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Gynaecology

Oral nifedepine vs. intra-venous labetalol in management of hypertension in severe pre-eclampsia

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ABSTRACT

Introduction: Pre-eclampsia (PE) continues to be a major obstetric problem in present day health care practice. It presents a great medical dilemma because it affects not only maternal health but also puts foetal development at risk.

Objectives: To compare oral nifedepine with intravenous labetalol in their efficiency to control hypertension in severe pre eclampsia (PE).

Methods: One hundred women with severe PE were randomized to receive either oral Nifedepine or intra venous Labetalol. Data collected was analysed using appropriate statistical tests. P value <0.05 was considered significant.

Results: The present study showed no significant difference between the Nifedipine and Labetalol groups with reduction in systolic, diastolic and mean arterial pressure (MAP) values after 30 minutes of drug administration.

Conclusion: Both oral nifedepine and intra venous labetalol are highly effective in acute and rapid control of hypertension in severe PE.

KEYWORDS : Pre eclampsia (PE), Intravenous (IV) labetalol, Oral nifedepine

Introduction

Hypertensive disorders of pregnancy are the most common medical disorders of pregnancy and are associated with increased maternal and perinatal risks[1],incidence in India is 10-20%. The severity of hypertension is described by various parameters like diastolic blood pressure 110 mmHg or higher, proteinuria (persistent 2+ or more), headache, visual disturbances, upper abdominal pain, oliguria, convulsion (eclampsia), elevated serum creatinine, thrombocytopenia, liver enzyme elevation, foetal growth restriction and pulmonary edema[2,3].

The risk for the foetus includes perinatal death, intrauterine growth restriction, hypoxia and preterm delivery. The latter often iatrogenic due to concerns regarding maternal safety. Delivery of the placenta is the only known cure for pre-eclampsia (PE). There is general consensus that maternal and foetal risks are decreased by antihypertensive treatment that acutely lowers severely elevated BP. The main goal of treatment is to safeguard the mother from the development of acute complications like cerebrovascular accidents, eclampsia, target organ damage [2] and maternal mortality while delivering a healthy infant[4].

It is very important to avoid inducing hypotension for two primary reasons: (i) The maternal cererbrovasculature may lose its auto regulatory ability at the levels of BP being treated, particularly if the woman's BP has been, in the recent past, much lower (e.g.: 100/60 mm Hg); (ii) the utero placental circulation is unable to auto regulate blood flow, so that maternal hypotension may precipitate foetal distress and an otherwise undesirable delivery and foetal death may occur where the foetus is already severely compromised[5].

There have been a lot of research and studies done regarding the drug of choice for treatment of hypertension. According to the consensus report on high blood pressure, the ideal anti-hypertensive drug should be potent and safe, rapidly acting, controllable and without detrimental maternal or foetal side effects [6]. The ultimate goal of any protocol for management of PE must be maternal safety first [3] followed by delivery of a new born in optimal condition with maximal chances for survival.

Intravenous hydralazine, a direct vasodilator, has been the first choice of drug for treating severe hypertensive emergencies in pregnancy with acceptable immediate maternal side effects (tachycardia, headache, ventricular arrhythmias) and a low incidence of short- or long-term foetal effects (rarely, thrombocytopenia) [7]. Studies have revealed that intra venous labetalol had similar efficacy if not more [8, 9]. Another drug that has frequently been used is oral nifedepine. One study showed a significant increase in uteroplacental blood flow that was not observed with other drugs [10]. The choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug, and on what is known about adverse effects [8].

Previous few studies that have been done, concluded that both regimens are efficacious, have predictable and quick response the acute control of severe hypertension in pregnancy with nifedepine achieving a more rapid response with increased cardiac index and urine output [4]. The side effects profile was tolerable and comparable [11]. These studies were either done in a western set up [11] or inadequately powered with a small sample size [12].

We chose to perform a study comparing oral nifedepine and intravenous labetalol, in their rapidity and efficacy in controlling hypertension and side effect profile as with an adequate sample size in a tertiary care obstetric centre in South India.

Materials & methods

This prospective double blinded study was conducted in a tertiary care centre for obstetrics; Cheluvamba hospital attached to Mysore Medical College and Research Institute. Inclusion criteria were, age – 18 to 45 years, singleton pregnancy with vertex presentation, women of more than 28 weeks gestation with severe PE, patients with imminent symptoms, patients with or without end organ damage. Women with multiple gestation, comorbid conditions which have an implication on blood pressure, pre pregnancy hypertension, those on anti-hypertensive (during ante natal period or within 72 hour prior to admission) and refusing consent were excluded.

Pregnant women of 28 weeks gestation or more with severe PE who fulfilled the inclusion criteria were admitted to labour ward in Cheluvamba hospital attached to Mysore Medical College and Research Institute, during the study period from January 2012 to July 2014 were randomized to two groups. Group A were those who received oral nifedepine and Group B were those who received intravenous labetalol.

A detailed history regarding antenatal care, past medical, surgical, family and obstetric history was taken. A general, physical and systemic examination was done. Investigations will include urine protein, complete haemogram, renal and liver function tests, serum lactate dehydrogenase, serum uric acid, ultra sonogram for foetal growth and liquor and fundoscopy.

Group A patients received oral capsule nifedepine 10mg stat followed by 10 mg every 30 minutes up to a maximum of 80 mg till the desired BP was achieved. Once the target BP was achieved, patients received a maintenance dose of nifedepine 10mg sixth or eighth hourly. **Group B** patients were administered 20 mg labetalol intra venous stat; repeat 20–80 mg intra venous every 30 minutes to a maximum of 220 mg till target blood pressure is achieved (then switch to oral 100 mg 12th hourly). The dosing regimens are in accordance with that of ACOG recommendations [13] except that labetalol was given every 30 min in order to compare with that of nifedepine. All patients with imminent eclampsia received prophylactic dose and those with eclampsia received therapeutic dose of magnesium sulphate.

The point of BP control was taken as a systolic BP between 140-150 mmHg and diastolic BP between 90-100 mm Hg. The primary outcome was number of doses required to achieve target BP and time required to reduce the MAP by 25% [13, 14].

Demographic, relevant clinical and laboratory parameters were recorded. It included blood pressure (systolic, diastolic and mean arterial pressure) measurement every 30 minutes till the target BP was reached and thereafter at regular intervals for 24 hours, time taken to achieve target blood pressure, dose required to achieve target blood pressure, urine output every 30 minutes, cross over between groups, additional drugs required due to failure of response to nifedepine or labetalol. Resurgence of hypertensive crisis, maternal side effects like hypotension, maternal tachycardia, headache, flushing, nausea and vomiting, dizziness, abruption or cardiovascular accidents after starting the antihypertensive drug, foetal side effects, expedited or expectant delivery, mode of delivery was noted.

Data was analysed using unpaired t test for quantitative data which were expressed as mean ± standard deviation or median and range; Chi square test for categorical data which were expressed in percentage. Data were analysed using IBM SPSS statistics 20. P value <0.05 was considered significant.

Results:

Demographic and Obstetric parameters of patients are as shown in **Table 1**.

Table 1: Demographic and Obstetric parameters

		Group A n = 50	Group B n= 50	Total	P value
Age	<20 years	19 (38.0%)	13 (26.0%)	32 (32.0%)	0.074
	21 – 25	18 (36.0%)	29 (58.0%)	47 (47.0%)	
	26 – 30	10 (20.0%)	8 (16.0%)	18 (18.0%)	
	31 – 35	3 (6.0%)	0 (0%)	3 (3.0%)	
Gravid Index	G1	27 (54.0%)	30 (60.0%)	57(57.0%)	0.65
	G2	18 (36.0%)	15 (30.0%)	33 (33.0%)	
	G3	5 (10.0%)	5 (10.0%)	10 (10.0%)	
Gestational age in weeks	28 – 32 weeks	3 (6.0%)	5(10.0%)	8(8.0%)	0.35
	32+-36 weeks	11(22.0%)	6(12.0%)	17(17.0%)	
	36+ weeks	36(72.0%)	39(78.0%)	75(75.0%)	

Parameters related to blood pressure are as shown in **Table 2**.

Table 2: Parameters related to blood pressure

Parameters		Group A n = 50	Group B n = 50	P value
BP at admission in mm Hg; mean	SBP	158.80±12.0	161.12±14.7	0.70
	DBP	110.4±8.26	111.7±7.17	0.382
	MAP	128.5±10.19	129.8±8.86	0.495
BP 30 minutes after drug administration in mm Hg; mean	SBP	155.12±10	156.4±11.9	0.564
	DBP	104.0±5.8	102.8±5.3	0.607
	MAP	121.2±6.8	121.8±8.5	0.698
Reduction in BP 30 minutes after drug administration in mm Hg; median	Red - SBP	4 (0 – 10)	5 (1 – 10)	0.254
	Red - DBP	5 (1 – 11)	6 (1 – 11)	0.413
	Red -MAP	7 (0 – 14)	8 (1 – 14)	0.323
Doses required to achieve target BP	1	14 (28.0%)	18(36.0%)	0.312
	2	15 (30.0%)	13 (26.0%)	
	3	11 (22.0%)	12(24.0%)	
	4	6 (12.0%)	7 (14.0%)	
	5	4 (8.0%)	0 (0%)	
Cross over		0 (0%)	1 (0.5%)	
Time required to reach target BP in minutes; mean		71.4±32.796	64.8±30.276	0.35
Need for other antihypertensives including MgSO4		13 (26%)	14 (28%)	0.822
BP – Blood pressure; SBP – Systolic BP; DBP –Diastolic BP; MAP – Mean arterial pressure; MgSO4 – Magnesium sulphate				

Maternal mortality, morbidity and side effects are as shown in **Table 3.**

Table 3:Maternal mortality, morbidity and side effects.

Parameters		Group A N – 50	Group B N – 50	P value
Mortality		0 (0%)	0 (0%)	
Morbidity	Resurgence	6(12%)	7(14%)	P > 0.05
	Eclampsia	2(4%)	4(8%)	
	HELLP	4(8%)	6(12%)	
	Abruption	4 (8%)	5(10%)	
Side Effects	Flushing	4 (8%)	5(10%)	P > 0.05
	Tachycardia	4(8%)	5(10%)	
	Head ache	4(8%)	3(6%)	
	Nausea	0(0%)	5(10%)	P – 0.02
HELLP acronym – Hemolysis, Elevated liver enzymes, Low platelet count				

Mode of delivery was comparable between the groups. In group A 72% (36) delivered vaginally; 4% (2) were assisted instrumental deliveries and 24% (12) had a caesarean delivery where as in group B it was 64% (32), 16% (8) and 20% (10) respectively (P - > 0.05).

Foetal parameters are as shown in **Table 4**.

Table 4: Foetal Parameters

Parameters	Group A; n= 50	Group B; n = 50	P value
Foetal heart rate (FHR) variability	2 (4%)	5(10%)	P > 0.05
Birth Weight in Kg ; mean	2.11±0.57	2.26±0.62	
APGAR @ 5 minutes; mean	6 (3-10) 6.31±0.87	6 (3-10) 5.77±1.5	
IUGR	10 (20%)	7(14%)	
IUD 5	5 (10%)	7(14%)	
NICU admission	16(32%)	13 (26%)	
APGAR acronym – Appearance, Pulse, Grimace, Activity, Respiration; IUGR – Intra-uterine growth retardation; IUD – Intra-uterine death; NICU – Neonatal Intensive care unit			

Discussion

Pre eclampsia (PE) is seen clinically as a syndrome ranging from mild clinical hypertension and proteinuria to a severe form of rapid fulminant endothelial disease with multi organ failure and death of mother and foetus. By measuring the oxygen delivery index and oxygen consumption index in severe PE Belfort et al [14] showed that it was a fixed tissue oxygen extraction states very much like sepsis. With significant endothelial damage, tissues lose their ability to modify oxygen extraction from blood, and oxygen consumption at the tissue level becomes dependent solely on oxygen delivery. The optimal management of severe PE is controversial.

Recent enquiry into Maternal and Child Health (CEMACH) report has attributed the occurrence of fatal Intracranial haemorrhages to inadequate treatment of severe systolic hypertension (≥ 160mmHg) in women with PE, and recommends urgent and effective antihypertensive treatment for such cases [10]. Recent guidelines from the National Institute for Health and Clinical Excellence, UK, recommends treatment of severe hypertension of pregnancy with labetalol (oral or intravenous), intravenous hydralazine or oral nifedepine as first line antihypertensives within the ICU setting [15]. The long standing standard hydralazine has received recent scrutiny because of a high incidence of overshoot hypotension. Fenakel et al. [3] found nifedepine to be a more effective and safer alternative to hydralazine, whereas, Mabie et al [4] found labetalol to be as efficacious as hydralazine with a lower incidence of overshoot hypotension. Thus, many clinicians now think of nifedepine and Labetalol as first line alternatives to hydralazine in the management of severe PE; hence a study to compare the hemodynamic effects of nifedepine and labetalol was warranted.

The primary outcome of our trial was the time taken to achieve target systolic BP (SBP) of ≤150mmHg and Diastolic BP (DBP) of ≤ 100mmHg (Both targets are to be fulfilled), and total number of antihypertensive doses required to achieve target blood pressures. In the present study, 14 (28%) Patients in nifedepine group and 18 (36%) patients in labetalol group achieved target BP with a single dose of respective drug with a non-significant (P - 0.312). One Patient in our Labetalol group failed to achieve target BP with the maximum allocated dose of 220mg necessitating a crossover after which BP was controlled with two more doses of nifedepine. These findings were similar to studies by Raheem et al [11].

The mean SBP, DBP and MAP at admission was comparable between the two groups and it was similar 30 minutes after administration of the respective drugs (P > 0.05). In the present study, the average time required to achieve target BP in minutes was 71.4±37.7 in nifedepine group and 64.8±32 in labetalol group, which was not significantly different (P - 0.35). Studies done in the past by Raheem et al [11] and Hashem M [16] had similar conclusion. The drug regimen used in that study was higher than that in our study; they used oral nifedepine dose (10mg stat followed by 20mg for further 4 doses as compared to using a flat 10mg dose throughout in our regimen. Vermillion's [13] target SBP was higher but their diastolic BP was similar to ours (<160 and <100 vs. ≤ 150 and ≤100mmHg) indicating more difficulty in achieving target BP in our trial.

In the present study minor side effects including headache, flushing and tachycardia was observed with similar frequency in both groups. Significant minor side effect exclusive to labetalol group was nausea (P < 0.05) which was transient and non-detrimental to the patient. Side effect profile was similar to previous studies [11].

In our study, adverse maternal outcomes were as follows: the nifedepine group encountered four (8%) cases of abruption, four (8%) cases of HELLP syndrome and two (4%) developed convulsions. In labetalol group we had six (12%) cases of HELLP syndrome, four (8%) cases of eclampsia and five cases of abruption. These were managed accordingly. Resurgence of hypertension was seen in six (12%) and seven (14%) patients in nifedepine and labetalol group respectively; which were controlled with fresh regimens of the same drug category. There were no cases of SICU admission, postpartum hemorrhage (PPH), manual removal of placenta (MRP), overshoot hypotension in either of the groups. There was no maternal mortality in the study. Maternal safety profile has been confirmed by studies in the past [11, 13].

In our study, 13 (26%) patients in nifedepine group and 14 (28%) patients in labetalol group were given magnesium sulphate (MgSO4) prophylaxis in view of impending symptoms along with respective antihypertensive drugs. Data (Magpie trial) suggests that overlapping of exposures to nifedepine and is well tolerated [1]. Magnesium salts also potentiate the hypotensive action of nifedepine, because both drugs act on calcium channel pathway. There is a synergistic action of MgSO4 and labetalol [18]. But neither of the groups had any episode of overshoot hypotension.

Foetal heart rate abnormality was observed in two (4%) cases in the nifedepine group and in five (10%) in labetalol group (P > 0.05), three out of the five cases in the labetalol group were extremely growth restricted babies and hence variability may be attributed to chronic anoxia and placental insufficiency.

With respect to mode of delivery 36 patients (72%) in nifedepine group delivered vaginally, two (4%) were assisted Instrumental deliveries and 12 (24%) had a caesarean delivery. Indication for caesarean section (CS): eight (16%) were maternal, comprising of four (8%) failed inductions, two (4%) cephalo-pelvic disproportion (CPD) and two (4%) for failure to progress. Five (10%) were for foetal indications (foetal distress). In the labetalol group, 32 (64%) delivered vaginally, 8 (16%) were assisted Instrumental deliveries and 10 (20%) had a CS. Indication for CS: four (8%) were due to maternal causes, comprising of three (6%) failed inductions, one (2%) CPD and six (12%) were due to foetal causes, comprising of one (2 %) cord prolapse, three (6%) for meconium stained liquor at admission with unfavourable cervix and two (4%) for persistent occipito-posterior. None of the cases in either of the groups underwent CS due to uncontrolled hypertension.

Incidence of still birth was 10% in nifedepine group and 14% in labetalol group. The most common cause being abruption and severe IUGR. 16 (32%) babies in nifedepine groups and 13 (26%) in labetalol group required admission to NICU, the most common indication being prematurity [17, 18].

Conclusion:

Oral nifidepine and intra venous labetalol are equally efficacious for acute and rapid control of hypertension in severe pre eclampsia. Nifidepine is cheap, easily available and administrable orally making it ideal for use even in low resource and peripheral settings, but not suitable in an acute setting of concurrent eclampsia or comatose patients. Labetalol is more expensive, needs to be administered intra venously and has the advantage of use in an acute setting of concurrent eclampsia and in delirious or comatose patients. The lack of availability and trained personnel for drug administration in low resource and peripheral settings works to its disadvantage.

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