Observational Study

Evaluation of antihypertensive efficacy of intravenous labetalol versus oral nifedipine in preeclamptic hypertensive emergency : a randomised controlled trial

Madhusudan Haldar[1], Shamim Khandaker[2], Dip Sarkar[3]

To compare oral nifedipine with intravenous labetalol in their rapidity to control preeclamptic hypertensive emergencies. The primary outcome is number of doses required to achieve a target blood pressure of <150/100 mmHg. This is a double blinded randomised controlled trial. Patients are randomised to receive nifedipine (10 mg tablet initially followed by 20mg tablet every 20 minutes, orally, up to five doses) and intravenous placebo saline injection or intravenous labetalol injection (in an escalating dose regimen of 20, 40, 80, 80 and 80 mg) and a placebo tablet every 20 minutes until the target blood pressure of <150/100 mmHg is achieved. Crossover treatment is effected if the initial treatment regimen is unsuccessful. In this study 32 patients have been included in labetalol group and 28 patients in nifedipine group. Labetalol controls systolic BP in range of 170-180 mm Hg with fewer doses than nifedipine (70% with 1st dose by labetalol vs 33% with 1st dose by nifedipine). Similarly, labetalol controls diastolic BP in range of 110-120 mm Hg with fewer doses than nifedipine (76% with 1st dose by labetalol vs 47% with 1st dose by nifedipine). Overall, control of BP achieved with single dose in 78% of cases in labetalol group vs 39% of cases in nifedipine group. To compare with nifedipine, labetalol group has carried a better control of hypertension. Both systolic and diastolic blood pressure is controlled with fewer doses with labetalol.

[*J Indian Med Assoc* 2018; **116:** 19-21]

Key words **: Hypertension, labetalol, nifedipine, pre-eclampsia, pregnancy.**

Some form of hypertension occurs in approximately 15-20% of pregnancies[1]. According to World Health organization, hypertension disease during pregnancy is a major cause of perinatal mortality and morbidity. The concept of hypertension is artificial, with an arbitrary threshold used to divide a continuously distributed variable into two artifactual categories of normotension and hypertension. The conventional dividing line is 140/90 mmHg[2]. Use of diastolic blood pressure of 90 mm Hg or greater is advantageous as readings above this level are beyond 2 standard divisions in normal pregnant women and perinatal mortality significantly increased above a diastolic BP of 85 mm Hg. Severe hypertension in pregnancy is defined as systolic BP $\geq$ 170 mm Hg and/or diastolic BP $\geq$ 110 mm Hg[3]. This represents the level of BP above which cerebral autoregulation is overcome in normotensive individuals with the risk of cerebral haemorrhage and hypertensive encephalopathy. Both systolic and diastolic hypertension increases the risk of cerebral hemorrhage[4].

Department of Obstetrics & Gynaecology, North Bengal Medical College, Sushrutanagar, Darjeeling 734011

[1]MD (Obstet & Gynaecol) (JIPMER), Assistant Professor

[2]MS (Obstet & Gynaecol), Medical College and Hosptial, Kolkata 700073, RMO *cum* Clinical Tutor, North Bengal Medical College, Sushrutanagar, Darjeeling 734011

[3]MBBS (Obstet & Gynaecol), Postgraduate Trainee, North Bengal Medical College, Sushrutanagar, Darjeeling 734011

Severe hypertension should be stabilised prior to delivery by labour induction or caesarean section to avoid either fluctuations or exacerbations of blood pressure during labour or anaesthesia. So prompt and effective blood pressure control will allow the definitive treatment of delivery of the in cases of severe hypertension in late pregnancy.

To our knowledge, no study comparing labetalol and nifedipine in hypertensive emergencies of pregnancy has been undertaken on Indian population. The aim of the study is to compare oral nifedipine with intravenous labetalol in their rapidity to control preeclamptic hypertensive emergencies.

Methodology :

We performed a double-blind randomised trial in hypertensive emergencies in preeclampsia. This study is carried out in the department of Obstetrics and Gynaecology at North Bengal Medical College from 2010 February to March 2011.

Pregnant women at >32 weeks of gestation with sustained severe hypertension were approached by their provider for enrolment in the trial. Sustained severe hypertension in this study has been defined as a systolic BP = 170 mm Hg or diastolic BP $\geq$ 110 mm Hg on two occasions at least 4 hours apart. The latest blood pressure reading prior to enrolment must fulfil the criteria of severe hypertension. Other inclusion criteria were medical decision to rapidly control blood pressure and maternal heart

rate >60 and <120 bpm. Women with a history of cardiac arrhythmia, heart failure, asthma, allergy to either nifedipine or labetalol, non-pregnancy related hypertension and any antihypertensive treatment in the preceding 72 hours were excluded from the study.

Women who agreed to participate provided written informed consent. The study was approved by the medical ethics committee of the West Bengal University of health sciences.

To detect a 20% difference (power of the study 90%) in time interval to achieve therapeutic goal (reduction of risk) with α=0.05 (alpha error); it is determined to 60 patients would be needed for the study. The cases are studied alternatively in a random manner by coin toss method. Enrolled patients are randomised to receive either oral nifedipine with intravenous placebo containing 2 ml normal saline or intravenous labetalol with oral placebo tablet. Both the drugs are packed in a same colour packet. The on duty sisters give the medicines to the patients. Both the patients and on duty sister (who gives the medicine to the patients) are blinded to the randomisation.

Labetalol is given intravenously 20 mg over 2-3 minutes; repeat after every 20 minutes total upto 5 doses (20, 40, 80, 80, 80 mg) till therapeutic goal blood pressure achieved. Labetalol is available in 2 ml ampoule. After giving each dose, change in BP is recorded. Nifedipine is given orally 10 mg tablet followed by 20 mg tablet orally (maximum 5 doses) at 20 min interval until BP goal is achieved. Blinded crossover would occur if the therapeutic goal was not achieved after 5 doses.

BP is recorded with same instrument each time (digital sphygmomanometer) in semi recumbent position. The point of disappearance of sound (Korotkoff's sound V) is taken as diastolic blood pressure. Once blood pressure was <150/100 mmHg, no further trial medication is given.

After the successful control of blood pressure further antihypertensive therapy, as chosen by the provider, is typically started 2 hours after the last trial medication, and delivery of the baby as the definitive treatment for severe pregnancy-induced hypertension can be started for participants at or near term, as standard practice. Stabilised patients who are to be managed expectantly are discharged to the normal ward for further observation.

The primary outcome of the trial is the time taken to achieve the target systolic blood pressure of <150 mmHg and diastolic blood pressure of <100 mmHg (both targets had to be fulfilled). Secondary outcomes are total number of antihypertensive doses to achieve target blood pressure, systolic and diastolic blood pressure and maternal heart rate profile during the first hour, CTG abnormality, maternal hypotension (blood pressure <90/ 60 mmHg), the side-effects profile and perinatal outcomes.

Data was entered into spss 16 (SPSS Inc., Chicago, IL, USA). Normally distributed continuous data were analysed with the Student's t-test; non-normally distributed or ordinal data were analysed with the Mann–Whitney U-test. All tests were two sided and $P < 0.05$ was taken as the level of significance.

Results :

In this study 32 patients have been included in labetalol group and 28 patients in nifedipine group. Age distribution is as follows (Table 1). 75% of patients are primigravida in labetalol group and 78.5% of patients are primigravida in nifedipine group. 44% of patients are preterm in labetalol group and 61% of patients are preterm in nifedipine group.

Table 1 — *Age distribution*

Age in years	Labetalol group (N=32)		Nifedipine group(N=28)	
	No of cases	% of cases	No of cases	% of cases
16-20	16	50%	13	46%
21-25	11	34%	10	36%
26-30	4	12.5%	4	14%
31-35	1	3%	1	3.5%

Patients who received treatment are classified according to severity of blood pressure are as follows (Table 2 and 3). 31% of cases in labetalol group and 43% of cases of nifedipine group are in systolic BP range of 170-180 mm Hg. Similarly 90% of cases in labetalol group and 68% of cases in nifedipine group are in diastolic BP range of 110-120 mm Hg.

Table 2 — *Severity of Preeclampsia according to systolic BP*

SBP (mmHg)	Labetalol (N=13)	Nifedipine (N=17)
170-180	10	12
181-190	1	3
191-200	1	2
>200	1	0

Table 3 — *Severity of Preeclampsia according to diastolic BP*

DBP (mmHg)	Labetalol (N=30)	Nifedipine (N=21)
110-120	29	19
>121	1	2

Labetalol controls systolic BP in range of 170-180 mm Hg with fewer doses than nifedipine (70% with 1st dose by labetalol *versus* 33% with 1st dose by nifedipine). Similarly, labetalol controls diastolic BP in range of 110-120 mm Hg with fewer doses than nifedipine (76% with 1st dose by labetalol *versus* 47% with 1st dose by nifedipine).

Overall, control of BP achieved with single dose in 78% of cases in labetalol group *versus* 39% of cases in nifedipine group (Table 4).

Only one case complained of headache in labetalol group compared to 3 cases in nifedipine group. 4 and 2 cases of nifedipine group are complained of palpitation and reduced urine output compared to none in labetalol group. Overall, 93.75% cases in labetalol group has no side effect compared to 64.28% cases in nifedipine group (P=0.01).

Delivery by vaginal route in labetalol group is 68.7% and in nifedipine group is 57% (P=0.507). Birth weight <2.5 kgs are 50% in labetalol group and 46.4% in

nifedipine group (P=0.986). Birth asphyxia occurs in 21.5% of cases in labetalol group and in 32% of cases in nifedipine group (P=0.363). Perinatal mortality is 31 per 1000 live birth in labetalol group compared to 71 per 1000 live births in nifedipine group.

Table 4 — *Control of BP <150/100 mm Hg with single vs multiple doses*

Dose	Labetalol (N=32)	Nifedipine (N=28)
1st dose	25(78%)	11(39%)
2nd dose	7(22%)	12(43%)
3rd dose	0	5(18%)
Cross over	0	0

Conclusion :

The goal of treating hypertension is to reduce maternal risks; the agents selected must be efficacious and safe for the fetus. The Cochrane review concluded that until better evidence is available, the choice of antihypertensive for the treatment of very high blood pressure in pregnancy should depend on the clinician's experience with a particular drug and on known adverse effects[5]. We set a target blood pressure of =150/100 mmHg for our patients, with the dosing regimen to be stopped once the goal is achieved. This target blood pressure is in keeping with Sibai's suggestion to keep systolic blood pressure between 140 and 155 mmHg and diastolic blood pressure between 90 and 105 mmHg in severe pre-eclampsia[6]. In our study, intravenous labetalol is more efficacious (efficacy=0.989) than oral nifedipine after the 1st dose to control hypertensive emergency in cases of preeclampsia (79% vs 40%). Number needed to treat (NNT) is 3 ie, if 3 patients are treated with nifedipine, one will be benefitted if treated by labetalol. Rate of birth asphyxia and birth weight <2.5 kgs are marginally better in labetalol group although statistically not significant. Perinatal mortality rate (PMR) almost doubled in nifedipine group (71 *versus* 31 per 1000 live births) but larger study is needed.

The choice of proper antihypertensive in preeclamptic hypertensive emergency is ever changing. The finding of Vermillion *et al*[7]. is that to achieve target blood pressure the oral nifedipine regimen is more rapidly effective and requires fewer drug doses compared with an intravenous labetalol regimen. The study of Raheem *et al*[8]. concluded that Oral nifedipine and intravenous labetalol regimens are similarly effective in the acute control of severe hypertension in pregnancy. However, our study reveals that intravenous labetalol is more effective than oral nifedipine in hypertensive emergencies in preeclampsia. More such randomised controlled trails are needed to select proper antihypertensive for management of preeclamptic hypertensive emergencies.

Reference

1 The Guidelines subcommittee of the WHO/ISH Mild Hypertension Liaison Committee. 1999 World Health Organization D International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; **17:** 151-83.

2 The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1999; 2413-46.

3 Consensus report: National High Blood Pressure Education Programme Working Group Report on High Blood Pressure in pregnancy. *Am J Obstet Gynecol* 1990; **163:** 1689-712.

4 Buchbinder A, Sibai BM, Caritis S, Macpherson C, Hauth J, Lindheimer MD, *et al* — Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. *Am J Obstet Gynecol* 2002; **186:** 66-71.

5 Duley L, Henderson-Smart DJ, Meher S — Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev* 2006; **3:** CD001449.

6 Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003;102:181–92.

7 Vermillion ST, Scardo JA, Newman RB, Chauhan SP — A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol* 1999; **181:** 858-61.

8 Raheem IA, Saaid R, Omar SZ, Tan PC — Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. *BJOG* 2012; **119:** 78-85.