al found 36 out of 50 patients were Primigravida in his study, Shekhar et al found 58 out of 60 patients were Primigravida and Swapan et al found 49 out of 100 patients were Primigravida in their study.[17–19]

In our study 29 (58%) patients were in a booked status position among them 15 belonged to Group A and 14 belonged to Group B. 21 (42%) patients were in an unbooked status position among them 10 belonged to Group A and 11 belonged to Group B. This was in a comparison in a similar study conducted by Alam A et al where he found 62.5% patients in booked status.[20]

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%) 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.[17–19] Hence severe pre-eclampsia condition is often seen in late trimester of pregnancy.

The progressive risk of preeclampsia in obese is elucidated in the study by Sibai and colleagues.In our study also majority of the patients i.e. 56 (52.8%) patients had a BMI of ≥30kg/m2 among them 29 belonged to Group A and 27 belonged to Group B. The mean BMI of Group A and Group B patients were 30.73 ±2.98 and 30.82 ±3.11 respectively. This findings are in a comparison with a similar study conducted by Alam A et al. where he found 56.25%[45] patients had a high BMI among them 23 belonged to Labetalol group and 2 belonged to Nifedipine group.[20] Vaginal delivery rate in the intravenous Labetalol group (Group A) was 66% while in oral Nifedipine group (Group B) it was 73.6%. Caesareans section rate was 34% and 26.4% in the intravenous Labetalol and oral Nifedipine group respectively. While comparing we found no statistical significant difference as the p value was 0.397. In a study by Satyalakshmi et al[21] 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[22] 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. In labetalol group 21 patient (42%) had a LSCS and 29 patients (58%) had a normal delivery.

Table 8: Incidence of adverse effects

Adverse Effects	Group A Intravenous Labetalol (n=53)		Group B Oral Nifedipine (n=53)		p Value
	Frequency	Percentage	Frequency	Percentage	
No Notable adverse events	32	60.4	31	58.5	0.499
Nausea	9	17.0	7	13.2	0.391
Vomiting	0	0.0	3	5.7	0.119
Palpitation	5	9.4	5	9.4	0.369
Headache	5	9.4	5	9.4	0.369
Chest pain	0	0.0	0	0.0	-
Shortness of breathing	2	3.8	0	0.0	0.235
Tingling of scalp	0	0.0	0	0.0	-
Flushing of face	0	0.0	2	3.8	0.235

Swapan et alin their study showed that there was no significant difference in the mode of delivery between two groups with a 'p' value of 0.365.[19] But spontaneous vaginal delivery was more in the Labetalol group i.e. 28% when compared to the Nifedipine group i.e. 14%. These results were more or less similar to the results of the study conducted by Raheem et al.

Rose D T et alin a similar study showed that Labetalol Group had 24% delivered by caesarean section and in nifedipine group, 30% needed caesarean section and the difference was not statistically significant.

Sujit et alin their study showed, there is no significant difference in the mode of delivery between two groups. But in labetalol group there was more normal vaginal delivery compared to nifedipine group (p value =.026).

Total 26 newborns of both groups had an admission in NICU among them 11 belonged to Group A and 15 belonged to Group B. Above analysis over NICU admission of newborns of both groups we found no significant difference as the p value was 0.366.

Similar study by Rose DT et al showed 8% newborns of labetalol group and 10% newborns of nefidipine group had an admission in NICU with no significant difference (p value= 0.132).[23]

Sujit et al. in their study showed insignificant variation in percentage of NICU admission in the both group (labetalol group 14% versus nifedipine group 4%; p value =.081).[24] In the study conducted by Raheem et al., results were similar (3 cases in both groups) with 'P' value 1.0(20). Shekhar et al in their study also showed insignificant 'p' value in terms of NICU admission in both groups (labetalol group 6.7% versus nifedipine group 13.3%).[18]

Neonatal outcome was accounted after discharge of the mother. 5.7% babies of Group A and 9.4% 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= 0.462).

Dr Das S et al, and Padmaja A et al. also recorded comparable perinatal death.[17,25]

Adverse effects were not reported in majority of the recruited patients. The commonest adverse effect was nausea in both groups.

Hangarga US et al showed in their study the commonest adverse effects were occipital headache, postural hypotension, tachycardia and depression.[22] The tachycardia and occipital headache more common in nifedipine group as comparated to labetalol group.

Swapan et al showed the comparison of adverse effects of the drugs. 4% patients had headache in the Labetalol group.[17] In the Nifedipine group 4% of the patients had postural hypotensive, 6% of them had drowsiness.

Dhali B et al, in their study recorded similar percentage of eclampsia; 6% and 2% respectively.[26] Placental abruption was found in 1 (2.5%) patient in each group, similar to the study conducted by Sujit et al.[24]

Adverse effects profile of the present study was comparable with the study conducted by Raheem IA et al.[17] 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.

5. Conclusion

At the end of our study we come to the conclusion that Hypertensive disorders of pregnancy is one of the most common causes of the highest maternal mortality in India and globally as well. Both intravenous Labetalol and oral Nifedipine are efficacious having minimal side effects; however oral Nifedipine controls hypertension more rapidly compared to intravenous Labetalol. From perinatal outcome also it is concluded that oral Nifedipine showed better result compared to intravenous labetalol. Neither of the drugs was associated with any hazardous effect on maternal and perinatal outcomes. The commonest adverse effect was nausea in both groups. Both drugs are well tolerated by the pregnant hypertensive women with no notable adverse effects both on mother and fetus.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

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Author biography

Pratibha Kumari, Senior Resident

Onam Kumari, PG Student

Sangeeta Pankaj, Professor & Head

Kumudini Jha, Professor & Head

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