**Original Research Article**

# A study of oral Nifedipine and intravenous Labetalol in severe hypertension in pregnancy at teaching hospital

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## Abstract

**Background:** Hypertensive disorders of pregnancy, including preeclampsia, complicate up to 10% of pregnancies worldwide, constituting one of the greatest causes of maternal and perinatal morbidity and mortality worldwide.

**Aim:** To compare intravenous Labetalol with oral Nifedipine in their rapidity to control hypertensive emergencies of pregnancy.

**Materials and methods:** Pregnant woman with severe gestational hypertension ≥ 160/110 mm of Hg were randomized to receive intravenous Labetalol injection (in an escalating dose regimen of 20, 40, 80, 80 and 80 mg) or Nifedipine (10mg tab orally upto 5 doses ) until the target blood pressure of 150/90mm of Hg was achieved. Crossover treatment was effected if the initial treatment regimen was unsuccessful.

**Results:** Mean time required 47 ± 14 mins in the Labetalol groups and 45 ± 15minutes in the Nifedipine group. This comparison showed no difference in the two groups with a 'P' value of >0.05. The mean amount of drugs required to achieve BP 150/90mm of Hg were 96 ± 38in the Labetalol group and 23 ± 13mg in the Nifedipine group. And this comparison showed no difference statistically with a 'P' value of >0.05. Most of the patients were controlled by 2 doses of each drug, 56% in the Labetalol group and 62% in the Nifedipine group. 12% and 14% in the Labetalol and Nifedipine group respectively were not controlled by 5 doses of either drug and required crossover drug therapy. Most of the patients were controlled by two doses of each drug, 50% in the Labetalol group and 60% in the Nifedipine group. 12.5% and 17.5% in the Labetalol & Nifedipine group respectively were not controlled by 5 doses of either drug andrequires crossover drug therapy.

**Conclusions:** Labetalol is both effective and safe in severe HTN.ACOG recommends labetalol as an appropriate first line treatment in severe HTN in pregnancy.

**Key words**

Hypertension in Pregnancy, Severe hypertension, Intravenous Labetalol.

## Introduction

Hypertensive disorders are the most common medical complications of pregnancy and are an important cause of maternal and perinatal morbidity and mortality worldwide [1]. Hypertension in pregnancy is still a leading cause of maternal and perinatal morbidity and mortality. Incidence is as high as 10-15% with estimated 50,000-60,000 preeclampsia-related deaths per year worldwide. For every preeclampsia-related death that occurs in the United States, there are probably 50-100 other women who experience "near miss" significant maternal morbidity. Early diagnosis and timely intervention prevents grave complications. Hypertension is considered severe if there is sustained elevation of systolic pressure to160mmhg and diastolic pressure to110 mmHg for at least 6hrs .Severe hypertension in pregnancy should be treated promptly to prevent eclampsia, cerebrovascular accident, congestive cardiac failure, pulmonary edema and placental abruption to decrease maternal and perinatal morbidity and mortality. Controlling blood pressure is the optimal intervention to prevent deaths due to stroke in women with preeclampsia Acute-onset, severe systolic hypertension (greater than or equal to 160 mm Hg); severe diastolic hypertension (greater than or equal to 110 mm Hg); or both can occur in the antepartum, intrapartum or postpartum period. Intravenous (IV) labetalol and hydralazine have long been considered first-line medications for the management of acute-onset, severe hypertension in pregnant women and women in the postpartum period.

Labetalol is a non-selective Beta-Blocker and Postsynaptic alpha1 adrenergic Blocker. The ratio of Alpha to Beta blockage is 1:3 and 1:7 with oral and IV administration respectively. It slows heart rate and decreases systemic vascular resistance. Shows dose related fall in blood pressure without reflex tachycardia. Increase in exercise induced BP and heart rate are blunted. Elevated levels of plasma renins are reduced. Metabolism is mainly through conjugation to glucuronide metabolites. Excreted in urine and via bile in feces.55%-60% appears in urine unchanged or as a conjugate within 1$^{st}$24hours.Crosses placental barrier in humans. Negligible amounts crossed BBB in animal studies. As 50% is protein bound, <1% is removed by either peritoneal or hemodialysis. It is available as100mg tab, given as100mg bid to a max of 2,400mg/day. Injectable preparation is available as 2ml ampoule (5mg/ml).It is given intermittently as 0.25mg/kg slowly over 2min as IV bolus repeated at 10-15 min intervals at 0.5 mg/kg till baseline blood pressure is achieved and up to a max of 300mg.

Can also be given as slow continuous infusion diluted with any of the IV fluids -40ml in 160ml such that 200ml contains 200mg or 1mg/ml administered at a rate of 2ml/2mg/min or 40ml/250ml fluid=200mg in250ml=2mg/3ml given at a rate of 3ml/2mg / min. Woman should be hospitalized and kept in supine position for 3hours.Rate of infusion is adjusted according to response using a graduated burette or an infusion pump till satisfactory response is achieved and then switched over to oral preparation. Half life of IV preparation is 5-6hours and of oral is 6-8hours.Total body clearance is 33ml/min/kg and not altered with impaired hepatic or renal function. Bioavailability is increased in hepatic impairment due to decreased first pass metabolism.

Blood pressure and pulse rate are monitored before and after giving the dose. Look for any

symptoms suggestive of side effects. Common side effects are postural hypotension, fatigue, headache dizziness nausea, vomiting, nasal stuffiness, flushing of skin and tingling of scalp etc. Use with caution in patients with asthma, bronchitis, diabetes mellitus, hepatic or renal impairment and in hyperthyroidism. Routine laboratory tests are not required before or after IV Labetalol .It can be used with other antihypertensive drugs should be used with caution with frusemide [1].

A metaanalysis of randomized clinical trials using Hydralazine for the treatment of severe hypertension in pregnancy concluded that the evidence does not support the use of these agents as first line drug when compared with Labetalol and Nifedipine [2]. Hence, the aim of the present study is to compare the two most commonly used drug in India, i.e. oral Nifedipine and IV Labetalol in terms of efficacy, time required and doses required to achieve desired level of blood pressure, safety profile and adverse effect of the drug and also to observe the fetomaternal outcomes.

## Materials and methods

This hospital based prospective randomized comparative study was carried out in the department of Obstetrics from February 2013 to March 2014 in one year period in 80 pregnant women with severe hypertension. The study protocol was approved by ethical committee of the institution and the written informed consent was taken from all the study participants.

Inclusion criteria for the study were patients with systolic BP ≥ 160mm of Hg and diastolic BP ≥ 110mm of Hg, proteinuria >300mg / 24 hrs urine or +1 or greater in random urine dipstick, and the gestational age > 34 weeks up to 41 weeks. But the patients of eclampsia, known heart disease, DM or other medical disorders, systolic BP < 160mm of Hg and diastolic BP <110 mmHg absence of significant proteinuria and gestational age< 34 weeks and more than 41 weeks were excluded from study population.

In this study 100 mothers with BP ≥ 160/110mm of Hg and proteiuria+1 or greater in random urine dipstick were randomly allocated by computer generated numbers into two groups (Group A and Group B), 40 in each group.

In group L Labetalol injection 20mg was given intravenously and was repeated at 20 mins interval in an escalating dose regimen of 40, 80, 80 and 80 mg up to maximum of 300 mg to achieve the target blood pressure.

In Group N Nifedipine 10 mg was given orally 20 mins interval up to a maximum of 5 doses i.e. 50 mg.

The target BP to be achieved was 150/90 mm of Hg and at this point study regimen was stopped. After the successful control of BP further antihypertensive was given orally as chosen by provider. The time interval and doses of drugs required to reach the target BP was noted by the two drugs separately. Adverse effect of the drugs if any was detected carefully and treated accordingly. It was also to be noted if any additional drugs or crossover of drug was required if the BP was not controlled with study regimen. The primary outcome was the time interval required to achieve the targeted BP i.e. systolic BP of ≤ 150mm of Hg and diastolic BP of ≤ 90mm of Hg. Secondary outcome analyzed included agent failure, maternal adverse effects like eclampsia, renal failure, stroke, and heart failure. Additionally, neonatal outcomes like low birth weight, low apgar score and neonatal hyper bilirubinemia and NICU admission were analysed as secondary outcomes.

Data was entered into SPSS. Analysis was based on the intention to treat. All tests were two sided and P < 0.05 was considered significant. Participants were analyzed on an intention-to-treat basis.

## Results

Most of the patients were aged between 19-35 years. Maximum patients of severe pre-

eclampsia were primigravida in both groups, 50% in the Labetalol group and 52.5% in the Nifedipine group. Most patients with pre-eclampsia belonged to 36-37 weeks of gestational age, 82.5% in the Labetalol group and 87.5% in the Nifedipine group. A significant higher incidence of vaginal delivery was found in the Labetalol and Nifedipine group as 45% and 47.5%. Cesareans section rate was 55% and 52.5% in the Labetalol and Nifedipine group respectively (**Table – 1**).

**Table - 1:** Comparison of Demographic Distribution of the two groups.

| **Age in years** | **Group-L(N=40)** | | **Group-N (N=40)** | | **P-Value** |
|---|---|---|---|---|---|
| 19-23 | 10 | 25 | 11 | 27.5 | >0.05 |
| 24-28 | 13 | 32.5 | 12 | 30 | |
| 29-33 | 12 | 30 | 10 | 25 | |
| 33-35 | 5 | 12.5 | 7 | 17.5 | |
| **Gravida** | | | | | |
| Primi | 20 | 50 | 21 | 52.5 | >0.05 |
| G2 | 12 | 30 | 10 | 25 | |
| G3 | 6 | 15 | 8 | 20 | |
| >G3 | 2 | 5 | 1 | 2.5 | |
| **Gestational Age in weeks** | | | | | |
| 36-37 | 33 | 82.5 | 35 | 87.5 | >0.05 |
| 38-39 | 4 | 10 | 3 | 7.5 | |
| > 40 | 3 | 7.5 | 2 | 2.5 | |
| **Mode of delivery** | | | | | |
| Vaginal | 18 | 45 | 19 | 47.5 | >0.05 |
| LSCS | 22 | 55 | 21 | 52.5 | |

**Figure - 1:** Comparison between Systolic and Diastolic BP of the two groups.

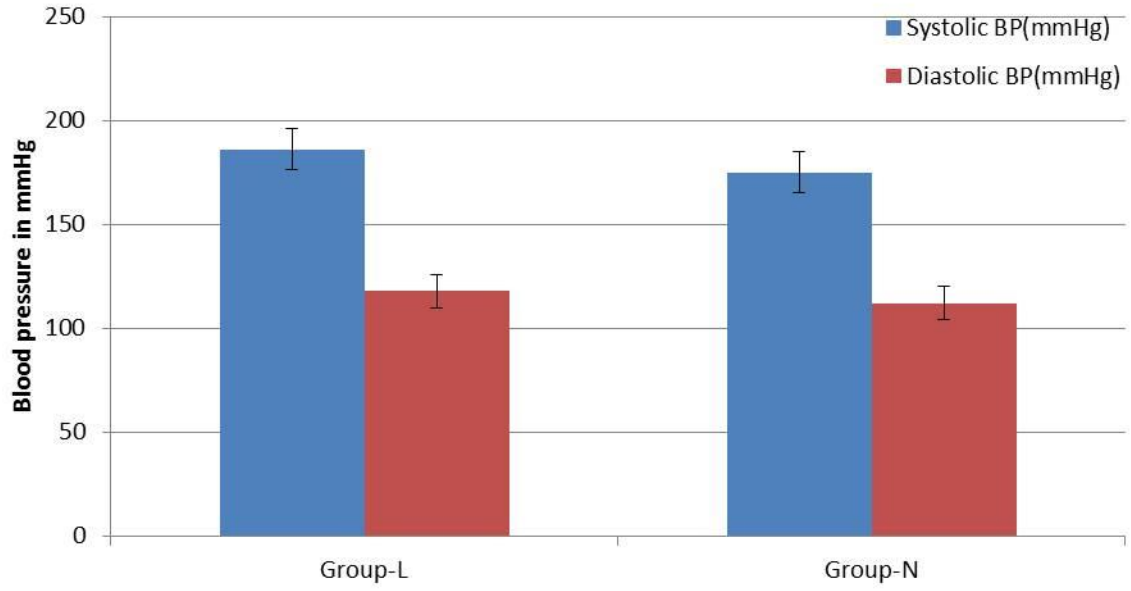

**Table - 2:** Time taken and total antihypertensive doses required to control BP between two groups.

| Variables | Group-L | Group-N | p-Value |
|---|---|---|---|
| Time taken (in mins) | 47 ± 14 | 45 ± 15 | >0.05 |
| Total antihypertensive doses (mg) requires to achieve BP 150/90mm of Hg | 96 ± 38 | 23 ± 13 | >0.05 |

**Table - 3:** Comparison of Number of doses of drugs required to control BP and requiring crossover treatment to control BP between two groups.

| Doses | Group-L | | Group-N | |
|---|---|---|---|---|
| 1 | 8 | 20 | 5 | 12.5 |
| 2 | 20 | 50 | 24 | 60 |
| 3 | 4 | 10 | 2 | 5 |
| 4 | 3 | 7.5 | 1 | 2.5 |
| 5 | 0 | 0 | 1 | 2.5 |
| Crossover | 5 | 12.5 | 7 | 17.5 |
| Total | 40 | | 40 | |

**Table - 4:** Comparison of adverse effects of drugs between two group.

| Adverse effects | Group-L | Group-N |
|---|---|---|
| Nausea and vomiting | 0 | 0 |
| Postural hypotension | 0 | 3 |
| Drowsiness | 0 | 2 |
| Headache | 2 | 0 |
| Depression | 0 | 0 |
| Shortness of breath | 0 | 0 |
| Hypersensitivity | 0 | 0 |
| Total | 2 | 5 |

**Table - 5:** Comparison if Neonatal Outcome between two groups.

| Neonatal Outcome | Group-L | Group-N | P-Value |
|---|---|---|---|
| Birth weight in kg | 2.5 ± 0.51 | 2.4 ± 0.6 | 0.07 |
| 5 min Apgarscore>7 | 31 (77.5%) | 30 (75%) | 0.85 |
| Hyperbilirubinaemia | 4 (10%) | 3 (7.5%) | 0.95 |
| IUGR | 6(15%) | 4(10%) | |
| Perinatal | 1 (2%) | 1 (2%) | |

Mean SBP was 185 ± 10 mm of Hg in the Labetalol group and 173± 10 mm of Hg in the Nifedipine group, which was statically not significant as 'P' value was 0.669. Mean diastolic BP was 119 ± 8 mm of Hg in the Labetalol group and 110 ± 8mm of Hg in the Nifedipine group which was also statistically insignificant and 'P value was 0.745 (**Figure – 1**).

The mean time required 47 ± 14 mins in the Labetalol groups and 45 ± 15minutes in the

Nifedipine group. This comparison showed no difference in the two groups with a 'P' value of >0.05. The mean amount of drugs required to achieve BP 150/90mm of Hg were 96 ± 38in the Labetalol group and 23 ± 13mg in the Nifedipine group. And this comparison showed no difference statistically with a 'P' value of >0.05 (**Table – 2**).

Most of the patients were controlled by 2 doses of each drug, 56% in the lebetalol group and 62% in the Nifedipine group. 12% and 14% in the Labetalol and Nifedipine group respectively were not controlled by 5 doses of either drug and required crossover drug therapy.

Most of the patients were controlled by two doses of each drug, 50% in the Labetalol group and 60% in the Nifedipine group. 12.5% and 17.5% in the Labetalol and Nifedipine group respectively were not controlled by 5 doses of either drug andrequires crossover drug therapy (**Table – 3**).

5% patients had headache in the Labetalol group. In the Nifedipine group 7.5% of the patients had postural hypotensive, 5% of them had drowsiness (**Table – 4**).

Mean birth weight 2.5 ± 0.51kg in the Labetalol group and 2.4 ± 0.6 kg in the Nifedipine group, which was statistically not significant. On measuring and comparing the 5 minsAPGAR score most of the babies having 5 mins APGAR score greater than 7 i.e. 77.5% in the Labetalol group and 75% in the Nifedipine. Hyperbilirubinaemia were 10% to 7.5% in the Labetalol group and Nifedipine group respectively. IUGR neonates were 15% and 10% in the Labetalol and Nifedipine group respectively. There was 1 perinatal death in each group (**Table – 5**).

## Discussion

Two thirds of the maternal deaths in the most recent *Confidential Enquiries* report from the United Kingdom for 2003–2005 resulted from either cerebral hemorrhage or infarction. The degree of systolic hypertension (as opposed to the level of diastolic hypertension or relative increase or rate of increase of mean arterial pressure from baseline levels) may be the most important predictor of cerebral injury and infarction. Thus, systolic blood pressure (BP) of 160 mm Hg or greater widely is included as part of the definition of severe hypertension in pregnant women or women in the postpartum period. Pregnant women or women in the postpartum period with acute-onset, severe systolic hypertension; severe diastolic hypertension; or both require antihypertensive therapy. The goal is not to normalize BP, but to achieve a range of 140–150/90–100 mm Hg in order to prevent repeated, prolonged exposure of the patient to severe systolic hypertension, with subsequent loss of cerebral vasculature autoregulation. When this happens, maternal stabilization should occur before delivery, even in urgent circumstances [3].

In our study mean time required to achieve target BP were 47 ± 14 mins in the Labetalol groups and 45 ± 15minutes in the Nifedipine group with the 'P' value of 0.5 which is in aggrement with. Swapan Das, et al. [4]. In the study conducted by Raheem, et al. [5] results showed that the median time taken to achieve target BP was 30 mins (interquartile range 22.5 to 67.5 mins) versus 45 mins (IQR 30-60 min) for Nifedipine and Labetalol respectively (P=0.59).

Systolic BP was 185 ± 10 mm of Hg in the Labetalol group & 173± 10 mm of Hg in the Nifedipine group, which was statically not significant as 'P' value was 0.669. While in the study of Raheem, et al. [5]; the mean systolic BP was 175 (170-180) mm of Hg in Nifedipine group and 170 (165-180) mm of Hg in Labetalol group with 'P value 0.25. As per Swapan Das, et al. [4]; it is systolic BP was 186.2 ± 12 m of Hg in the Labetalol group and 175 ± 12 mm of Hg in the Nifedipine group.

In our present study, diastolic BP was 119 ± 8 mm of Hg in the Labetalol group and 110 ± 8mm

of Hg in the Nifedipine group which was also statistically insignificant and 'P value was 0.745. Raheem, et al. [5] showed that the man diastolic BP was 110 (110-116) mm of Hg in Nifedipine group and 108 (100-112) mm of Hg in Labetalol group with a P value of 0.012. Swapan Das, et al. [4] showed diastolic BP was 118.11 ± 8 mm of Hg in the Labetalol group and 112 ± 8 mm of Hg in the Nifedipine group.

In our present study most of the patients were controlled by two doses of each drug, 56% in the Labetalol group and 62% in the Nifedipine group which is coincident with Swapan Das, et al. [4] study. As per study done by Raheem, et al. [5], average number of total antihypertensive doses to achieve BP ≤ 150/100 mm of Hg were two (1.5-4.5) in the Nifedipine group, whereas three (2-4) in Labetalol group as compared to two doses for both groups in our study. Our study showed that 12% and 14% of patients in the Labetalol and Nifedipine group respectively required crossover therapy, whereas in the study of Raheem, et al. [5] 20% of patients in each group required crossover therapy.

In our study the mean birth weight was 2.5 ± 0.51kg in the Labetalol group and 2.4 ± 0.6 kg in the Nifedipine group, which was statistically not significant which agrees with Swapan Das, et al. [4]. In the study of Raheem, etal. [5] the average birth weight in both the group were 2.9 kg with an interquartile range of 2.2 – 3.1 kg in the Nifedipine group and 2.7 – 3.2 kg in the Labetalol group. Many others also studied on other anti hypertensives also [6-9].

As per NICE clinical guideline 107 - Hypertension in Pregnancy [10] the first line antihypertensive which can be used in severe pregnancy induced Hypertension are Labetalol (Oral / intravenous), Hydralezine (intravenous) or Nefidipine (oral). Of those we had chosen intravenous Labetalol and oral Nifedipine for controlling the blood pressure in severe pre-eclampsia.

## Conclusion

A hypertensive disorders of pregnancy is one of the life threatening complication encountered in obstetrics. Management of hypertension in pregnancy is a challenging task, because drastic reduction of BP leads to uteroplacental insufficiency and that may lead to intrauterine fetal death and continuation of pregnancy with severe hypertension leads to adverse feto-maternal outcome. Therefore, there is a need for an ideal antihypertensive agent for effective control of severe hypertension in pregnancy.

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