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# A COMPARATIVE STUDY ON TO ANALYZE EFFICACY OF INTRAVENOUS LABETALOL VERSUS ORAL NIFEDIPINE IN HYPERTENSIVE EMERGENCIES OF PREGNANCY PATIENTS: A RANDOMIZED CONTROLLED TRIAL

**Pharmacology**

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## ABSTRACT

**Background:** Hypertension is the most common medical problem encountered during pregnancy. Antihypertensive drugs are often used to lower blood pressure with the aim of preventing its progression to adverse outcomes for the mother and the fetus. Hence, this study was planned to assess and compare efficacy of intravenous labetalol and oral nifedipine in hypertensive emergencies of pregnancy patients.
**Methods:** The present study was prospective, randomized comparative clinical trial conducted on 100 patients in the department of Obstetrics & Gynaecology, GMC, Azamgarh during the period of June 2020 to July 2021 following approval from institutional ethical committee.
**Results:** The mean age in labetalol and nifedipine groups was 22.61 and 23.02 years. 42% patients enrolled in the study were of primigravida. The majority of the patients had gestational age of 34 to 36 weeks constituting 46%. 59 patients had a body mass index exceeding 30 belonging to the category obesity. The mean systolic blood pressure in Labetalol group was 169 mm Hg whereas it was 173 mm Hg in nifedipine group. The mean diastolic blood pressure was 109 mm Hg and 112 mm Hg in the Labetalol group and Nifedipine group. Mean time required to control BP were 51.50 min in the Labetalol groups and 48.0 min in Nifedipine group. Mean number of doses required to achieve target BP in labetalol group 2.08 and in nifedipine group was 2.02. Mean birth weight was 2.102 ± 0.54 kg in the Labetalol group and 2.25 ± 0.68 kg in the Nifedipine group. Incidence of perinatal mortality was 4% in our study.
**Conclusions:** Both intravenous Labetalol and oral Nifedipine are equally efficacious and can be used as first line drugs for the use in blood pressure control of hypertensive emergency of pregnancy.

## KEYWORDS

Pregnancy, Hypertension, Labetalol, Nifedipine, Efficacy

## INTRODUCTION

Hypertension in pregnancy, called a disease of degree is more of a sign than a disease by itself. With various advancements in the pathophysiology and various insights into the prevention of this disease, effective and timely control of hypertension is still the most imperative step in the management.

Hypertensive disorders of pregnancy are the common medical disorders in pregnancy. The prevalence of hypertension in reproductive-aged women is estimated to be 7.7%.[1] Hypertensive disorders of pregnancy, an umbrella term that includes preexisting and gestational hypertension, preeclampsia, and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality. It has effects both on expectant mother and fetus. The impact due to hypertensive disorders in pregnancy on maternal and neonatal mortality and morbidity is very high in India and other developing countries.[2]

It has been estimated by WHO (World Health Organization) that worldwide approximately 50,000 women will die each year from hypertensive disorders of pregnancy.[3] Severe pre-eclampsia requires prompt treatment because of risk of cardio-vascular accident, to prevent intra cerebral haemorrhage, hypertensive encephalopathy and other target organ damage.[4,5] It also presents an increased risk of complication for the foetus including prematurity, low birth weight, NICU admission and even fetal death.[5, 6,7] In addition to the risk they present to the pregnancy, hypertensive disorders of pregnancy have been linked to future high blood pressure and cardio-vascular diseases in woman.[8]

There is no consensus on the relative efficacy and safety of the medications to treat severe hypertension in pregnancy. Today, though many antihypertensive medications are available and widely used for the treatment of PIH, the physicians still have to deal with many challenges. Effective pharmacologic therapy modifies the course of the disease. The effective use of anti-hypertensive therapy should be based on well designed controlled clinical trials and the experience of the clinician with the drugs.

In order to mitigate the morbidity and the mortality, numerous antihypertensive agents are being used to control blood pressure in severe preeclampsia. Numerous reports signify that reducing severe hypertension reduces maternal death.[9] Antihypertensive drug in pregnancy should effectively reduce the blood pressure of the mother, should not cause acute hypotension, should not have any deleterious effects on the fetus in utero, and should not have any adverse interaction with other drugs including those commonly used in pregnancy and in labour. The use of the drug should modify the course of the disease and it should prevent the development of complications.

The most commonly used hypertensive agents for hypertensive emergencies in pregnancy are Nifedipine, Labetalol and hydralazine. Hydralazine, diuretics and alpha methyl dopa are not recommended for use in severe hypertension as first line drugs due to adverse maternal, fetal outcomes and late onset of action of the latter. Nifedipine has the advantage of being cost effective, rapid onset of action, long duration of action and can be administered orally, however it is known to cause sudden maternal hypotension and fetal distress caused by placental hypoperfusion, palpitation and transient neuromuscular weakness when used concomitant with magnesium sulphate. Intravenous Labetalol is considered to control severe hypertension in pregnancy. Its advantages include little placental transfer, less palpitation and less maternal tachycardia, however neonatal hypotension and neonatal bradycardia has been observed in some trials and is not as cost effective as Nifedipine.[10]

The optimal management of PIH somewhat controversial. Hence, the aim of the present study was to compare the efficacy of oral Nifedipine and IV Labetalol in terms of clinical effectiveness and other variables in a tertiary care teaching hospital.

## AIM & OBJECTIVES

### Aim

The aim of the study is to compare clinical effectiveness of intravenous Labetalol with oral Nifedipine in hypertensive emergencies of pregnancy patients.

### OBJECTIVES

**The present study is undertaken**

1. To study demographic profile of patients.

2. To study the efficacy and safety of intravenous labetalol and oral nifedipine.
3. To study the effect of intravenous labetalol and oral nifedipine on various variables and compare the same.
4. To evaluate perinatal outcome in both the groups.

## MATERIAL & METHODS

The present study was prospective, randomized comparative clinical trial conducted in the department of Obstetrics & Gynaecology, GMC, Azamgarh during the period of June 2020 to July 2021 following approval from institutional ethical committee. Written consent was obtained prior to the study. One hundred consecutive patients satisfying the inclusion criteria were recruited in the present study.

## INCLUSION CRITERIA

1. Age – 18 to 35 years.
2. All pregnant women of 20 weeks gestation or more.
3. Sustained severe hypertension: Systolic blood pressure ≥ 160 mm Hg ; diastolic blood pressure ≥110 mm Hg; or a mean arterial pressure of > 125mmHg, lasting for 15 minutes or more in the past 4 hours on at least 2 occasions.

## EXCLUSION CRITERIA

1. Patients with essential hypertension.
2. Exposure to either drugs prior to the study
3. H/o cardiac disease, bronchial asthma, hematological disorder, Diabetes, Liver disorders
4. Allergy to labetalol or nifedipine

## METHODOLOGY

A thorough history was elicited from the patients regarding age, parity, socio economic status, history suggestive of imminent symptoms. Their past history regarding bronchial asthma, cardiac diseases, prior drug intake for hypertension and other medical disorders were also obtained. 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. Enrolled patients will be randomized to receive either oral nifedipine or intravenous labetalol.

Patients were randomly assigned to be started either with intravenous labetalol (study group) or oral nifedipine (control group) until satisfactory B.P control were achieved.

**Group A:** Injection Labetalol 20 mg i.v bolus over 10 minutes repeated every 20 minutes increasing to 40, 80, 80, to maximum of 220 mg.

**Group B:** Oral Nifedipine 10 mg stat and then repeated at 45 minutes interval till satisfactory B.P were achieved. Maximum dose were 5 doses.

During the study period maternal blood pressures were recorded at every 15 minutes interval till first 30 minutes after achieving target blood pressure less than or equal to 150/100 mmHg, thereafter every 30 minutes for next 2 hours then every hourly. Continous maternal vital parameters and electronic fetal monitoring were done. CTG trace were taken at the beginning and then one at the end of the study.

Treatments were considered as failure if blood pressure were not decreased even after increasing the dose to maximum. Additional antihypertensive agent were added and managed accordingly. If patient developed hypotension BP <90/60mmHg then the trial was terminated and patient were treated with iv fluids and ionotropes as needed.

Maternal complications like imminent signs, abruption, pulmonary oedema, oliguria, renal failure were looked for. Most of the patients delivered at term spontaneously while some needed induction. Birth weights, signs of prematurity of all babies were noted.

## STATISTICAL ANALYSIS

All the data were entered consecutively in a predefined data information sheet and analysis was done using SPSS 20 software. Differences in categorical and continuous data were assessed using the Chi square test and Student't' test, respectively. The statistical tests were considered significant if the calculated p value was less than 0.05.

## RESULTS

Following results were obtained from the study.

- In our study, there was no significant difference in ages of the recruited patients in both the groups. The mean age in labetalol and nifedipine groups was 22.61 and 23.02 years respectively. The majority of the patients had an age belonging to the category of 21 to 29 years. 16 % and 22% from group A and group B respectively had ages 20 years and below as shown in table no 1.

**Table no 1: Comparison of Age Distribution of the two groups**

| S. No | Age | GROUP A Labetalol (n=50) | | GROUP B Nifedipine (n=50) | | Total (%) |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| 1. | ≤ 20 years | 8 | 16 | 11 | 22 | 19 (19) |
| 2. | 21 to 29 years | 29 | 58 | 32 | 64 | 61 (61) |
| 3. | ≥ 30 years | 13 | 26 | 07 | 14 | 20 (20) |
| MEAN (S.D) | | 22.61 ( 3.95) | | 23.02 ( 4.20) | | |
| STATISTICAL INTERFERENCE | | t = 0.181, d.f = 3, P = 0.816 | | | | |

- On analyzing parity in our study, there was no significant difference in the parity of both the groups. Majority of the patients constituting 46% of group A and 38% of group B were primigravida. 42% enrolled in the study were primigravida. There is a higher incidence of preeclampsia in the first pregnancy as shown in table no 2.

**Table 2: Gravida Distribution of the two groups**

| S. No | Parity | GROUP A Labetalol (n=50) | | GROUP B Nifedipine (n=50) | | Total (%) |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| 1. | Primi | 23 | 46 | 19 | 38 | 42 (42) |
| 2. | G1 | 12 | 24 | 15 | 30 | 27 (27) |
| 3. | G2 | 08 | 16 | 10 | 20 | 18 (18) |
| 4. | G3 | 07 | 14 | 06 | 12 | 13 (13) |
| STATISTICAL INTERFERENCE | | $\chi$ 2=5.354, d.f = 2, P= 0.067 | | | | |

On comparing gestational age between 2 groups in our study, amongst 3 of the recruited patients, 2 in group A and 1 in group B had early onset disease at gestational age less than 24 weeks. The majority of the patients had gestational age of 34 to 36 weeks constituting 46% on the whole with 44% and 48% respectively in group A and B. The recruited patients did not significantly differ in gestational age as shown in table no 3.

**Table 3: Comparison of Gestational Age of the two groups**

| S. No | Gestational Age | GROUP A Labetalol (n=50) | | GROUP B Nifedipine (n=50) | | Total (%) |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| 1. | ≤ 24 WEEKS | 02 | 4 | 01 | 2 | 03 (3) |
| 2. | 25 to 28 WEEKS | 05 | 10 | 03 | 6 | 08 (8) |
| 3. | 29 to 33 WEEKS | 17 | 34 | 19 | 38 | 36 (36) |
| 4. | 34 to 36 WEEKS | 22 | 44 | 24 | 48 | 46 (46) |
| 5. | ≥ 37 WEEKS | 04 | 8 | 03 | 6 | 10 (10) |
| STATISTICAL INTERFERENCE | | $\chi$ 2= 1.257, d.f = 3, P= 0.921 | | | | |

- The present study reports showed that, 59 patients had a body mass index exceeding 30 belonging to the category obesity. There is no significant difference in the body mass index between the two groups as shown in table no 4.

**Table 4: Comparison of body mass index of the two groups**

| S. No | Age | GROUP A Labetalol (n=50) | | GROUP B Nifedipine (n=50) | | Total (%) |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| 1. | 25 to 29.99 kg/m2 | 19 | 38 | 22 | 44 | 41 (41) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2. | ≥ 30 kg/m2 | 31 | 62 | 28 | 46 | 59 (59) |
| MEAN (S.D) | | 29.82 (2.02) | | 31.71 (2.60) | | |
| STATISTICAL INTERFERENCE | | χ2=2.517, d.f = 1, p= 1.205 | | | | |

- The present study reports showed that, baseline systolic blood pressure of the patients recruited in both the groups did not differ significantly. The mean systolic blood pressure in intravenous labetalol group was 169 mm Hg whereas it was 173 mm Hg in oral nifedipine group. 50% of patients in group A had a blood pressure range of 160 to 169 mm Hg while 46% of patients in nifedipine group had a blood pressure range of 170 to 179 mm Hg as shown in table no 5.

**Table 5: Comparison of SBP of the two groups**

| S. No | Age | GROUP A Labetalol (n=50) | | GROUP B Nifedipine (n=50) | | Total (%) |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| 1. | 160-169 mm Hg | 25 | 50 | 17 | 34 | 42 (42) |
| 2. | 170-179 mm Hg | 14 | 28 | 23 | 46 | 37 (37) |
| 3. | ≥ 180 mm Hg | 11 | 22 | 10 | 20 | 21 (21) |
| MEAN (S.D) | | 169 (7) | | 173(8) | | |
| STATISTICAL INTERFERENCE | | t= 0.354, d.f= 99, p= 0.925 | | | | |

- Our study reports showed that, baseline diastolic blood pressure did not vary significantly in the groups. The mean of the baseline diastolic blood pressure were 109 mm Hg and 112 mm Hg in the groups A and B, respectively. 58% and 62% in groups A and B had diastolic blood pressure more than 110 mm Hg as shown in table no 6.

**Table 6: Comparison of DBP of the two groups**

| S. No | Age | GROUP A Labetalol (n=50) | | GROUP B Nifedipine (n=50) | | Total (%) |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| 1. | < 110 mm Hg | 21 | 42 | 19 | 38 | 40 (40) |
| 2. | ≥ 110 mm Hg | 29 | 58 | 30 | 62 | 60 (60) |
| MEAN (S.D) | | 109 (8) | | 112(9) | | |
| STATISTICAL INTERFERENCE | | t= 0.158, d.f= 104, p= 0.762 | | | | |

- In present study on comparison of time taken to control BP between two groups, i.e. to achieve BP 150/100mm of Hg. The mean time required were 51.50 ± 11.85 mins in the Labetalol groups and 48.0 ± 6.25 minutes in the Nifedipine group. This comparision showed no difference in the two groups with a 'P' value of 0.358. Similarly on comparison of no. of doses of drugs required to control BP between two groups it was observed that most of the patients were controlled by two doses of each drug. Mean number of doses required to Achieve Target Bp in IV labetalol group 2.08 and in nifedipine group was 2.02. On comparison of the birth weight between the two groups, mean birth weight was 2.102 ± 0.54 kg in the Labetalol group and 2.25 ± 0.68 kg in the Nifedipine group, which was statistically not significant (P=0.082). Incidence of perinatal mortality was 4% in our study. Perinatal outcome was poor in 6% of babies in nifedipine group and 2% of babies in labetalol group.

**Table 7: Comparison of various variables between two groups**

| Variables | Group | N | Minimum | Maximum | Mean | S.D | P value |
|---|---|---|---|---|---|---|---|
| Time In Minutes To Achieve Target Bp | Intravenous Labetalol | 50 | 28 | 75 | 51.50 | 11.852 | 0.358 |
| | Nifedipine | 50 | 35 | 61 | 48 | 6.25 | |
| No. of Doses to Achieve Target Bp | Intravenous Labetalol | 50 | 1 | 3 | 2.08 | 0.258 | 0.421 |
| | Nifedipine | 50 | 1 | 3 | 2.02 | 0.425 | |
| Wt. of baby in (Kgs) | Intravenous Labetalol | 50 | 1.8 | 4.1 | 2.102 | 0.5440 | 0.082 |
| | Nifedipine | 50 | 1.2 | 3.6 | 2.256 | 0.685 | |

| PERINATAL OUTCOME | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | GROUP A Labetalol (n=50) | | GROUP B Nifedipine (n=50) | | |
| | | | Count | % | Count | % | Total (%) |
| Outcome | Bad | 50 | 1 | 2 | 3 | 6 | 4 (4) |
| | Good | 50 | 49 | 98 | 47 | 94 | 96 (96) |
| p=0.002* | | | | | | | |

## DISCUSSION

Hypertensive emergency in pregnancy is associated with a considerable morbidity and mortality in both maternal and neonatal populations. Hypertension remains the most commonly encountered medical condition in pregnant women. Various etiological theories for the pregnancy induced hypertension has been proposed. The common pathophysiological changes seen are imbalance between vasoconstrictor thromboxane A2 and vasodilator prostacyclin resulting in generalized vasospasm. This leads to endothelial damage resulting in release of vasoactive substances. The primary aim is to reduce the dangerously elevated blood pressure and ameliorate the severity of the disease.

When base line characters of Pre-eclampsia patients were analyzed, there was no significant difference in ages of the recruited patients in both the groups. The mean age in labetalol and nifedipine groups was 22.61 and 23.02 years respectively which was similar to the findings of study done by Sahai R et al[11] who reported mean age in Labetalol and nifedipine groups as 22.90 & 23.43 years. The majority of the patients in our study had an age group belonging to the category of 21 to 29 years which was contradictory to the study results of Subhedar V et al[12] who reported majority of patients in age group of 15-24 years.

Our study results showed that majority (42%) of the patients enrolled in the study were of primigravida which was contradictory to the study findings of hospital based studies of Prakash et al.[13] in which majority (57%) of patients were primigravida. In the present study, 46% of patients in Labetalol group and 38% of patients in Nifedipine group were primigravida. An earlier study by Duckitt et al also concluded primiparity as one of the risk factors for preeclampsia.[14]

On comparing gestational age in our study, amongst 3 of the recruited patients, 2 in Labetalol group and 1 in Nifedipine group had early onset disease at gestational age less than 24 weeks. The majority of the patients had gestational age of 34 to 36 weeks constituting 46% on the whole with 44% and 48% respectively in Labetalol group and Nifedipine group which was contradictory to the findings of Bhushan S et al[15] who reported majority of patients had gestational age of 38 to 39 weeks. However our study results was almost similar to the findings of Sahai R et al[11] who reported mean gestational age group as 37.4 weeks.

On analyzing body mass index, our study reports showed that 41 patients had a 25 to 29.99 kg/m2 body mass index while 59 patients had a body mass index exceeding 30 belonging to the category obesity. Not much of study has reported BMI in the literature. The progressive risk of preeclampsia in obese is elucidated in the study by Sibai and colleagues.[16] The risk is said to be increased by 13.3% in women with body mass index more than 35 kg/m2.

In our study baseline systolic blood pressure of the patients recruited in both the groups did not differ significantly. The mean systolic blood pressure in intravenous labetalol group was 169 mm Hg whereas it was 173 mm Hg in oral nifedipine group. 50% of patients in labetalol group had a blood pressure range of 160 to 169 mm Hg while 46% of patients in nifedipine group had a blood pressure range of 170 to 179 mm Hg. These findings were in accordance with the study result of Raheem et al[17] who reported mean systolic BP as 175 (170-180) mm of Hg in Nifedipine group and 170 (165-180) mm of Hg in Labetalol group with 'P value 0.25. However our study results was contradictory to the findings of Sahai R et al[11] who reported mean SBP in labetalol group was 184.67 mm Hg whereas it was 182.40 mm Hg in oral nifedipine group. According to the Cochrane database on review of drugs, the utility of the antihypertensive drug should be based on the experience of the clinician with respect to its utility and adverse effects.[18]

Our study reports showed that, baseline diastolic blood pressure did

not vary significantly. The mean of the baseline diastolic blood pressure were 109 mm Hg and 112 mm Hg in the Labetalol group and Nifedipine group, respectively. 58% and 62% in Labetalol group and Nifedipine group had diastolic blood pressure more than 110 mm Hg. These findings were contradictory to the findings of Sahai R et al[11] who reported mean DBP in labetalol group was 114.87 mm Hg whereas it was 116.07 mm Hg in oral nifedipine group.

In present study on comparison of time taken to control BP between two groups, i.e. to achieve BP 150/100mm of Hg, the mean time required were 51.50 ± 11.85 mins in the Labetalol groups and 48.0 ± 6.25 minutes in the Nifedipine group with a 'P' value of 0.358.These findings were comparable with the study results of Soujanya Sukhavasi et al.[19] Similarly on comparison of no. of doses of drugs required to control BP between two groups it was observed that most of the patients were controlled by two doses of each drug. Mean number of doses required in IV labetalol group 2.08 and in nifedipine group was 2.02. On comparison of the birth weight between the two groups. Mean birth weight was 2.102 ± 0.54 kg in the Labetalol group and 2.25 ± 0.68 kg in the Nifedipine group, which was statistically not significant (P=0.082). These findings were comparable with the study results of Soujanya Sukhavasi et al.[19]

Incidence of perinatal mortality was 4% in our study. Perinatal outcome was poor in 6% of babies in nifedipine group and 2% of babies in labetalol group which was contradictory to the finding of Soujanya Sukhavasi et al[19] who reported 4% perinatal mortality in their study.

## CONCLUSION

Management of severe preeclampsia is in the control of blood pressure, prevention of complications, fetal surveillance and expedition of delivery if indicated. In the present study, the trend in reduction of blood pressure in patients with sustained severe hypertension with the use of intravenous Labetalol and Nifedipine was compared.

Both oral nifedipine and intravenous Labetalol were equally effective in controlling blood pressure. Both drugs showed mo or mild adverse effects in mother and baby. However, Nifedipine is cheaper and convenient to administer. Therefore it is of importance in low resource settings. Intravenous Labetalol is important in patients who are unable to tae medicine orally. Both oral nifedipine and intravenous Labetalol are equally efficacious in controlling hypertension in pre-eclampsia / eclampsia. In conclusion, both intravenous Labetalol and oral nifedipine are equally efficacious and can be used as first line drugs for the use in blood pressure control of hypertensive emergency of pregnancy.

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**Ethical approval:** The study was approved by the Institutional ethics committee

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