

## Comparative Study of Intravenous Labetalol and Oral Nifedipine for Control of Blood Pressure in Severe Preeclampsia.

Dr. Swapan Das<sup>1</sup>, Dr. Swagata Biswas<sup>2</sup>, Dr, Prakash Das<sup>2</sup>,  
Dr. Biswajit Mahapatra<sup>3</sup>.

<sup>1)</sup> Assistant Professor, Department of Obstetrics & Gynaecology, Bankura Sammilani Medical College,  
Bankura, West Bengal, India.

<sup>2)</sup> PGT, Department of Obstetrics & Gynaecology, Bankura Sammilani Medical College, Bankura, West Bengal,  
India.

<sup>3)</sup> RMO cum Clinical Tutor, Department of Obstetrics & Gynaecology, Bankura Sammilani Medical College,  
Bankura, West Bengal, India.

### Abstract

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

**Design:** A hospital based prospective randomized interventional comparative study.

**Methods:** Pregnant woman with severe gestational hypertension  $\geq 160/110$  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:** The meantime required to achieve target blood pressure of 150/90mm of Hg were  $47.2 \pm 13.5$  mins in the Labetalol group and  $45.6 \pm 14.5$  mins in the Nifedipine group. ( $P=0.511$ ). 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.

**Conclusion:** Intravenous Labetalol and oral Nifedipine regimen are equally effective and well tolerated when used for the rapid control of the blood pressure in severe hypertension in pregnancy.

**Keywords:** Hypertension, pregnancy, Labetalol, Nifedipine, preeclampsia.

### I. Introduction

Severe pregnancy induced hypertension (PIH) is a disorder in pregnancy which is characterized by a systolic blood pressure of  $\geq 160$  mm of Hg and a diastolic blood pressure of  $\geq 110$  mm of Hg. Severe preeclampsia is characterised by PIH superimposed with proteinuria  $> 300$  mg per 24 hrs urine.<sup>1</sup>

Hypertensive disorders represents the most common medical complications of pregnancy with a reported incidence between 5-10%<sup>1</sup> and this hypertension which develops denovo in pregnancy appears to be unique to human.<sup>2</sup>

These disorders are a major cause of maternal and perinatal mortality and morbidity worldwide.<sup>1</sup> It is associated with 30% of all maternal deaths and as much as 22% of all perinatal deaths.<sup>3</sup> It has been estimated by WHO (World Health Organization) that worldwide approximately 50,000 women will die each year from hypertensive disorders of pregnancy.<sup>4</sup>

Severe PIH requires prompt treatment because of risk of cardio-vascular accident, to prevent intracerebral haemorrhage, hypertensive encephalopathy and other target organ damage.<sup>5,6</sup> it also presents an increased risk of complication for the fetus including prematurity, low birth weight, NICU admission and even fetal death.<sup>6-8</sup>

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.<sup>9</sup>

The most commonly used hypertensive agents for hypertensive emergencies in pregnancy are Nifedipine, Labetalol and hydralazine. 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<sup>10</sup>. 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<sup>10</sup>.

A meta analysis 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.<sup>11</sup> 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.

## II. Methods

This hospital based prospective randomised interventional comparative study was carried out in the department of Obstetrics and Gynaecology of Bankura Sammilani Medical College and Hospital, Bankura from April, 2013 to March 2014. 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  $\geq$  160mm of Hg and diastolic BP  $\geq$  110mm of Hg, proteinuria  $>$ 300mg / 24 hrs urine or +1 or greater in random urine dipstick, and the gestational age  $>$  34 weeks upto 41 weeks. But the patients of eclampsia, known heart disease, DM or other medical disorders, systolic BP  $<$ 160mm of Hg and diastolic BP $<$ 110mm of Hg, absence of significant proteinuria ( $<$ 300 mg / 24 hrs of urine) and gestational age  $<$ 34 weeks and more than 41 weeks were excluded from study population.

In this study 100 mothers with BP  $\geq$  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), 50 in each group.

In group A 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 upto maximum of 300 mg to achieve the target blood pressure. In Group B Nifedipine 10 mg was given orally 20 mins interval upto 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  $\leq$  150mm of Hg and diastolic BP of  $\leq$  90mm of Hg. Secondary outcome analyzed included agent failure, maternal adverse effects like eclampsia, renal failure, stroke, heart failure. Additionally, neonatal outcomes like low birth weight, low apgarscore and neonatal hyper bilirubinemia and NICU admission were analysed as secondary outcomes.

Numerical data obtained were statistically analysed with suitable statistical software. Normally distributed continuous data analysed with student's 't'-test and non-normally distributed data with Mann Whitney U-test. Categorical variance was analysed with Fisher's exact test. All tests are two sided and  $P<$ 0.05 will be taken as the level of significance.

## III. Results :

**Table – 1** shows age distribution of patients of both groups. All the patients were aged between 19-35 yrs. In the Labetalol group 48% of the patients were between 25-29 years & in the Nifedipine group 42% of all the patients were between 25-29 years. The minimum age in both the group was 25.4 years.

**Table – 2** shows the gravida distribution of patients studied in each group with a range of primigravida to 4<sup>th</sup> gravid. Maximum patients of severe pre-eclampsia were primigravida in both the groups, 58% in the Labetalol group & 50% in the Nifedipine group.

**Table – 3** shows the gestational age at presentation in each group. Most patients with pre-eclampsia belonged to 38-40 weeks of gestational age , 80% in the Labetalol group & 84% in the Nifedipine group.

**Table – 4** shows the type of symptoms presented by the patients. Most of the patients presented with oedema only, 76% and 82% in the Labetalol & Nifedipine group respectively. Only few patients had impending signs, 12% and 8% in the Labetalol & Nifedipine group respectively. They were statistically similar in two groups within 'P' value of 0.739.

**Table – 5** shows comparison of systolic & diastolic BP of the two groups. Mean SBP was  $186.2 \pm 12$  mm of Hg in the Labetalol group &  $175 \pm 12$  mm of Hg in the Nifedipine group, which was statically not significant as 'P' value was 0.669.

Mean diastolic BP was  $118.11 \pm 8$  mm of Hg in the Labetalol group and  $112 \pm 8$  mm of Hg in the Nifedipine group which was also statistically insignificant and 'P' value was 0.745.

**Table – 6** shows comparison of No. of doses of drugs required to control BP between two groups and no. of patients requiring crossover treatment to control BP between two groups. Most of the patients were controlled by two doses of each drug, 56% in the Labetalol group and 62% in the Nifedipine group. 12% and 14% in the Labetalol & Nifedipine group respectively were not controlled by 5 doses of either drug & requires crossover drug therapy.

**Table – 7** shows comparison of time taken and total antihypertensive doses required to control BP between two groups, i.e. to achieve BP 150/90mm of Hg. The mean time required were  $47.2 \pm 13.5$  mins in the Labetalol groups and  $45.6 \pm 14.5$  minutes in the Nifedipine group. This comparison showed no difference in the two groups with a 'P' value of 0.511.

The mean amount of drugs required to achieve BP 150/90mm of Hg were  $96 \pm 37.8$  in the Labetalol group and  $22.8 \pm 12.9$ mg in the Nifedipine group. And this comparison showed no difference statistically with a 'P' value of 0.511.

**Table – 8** shows mode of delivery of the two groups. Spontaneous vaginal delivery was more in the Labetalol group i.e 28% when compared to the Nifedipine i.e 14%. A significant higher incidence of induction of labour was found in the Nifedipine group i.e. 32%. Caesareans section rate was 46% and 54% in the Labetalol and Nifedipine group respectively.

**Table - 9** shows the comparison of adverse effects of the drugs. 4% patients had headache in the Labetalol group. In the Nifedipine group 4% of the patients had postural hypotensive, 6% of them had drowsiness.

**Table – 10** shows the comparison of the birth weight between the two groups. Mean birth weight was  $2.48 \pm 0.54$  kg in the Labetalol group and  $2.43 \pm 0.59$  kg in the Nifedipine group, which was statistically not significant (P=0.0689).

**Table – 11** shows comparison of neonatal outcome between two groups. On measuring and comparing the 5 mins APGAR score most of the babies having 5 mins APGAR score greater than 7 i.e. 90% in the Labetalol group & 92% in the Nifedipine. The comparison was statistically similar within 'P' value of 0.847. Hyperbilirubinaemia were 6% to 8% in the Labetalol group and Nifedipine group respectively. IUGR neonates were 20% and 30% in the Labetalol and Nifedipine group respectively. There was 1 perinatal death in each group. The comparison was statistically insignificant with P value of 0.957.

#### IV. Discussion

In our present study the results indicate that both intravenous Labetalol and oral Nifedipine are equally efficacious having minimal side effects. There was a similar study conducted by Raheem IA et.al<sup>12</sup> in January 2012 with the similar objective of comparing oral Nifedipine with intravenous Labetalol in their rapidity to control hypertensive emergencies of pregnancy.

In our study the mean systolic BP was  $186.2 \pm 12$  mm of Hg in the Labetalol group and  $175 \pm 12$  mm of Hg in the Nifedipine group with a 'P' value of 0.669. While in the study of Raheem et.al<sup>12</sup> 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.

In our present study the mean diastolic BP was  $118.11 \pm 8$  mm of Hg in the Labetalol group and  $112 \pm 8$  mm of Hg in the Nifedipine group with the 'P' value was 0.745. Raheem et.al<sup>12</sup> showed that the mean 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.

In our study the mean time required to achieve target BP were  $47.2 \pm 13.5$  mins in the Labetalol group &  $45.6 \pm 14.5$  mins in the Nifedipine group with the 'P' value of 0.511. In the study conducted by Raheem et.al<sup>12</sup> 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 & Labetalol respectively (P=0.59).

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. As per study done by Raheem et.al<sup>12</sup>, average number of total antihypertensive doses to achieve BP  $\leq 150/100$  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<sup>12</sup> 20% of patients in each group required crossover therapy.

The present study showed that there was no significant difference in the mode of delivery between two groups with a 'P' value of 0.365. 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<sup>12</sup> on January, 2012.

In our study the mean birth weight was  $2.48 \pm 0.54$  kg in the Labetalol group and  $2.43 \pm 0.59$  kg in the Nifedipine group. In the study of Raheem et.al<sup>12</sup> 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.

The principal findings of Vermillion et.al<sup>13</sup> was that to achieve target blood pressure the oral Nefidipine is more rapidly effective and requires fewer drug doses compared with an intravenous Labetalol regimen. Patient receiving oral Nefidipine more rapidly achieved the therapeutic blood pressure goal. in  $25.0 \pm 13.6$  mins as compared with  $43.6 \pm 25.4$  mins in those receiving Labetalol (P=0.002).

The Nefidipine group also required significantly fewer doses ( $1.5 \pm 0.5$  vs  $2.5 \pm 1.5$ , P< 0.001) to reach the blood pressure goal. Vermillion's J drug regimen used higher oral Nefidipine dose (10mg initially, then 20mg for a further four doses, as required), while we used a flat 10mg oral Nifedipine dose throughout and an intravenous Labetalol regimen of 20,40,80,80 and 80 mg as required which is identical to our regimen.

The Cochrane review<sup>14</sup> on drugs for the treatment of very high blood pressure in pregnancy conclude that until & unless better evidence is available the choice of antihypertensive should depend on the clinician's experience & familiarity with a particular drug, and its adverse effects. And our study clearly indicates that both intravenous Labetalol and oral Nifedipine are equally efficacious in controlling high blood pressure in severe PIH with minimal side effects.

The results of the study conducted by Shekhar et.at<sup>15</sup> showed that the median time taken to achieve target blood pressure was 40 mins (interquartile range 20-60 mins) for Nifedipine and 60 mins (interquartile range 40-85 min) for Labetalol with a P value of 0.008. while in our study the mean time required  $47.2 \pm 13.5$  mins in the Labetalol group and  $45.6 \pm 14.5$  mins in the Nifedipine group. Shekhar et.al<sup>15</sup> concluded by their trial that oral Nifedipine had lowered blood pressure more quickly than that of intravenous Labetalol during hypertensive emergency in pregnancy which was different from our present study.

As per NICE clinical guideline 107 - Hypertension in Pregnancy<sup>16</sup> the first line antihypertensive which can be used in severe pregnancy induced Hypertension are Labetalol (Oral / intravenous), Hydralazine (intravenous) or Nefidipine (oral). Of those we had chosen intravenous Labetalol and oral Nifedipine for controlling the blood pressure in severe pre-eclampsia. The blood pressure targeted in our study was 150/90mm of Hg which is also in keeping with the recommendation given in the Cochrane Review prepared and maintained by the Cochrane Collaboration and published in the Cochrane Library 2013, Issue 7<sup>14</sup>.

## V. 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 & 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.

Our present study compares the efficacy of oral Nifedipine and IV Labetalol in reaching the therapeutic goal. From the results of our study we can well conclude that both the Labetalol & Nifedipine regimen are equally effective & well tolerated when used for the rapid control of blood pressure in severe hypertension in pregnancy. But Nifedipine may be preferable as it is a simple, flat dose and is an oral regimen.

## Acknowledgement

We thank the colleagues & staff of the department of Obstetrics & gynaecology, Bankura Sammilani Medical College & Hospital, Bankura, for their assistance in completing this study.

**Table – 1 : Comparison of Age Distribution of the two groups.**

Age	Labetalol		Nifedipine		X <sup>2</sup> =2.2183	P=0.329
	No	%	No	%		
19 - 24	22	44	20	40		
25 - 29	24	48	21	42		
30 - 35	4	8	9	18		
<b>Total</b>	<b>50</b>	<b>100</b>	<b>50</b>	<b>100</b>		

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

GRAVIDA	LABETALOL		NIFEDIPINE		x <sup>2</sup> =1.9886	P=0.574
	No	%	No	%		
Primi	29	58	25	50		
G <sub>2</sub>	12	24	15	30		
G <sub>3</sub>	5	10	8	16		
G <sub>4</sub>	4	8	2	4		
<b>Total</b>	<b>50</b>	<b>100</b>	<b>50</b>	<b>100</b>		

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

G A (WKS)	LABETALOL		NIFEDIPINE		x <sup>2</sup> =0.849	P=0.325
	No	%	No	%		
36-37	7	14	6	12		
38-40	40	80	42	84		
> 40	3	6	2	4		
<b>Total</b>	<b>50</b>	<b>100</b>	<b>50</b>	<b>100</b>		

**Table – 4 : Comparison of symptoms of the two groups.**

SYMPTOMS	LABETALOL		NIFEDIPINE		x <sup>2</sup> =0.6048	P=0.739
	No	%	No	%		
Odema	38	76	41	82		
Asymptomatic	6	12	5	10		
Impending Signs	6	12	4	8		
<b>Total</b>	<b>50</b>	<b>100</b>	<b>50</b>	<b>100</b>		

**Table – 5 : Comparison between Systolic and Diastolic BP of the two groups.**

Variables	Labetalol (n=50) Mean ± SD	Nifedipine (n=50) Mean ± SD	P value
Systolic BP (mm of Hg)	186.2 ± 12	175 ± 12	P = 0.669
Diastolic BP (mm of Hg)	118.11 ± 8	112 ± 8	P = 0.745

**Table – 6 : Comparison of No. of doses of drugs required to control BP between two groups & no. of patients requiring crossover treatment to control BP between two groups.**

doses	No. of	Labetalol		Nifedipine	
		No.	%	No.	%
1		9	18	10	20
2		28	56	31	62
3		5	10	1	2
4		2	4	1	2
5		0	0	0	0
Crossover		6	12	7	14
<b>Total</b>		<b>50</b>	<b>100</b>	<b>50</b>	<b>100</b>

**Table - 7 : Comparison of time taken and total antihypertensive doses required to control BP between two groups i.e. to achieve BP 150/90 mm of Hg.**

Variables	Labetalol (n=50) Mean ± SD	Nifedipine (n=50) Mean ± SD	P value
Time taken (in mins)	47.2 ± 13.5	45.6 ± 14.5	P = 0.511
Total antihypertensive doses (mg) requires to achieve BP 150/90mm of Hg	96 ± 37.8	22.8 ± 12.9	P = 0.511

**Table – 8 : Mode of Delivery of two groups**

Mode of delivery	Labetalol		Nifedipine	
	No.	%	No.	%
Vaginal	27	54	23	46
i) SVD	14		7	
ii) Induced VD	13		16	
LSCS	23	46	27	54
<b>Total</b>	<b>50</b>	<b>100</b>	<b>50</b>	<b>100</b>

**Table – 9 Comparison of adverse effects of drugs between two groups**

Adverse effects	Labetalol	Nifedipine
Postural hypotension	0	2
Drowsiness	0	3
Headache	2	0
Nausea	0	0
Depression	0	0
Shortness of breath	0	0
Hypersensitivity	0	0
<b>Total</b>	<b>2</b>	<b>5</b>

**Table – 10 : Comparison of birth weight between two groups.**

Neonatal outcome	Labetalol (n=50) Mean ± SD	Nifedipine (n=50) Mean ± SD	P value
Birth weight (kg)	2.48 ± 0.54	2.43 ± 0.59	0.0689

**Table – 11 : Comparison if Neonatal Outcome between two groups**

Variable	Labetalol (%) (n=50)	Nifedipine (%) (n=50)	P value
5 min Apgarscore >7	45 (90%)	46 (92%)	0.847
Hyperbilirubinaemia	3 (6%)	4 (8%)	0.957
IUGR	10 (20%)	15 (30%)	
Perinatal death	1 (2%)	1 (2%)	

### Reference

- [1]. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Pregnancy Hypertension. Text Book of Williams Obstetrics. 23<sup>rd</sup> Edition. 2010 New York, McGraw Hill. 706-757 pp.
- [2]. McCarthy FP, Kingdom JC, Kenny LC, et al. Placenta 2011; 32(6): 413-9.
- [3]. Fernando Arias, Shirish Daftary, Amarnath Bhide, "Practical guide to high risk pregnancy and delivery" 3<sup>rd</sup> edition 2007.
- [4]. Khan KS et al. Lancet 2006; 367: 1066-74.
- [5]. National Institute of Health and Clinical Excellence. (2010). Hypertension in Pregnancy: The management of hypertensive disorders during pregnancy. NICE clinical guidelines 107. [online] Available from [www.nice.org.uk/nicemedia/live/13098/50418](http://www.nice.org.uk/nicemedia/live/13098/50418). Pdf.
- [6]. Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Obstet Gynecol 2003; 101 (2):289-96.
- [7]. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqel H, et al. Am J Obstet Gynecol. 2006 Apr; 194(4):921-31.
- [8]. Sibai GM AM J Obstet Gynecol 2003; 102: 181- 92.
- [9]. McDonald SD, Malinowski A, Zhou Q, et al. Am Heart J 2008; 156(5): 918-30.
- [10]. Rezaei Z, Rahimi FS, Pourmojib M, Youefzadeh-Fard Y, Motevalian M, et al. Acta Medica Iranica 2011; 49: 701-5.
- [11]. Magee LA, Cham C, Waterman EJ, et al. BMJ 2003; 327(7421): 955-60.
- [12]. Raheem IA, Saaid R, Omar SZ, Tan PC. Br J Obstet Gynaecol 2012; 119: 78-85.
- [13]. Vermillion ST, Scardo JA Am J ObstetGynecol. 1999; 181: 858-61.
- [14]. Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy (review). The Cochrane Collaboration, 2013, Issue – 7.
- [15]. Shekhar S, Sharma C, Thakur S, Verma S. OralNifedipine or Intravenous Labetalol for hypertensive emergency in pregnancy : a randomized controlled trial. Obstet Gynecol. 2013 Nov. 122(5) 1057-63.
- [16]. NICE clinical guideline 107 - Hypertension in pregnancy : the management of hypertensive disorders during pregnancy. Issued August 2010 last modified : January 2011.