Original Research Article

Intravenous labetalol vs. oral nifedipine in control of hypertensive emergencies in severe pre-eclampsia and eclampsia: a randomized control trial

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ABSTRACT

Background: Pre-eclampsia is a disorder peculiar to human pregnancy and accounts for a considerable proportion of both maternal and perinatal deaths. This study was undertaken to compare the efficacy of labetalol versus nifedepine in the treatment of hypertensive crisis, maternal and fetal outcomes and also prevention of further complications in patients admitted to department of OBG, VIMS, Ballari.
Methods: Total 100 women with severe preeclampsia and eclampsia who were admitted in the labour room at the Vijayanagar institute of medical sciences, Ballari over a period ranging from April 2013 to September 2014 who fulfilled the inclusion and exclusion criteria were included in this Open Label, prospective, randomized study. Patients were allocated into two groups; group A and group B and managed with Intravenous labetalol and oral nifedipine respectively after proper history, examination and investigations.
Results: We found that less number of doses were required to achieve target blood pressure in labetalol group (2.4±0.99) compared to nifedipine group patients who required more number of doses. (2.56±0.84) Even with fixed dose regimen (VIMS Regimen) of labetalol, our study showed more rapid decrease in blood pressure to target level with labetalol group (36±14.85 min) compared to nifedipine group (68.1±27.64 min) which was statistically significant (p=0.000).
Conclusions: The goal of treatment is to maintain BP at a level that minimizes maternal cardiovascular and cerebrovascular risk. Labetalol is better than nifedipine in the management of hypertensive crisis in severe preeclampsia and eclampsia.

Keywords: Preeclampsia, Eclampsia, Labetalol, Nifedipine

INTRODUCTION

Haemorrhage and hypertensive disorders are major contributors to maternal deaths in developing countries.[1] Hypertension in pregnancy is the second leading cause of maternal death, accounting for 20% of maternal deaths and presents an increased risk of complications for the fetus, including increased NICU involvement, preterm delivery and low birth weight and even fetal death. The studies have shown that early treatment of hypertensive crisis decreases not only the frequency of convulsions and associated maternal mortality and morbidity, but also the rate of neonatal complications.

Labetalol gives slow and steady (better) control of blood pressure compared to other antihypertensive agents.[2] Advantage of labetalol is that, it is available as both injectable and oral and time of onset of action is earlier

than Nifedipine. Nifedipine is easily available, cheap, and easily administrable and helps in rapid control of blood pressure. Since the literature of comparison of efficacy of these two drugs is scant in this part of the country, this study was undertaken to compare the efficacy of labetalol versus nifedepine in the treatment of hypertensive crisis, maternal and fetal outcomes and also prevention of further complications. Hypertensive disorders of pregnancy affect 5% of all pregnancies, 10% of first pregnancies and 20-25% of women with a history of chronic hypertension.[2] The term hypertensive crisis is defined as an elevation of the blood pressure to a degree which is potentially life-threatening and that requires immediate management in order to prevent end-organ damage.[3]

In eclampsia, the case fatality rate has been reported as 1.8% and a further 35% of women experience a major complication.[4] The two main goals of management of women with severe preeclampsia during labour and delivery are prevention of seizures or eclampsia and control of hypertension.[5] An effective anti hypertensive agent used is intra venous labetalol, an α1and a non selective β blocker for rapid control of blood pressure in severe pre eclampsia. It results in good and sustained control of BP. There is no tachycardia and BP is stabilized. Nifedipine is a Ca2+ channel blocker. A meta-analysis study done by Liu QQ et al in China on clinical efficacy and perinatal outcome of nifedipine for severe preeclampsia concluded that nifedipine is associated with greater effective control of blood pressure and prolongation of gestation, with no additional neonatal respiratory distress syndrome or perinatal deaths, compared with other antihypertensives for women with severe preeclampsia.[11] Nifedipine effectively lowers blood pressure without any apparent reduction in uteroplacental blood flow.[6] Oral nifedipine and IV labetalol equally effective for hypertension in pregnancy by Heidi Anne Duerr, MPH in 2012 concluded that "oral nifedipine and intravenous labetalol regimens are similarly effective in the acute control of severe hypertension in pregnancy. [12]

Aim and objectives

Aim and objectives of current research was to assess the time taken and the number of doses required to achieve target Blood pressure of ≤150/100 mmHg in labetelol group and nifedepine group was the primary objective of this study. Secondary outcomes like maternal side effects and fetal side effects and feto-maternal outcome were also measured.

METHODS

In this open label, prospective, randomized study, the admitted patients in the labour room at the Vijayanagar institute of medical sciences, Ballari over a period ranging from April 2013 to September 2014 were recruited for the study.

A bilingual, written informed consent was obtained before the cases included as study sample. Pregnant females newly diagnosed with blood pressure of >160/110 mmHg were included. Enrollment occurred antepartum, intrapartum and within 24 hours postpartum.

Inclusion criteria

Inclusion criterion for current study was; patients with severe preeclampsia/eclampsia and blood pressure of >160/110 mmHg.

Exclusion criteria

Exclusion criterion for current study was; H/O cardiac disease, H/O bronchial asthma, H/O allergy to labetalol or nifedipine, siabetic, liver disorders, maternal heart rate <60 or >120 beats per minute, renal disease, connective tissue diseases.

Selection of cases

A total of 100 patients attending the above teaching hospitals were allocated to two groups by using computer generated sequence of random number. Group A: received injection labetalol, VIMS regimen (rule of 15) - fixed dose regimen. Started with 15 mg slow i.v. over 2 min and repeated 15 mg every 15 minutes till the target BP achieved or upto15th dose. Patients who failed to achieve the target blood pressure even after the maximum dose received cross over regimen i.e. tablet nifedipine 10 mg every 30 minutes upto 8th dose or till the target BP achieved. Group B: received tablet nifedepine. Started with 10mg orally and then repeated in fixed regimen fashion every 30 minutes till the target blood pressure achieved or upto 8th dose. Patients who failed to achieve the target blood pressure even after the maximum dose received cross over regimen injection labetalol 15 mg every15 min till the target BP achieved or upto 15th dose. Patient developing recurrences of hypertensive crisis after achieving target blood pressure was again given the same additional antihypertensive. Severe PIH was defined as a sustained systolic blood pressure of >160 mmHg and diastolic blood pressure of >110mmHg on repeat measurement of 15 minutes apart in a lateral recumbent position with head of the bed elevation not exceeding 15 degree. Target BP to be achieved was ≤150/100 mmHg.

Injection MgSo4 was given to patients with eclapmsia in both group A and group B. A loading dose of 4 gm of 50% MgSo4 was given intravenously after diluting it in 20cc of 5% dextrose over 10-15min and simultaneously, 4 gm of undiluted 50% MgSo4 was administered intramuscularly (single dose regimen). If convulsions occurred within 30 minutes of starting the therapy, no additional MgSo4 was given. If the convulsions were not controlled even 30 minutes after giving the single dose MgSo4, it was considered as a recurrence. These patients were switched over to Sardesai's low dose MgSo4 regimen i.e. 4g of Mgso4 was given as a loading dose and

thereafter, 2g of MgSo4 (intramuscularly or diluted intravenously) was given as a maintenance dose every 3rd hourly. Demographic and standard laboratory data were collected on admission. Once patients were enrolled, vital signs were recorded every 15 minutes, including blood pressure measurement until the woman is stabilized and then every 30 minutes in the initial phase of assessment by a mercury columns sphygmo-manometer. The blood pressure cuff width was 15 cm and the length of the cuff was about 1.5 times mid arm circumference. Foetal monitoring was done by taking CTG trace at the beginning and then one at the end of the study/ two hours. Monitoring of the foetal heart rate and any abnormalities of it were noted. Maternal adverse effects like recurrence of convulsions in eclampsia patients, heart rate abnormalities, headache, nausea, dizziness were recorded. Fetal outcomes assessed by APGAR, meconium, NICU admission, Stillbirths, ENND etc. Patients were followed up till discharge.

Primary outcome measured in terms of number of doses and duration of the drug required to achieve the target blood pressure and secondary outcomes measured in terms of maternal morbidity and mortality and perinatal outcomes.

Statistical analysis

Statistical analysis was done by applying paired 't' test for the difference in pre- and post treatment values. For inter group analysis, we applied Chi-Square test, using SPSS vs18 (statistical package for social sciences) statistical software version 3.3, p<0.05 was regarded as significant with 95% confidence limits.

RESULTS

In labetalol group 78% (39) of patients were 16 to 25 years of age group and 22% (11) patients were 26 to 35 years of age group. In nifedipine group 70% (35) of patients were 16 to 25 years of age group and 30% (15) patients were in 26 to 35 years of age group. The mean age group in labetalol group was 22.64 ±4.2 years and in nifedipine group mean age group was 23.84±4.1years (Table 1). In labetalol group 34% (17) of patients were multigravidae and 44% (22) of patients were multigravidae in nifedipine group. 66% (33) of patients were primigravidae in labetalol group and 56% (28) of patients were in nifedipine group. So distribution based on obstetric data was not statistically significant in each group; p value = 0.611 (Table 1). Premonitory symptoms were seen in 46% (23) in labetalol group and 34% (17) in nifedipine group. Edema was seen in 82% (41) on patients in labetalol group and 90% (45) of patients in nifedipine group. In labetalol group 18% (9) of patients had anaemia and in nifedipine group 14% (7) had anaemia. In labetalol group 28% (14) of patients had altered consciousness and in nifedipine group 10% (5) had altered consciousness. This was statistically significant (p value = 0.022) (Table 1).The mean systolic

blood pressure was 180.16±11.42mmHg in labetalol group and 177.12±10.78 mmHg in nifedipine group. It was not statistically significant (p value=0.174). Mean diastolic was 123.20±8.33mm Hg in labetalol group and 120.88±7.16mm Hg in nifedipine group (p value= 0.139). The mean of mean arterial was 142.16±8.36mm Hg in labetalol group and 139.58±7.19 mmHg in nifedipine group (p value=0.101) (Table 1). The mean systolic blood pressure was 180.16±11.42 mmHg in labetalol group and 177.12±10.78 mmHg in nifedipine group. It was not statistically significant (p value=0.174). Mean diastolic was 123.20 ±8.33 mm Hg in labetalol group and 120.88±7.16 mmHg in nifedipine group (p value=0.139). The mean of mean arterial was 142.16±8.36 mmHg in labetalol group and 139.58±7.19 mm Hg in nifedipine group (p value =0.101) (Table 1).

In labetalol group mean number of doses required to achieve target blood pressure was 2.4±0.99 and in nifedipine group it was 2.56 ±0.84 (p value =0.385). This was not statistically significant. The mean duration in minutes required to achieve target blood pressure was 36±14.85 in labetalol group and 68.1±27.64 in nifedipine group which was statistically significant (p value=0.000). Number of days to normalize BP was 2.2±0.70 in labetalol group and 2.96±1.18 in nifedipine group. It was statistically significant (p value=0.000) (Table 2). Recurrence of convulsions was seen in 4% (2) in labetalol group and in 18% (9) in nifedipine group which was statistically significant (p value=0.025). 4% (2) required additional antihypertensives in labetalol group and 22% (11) in nifedipine group, which was statistically significant (p value=0.007) (Table 2). In nifedepine group, 30% (15) of patients had side effects among them dizziness was seen in 4% (2) of patients and headache in 26% (13). In labetalol group 20% (10) patients had side effects like dizziness in 4% (2) and nausea in 16% (8). This was statistically significant (p value=0.000) (Table 2).

Fetal distress was seen in 30% (12) of babies in labetalol group and 42.1 % (16) of babies in nifedipine group, which was not statistically significant (p value=0.479) (Table 3). In labetalol group 20% (10) were dead born and in nifedipine group 22.4% (11) were dead born. (Table 3). In labetalol group 80% (40) were live born and in nifedipine group 77.6% (38) were live born. This was not statistically significant (p value=0.765) (Table.3). NICU admission was required in 32.5% (13) of live born babies in labetalol group and 47.4% (18) in nifedipine group, which was not statistically significant (p value=0.181) (Table 3). In labetalol group 16% (8) were IUD, 4% (2) were stillborns and 8% (4) had ENND. In nifedipine group 20.4% (10) were IUD, 2% (1) were stillborns and 18.4% (9) had ENND. This was not statistically significant (p value=0.481) (Table 3).

Out of 17 in labetalol group who underwent C/S, 1 patient had PPH (5.9%), no one had hypotension and 2 patients (11.8%) had heart rate abnormalities. In

nifedipine 4 patients had PPH (19%), 6 patients had severe hypotension (28.6%) and 9 patients (42.9%) had heart rate abnormalities. The percentages of hypotension and heart rate abnormalities observed in nifedipine group were statistically significant (p value=0.019 and 0.043) (Figure 1).

Table 1: Patient characteristics in different groups of study participants (n=50).

Variable	Parameter	Group A	Group B	P value
Age group	16-25	39	35	
	26-35	11	15	0.362
Gravida	Multi	17	21	
	Primi	33	28	0.305
	Postpartum		1	
Presence of symptoms	Premonitory symptoms	23	17	0.221
	Oedema	41	45	0.249
	Signs of anaemia	9	7	0.585
	Altered consciousness	14	5	0.022
	Past H/O convulsions	5	10	0.161
Diagnosis	Severe preeclampsia	18	21	
	Imminent eclampsia	13	7	0.372
	Antepartum eclampsia	19	21	
	Post-partum eclampsia	0	1	
Presence of complications	HELLP syndrome	8	11	0.444
	Abruption	2	4	0.4
BP	Systolic BP	180.16	177.12	0.174
	Diastolic BP	123.20	120.88	0.139
	Mean arterial pressure	142.16	139.58	0.101
Blood parameters	Hb <10mg/dl	17	14	0.517
	Platelets <1.5 lakh	11	12	0.812
LFT	Elevated liver enzymes	2	4	0.4
	Raised LDH	21	26	0.316

Table 2: Distribution of patients based on the outcomes.

Outcome	Indicator	Group A	Group B	P value
Primary	No. of doses	2.4	2.56	0.385
	Duration in min	36	68.1	0.000
	No. of days to normalize	2.2	2.96	0.000
Secondary	Recurrence of convulsion	2	9	0.025
	Need to use additional antihypertensive	2	11	0.007
Side effects	Dizziness	2	2	
	Headache	0	13	0.000
	Nausea	8	0	

Table 3: Foetal outcomes among the different groups.

Outcome	Parameter	Group A	Group B	P value
Fetal distress	Presence	28	22	
	Absence	12	16	0.479
foetal outcome	Dead born	10	11	
	Live born	40	38	0.765
NICU admission	Yes	13	18	
	No	27	20	0.181
Perinatal mortality	IUD	8	10	
	Still birth	2	1	0.481
	ENND	4	9	

DISCUSSION

The goal of treatment is to maintain BP at a level that minimizes maternal cardiovascular and cerebrovascular risk. SBP >160 mmHg was the most important factor associated with a cerebrovascular accident in patients with severe preeclampsia and eclampsia. Paulino Vigil-De Gracia et al concluded that labetalol fulfills the criteria required for an antihypertensive drug to treat severe hypertension in pregnancy.[13] Labetalol has been suggested as the first-line agent for hypertension accompanying stroke in preeclampsia, in the light of evidence that it lowers cerebral perfusion pressure without affecting cerebral perfusion.[14] Our data supports recent guidelines and expert opinion that oral nifedipine and intravenous labetalol are suitable first-line antihypertensives for hypertensive emergencies of pregnancy.[15]
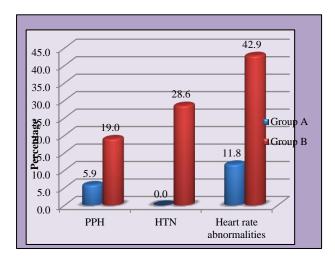

Figure 1: Intra operative complications in different groups.

In current study both the groups were demographically and characteristically comparable. Vermillion et al and Dhali et al studies have used 10mg of nifedipine initially followed by 20 mg upto 5 doses every 20 minutes.[8-10] Where as in Raheem et al and Shekhar et al used fixed dose of nifedipine 10 mg upto 5 doses.[7,9] Other studies have used escalating doses of labetalol for hypertensive crisis. In our study we used fixed doses of labetalol (VIMS Regimen) and fixed doses of nifedipine. Yet the efficacy of labetalol was similar or even better than the results of other studies which is indicated by the less number of doses required to achieve target blood pressure in labetalol group (2.4±0.99) compared to nifedipine group patients who required more number of doses (2.56±0.84).

Even with fixed dose regimen (VIMS regimen) of labetalol, our study showed more rapid decrease in blood pressure to target level with labetalol group (36±14.85 min) compared to nifedipine group (68.1±27.64) which was statistically significant (p value=0.000). This outcome was in contrast with similar studies which

showed that nifedipine more rapidly decreases blood pressure than labetalol.[8,9] Raheem et al study indicates that both labetalol and nifedipine are equally effective in controlling hypertension in pregnancy.[7]

In current study number of days to normalize the blood pressure on follow up was less with labetalol group (2.2±0.70) compared to nifedipine group (2.96±1.18) which was statistically significant (p value=0.000) In other studies this secondary outcome was not measured.[7-10] Our study showed recurrence of convulsions were more in patients who received nifedipine (18%) compared to labetalol group of patients (4%). This outcome was statistically significant (p value=0.025). This secondary outcome was not measured in other studies as patients with eclampsia were taken as one of the exclusion criteria in these studies. After extensive search in medscape we did not find any article to support this outcome. In our study out of 17 patients who underwent caesarean section in labetalol group, one patient had PPH and two of them had heart rate abnormalities i.e. bradycardia compared to 21 patients in nifedipine group 4 had PPH, 6 had hypotension and 9 had heart rate abnormalities i.e. profound tachycardia (p value=0.518). This outcome measure was not studied in other studies.[7-10] Side effects profile was similar in both the groups in other studies except for one case of profound hypotension with nifedipine in vermillion study.[7-10] In our study nifedipine group patients had more side effects than labetalol group (p value=0.000). There was no significant difference in the perinatal adverse outcomes like intrauterine fetal heart rate abnormalities, APGAR scores at 1 minute and 5 minutes, NICU admission and perinatal mortalities in both the groups. This finding is similar to the previous studies.

Limitations

Limitations of this study were small study group and observer bias as it was an open label randomised controlled trial.

CONCLUSION

Our study concludes that Labetalol is better than Nifedipine in the management of hypertensive crisis in severe preeclampsia and in eclampsia as it reduces the blood pressure more rapidly and constantly with better control on the recurrence of convulsions and ease of administration in altered consciousness. Labetalol is better than Nifedipine in terms of additional hypertensives required and number of days required to normalize the blood pressure and also with less side effects.

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