ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Oral Nifedipine versus Intravenous Labetalol in Hypertensive Emergencies of Pregnancy: A Randomised Trial.

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ABSTRACT

To compare the efficacy of oral nifedipine and IV labetalol in hypertensive emergencies of pregnancy and their effects on maternal and Perinatal outcome. Pregnant women with blood pressure ≥160/110 mmHg were subjected to the trial. Patients were randomised to receive nifedipine (10 mg orally, up to five doses) or intravenous labetalol injection (in an escalating dose regimen of 20, 40, 80, 80 and 80 mg) every 15 minutes until the target blood pressure of ≤150/100 mmHg was achieved. Crossover treatment was effected if the initial treatment regimen was unsuccessful. Primary and secondary outcomes like the time interval and number of doses required to achieve a blood pressure of ≤150/100 mmHg and adverse effects of the antihypertensive agents were reported. Patients received oral nifedipine achieved the goal therapeutic blood pressure more rapidly in 14.00±6.87 minutes (mean±SD) as compared with 25.17±12.76 minutes in those received intravenous labetalol ($p< 0.05$). The nifedipine group also require fewer doses (1.87±0.63 vs 2.53±0.97) than intravenous labetalol to reach the target blood pressure. Few adverse effects were reported but not significant. Overshoot hypertension was noted in patients treated with oral Nifedipine. Both oral nifedipine and IV labetalol are ultimately effective in reaching the therapeutic goal in hypertensive emergencies in pregnancy but nifedipine achieved the target blood pressure more rapidly and with fewer doses than labetalol. IV Labetalol is more effective in sustaining therapeutic level than oral nifedipine.

Keywords: Hypertension, Pregnancy, Labetalol, Nifedipine.

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ISSN: 0975-8585

INTRODUCTION

Hypertensive disorders represent the most common medical complications of pregnancy, with a reported incidence between 5-10% [1] and this hypertension which develops de novo in pregnancy appears to be unique to human [2].

The term hypertension in pregnancy is commonly used to describe a wide spectrum of patients who may have only mild elevations in blood pressure (BP) or severe hypertension with various organ dysfunctions. The three most common forms of hypertension are gestational hypertension, preeclampsia/eclampsia, and chronic essential hypertension [3]. However hypertensive crisis is particular challenge to treat which brings immediate risk to both the mother and fetus [4].

These disorders are a major cause of maternal and perinatal mortality and morbidity worldwide[1]. It is associated with 30% all maternal deaths and as much as 22% of all perinatal deaths [5]. It has been estimated by the WHO (World Health Organization) that worldwide approximately 50,000 women will die each year from hypertensive disorders of pregnancy [6].

Hypertension in pregnancy is considered severe if there are sustained elevations in systolic blood pressure (BP) greater than or equal to160 mm Hg and/ or diastolic BP greater than or equal to 110 mm Hg [7]. These levels represent cut off levels of overcoming cerebral auto regulation. It requires prompt treatment because of risk of cardiovascular accident, to prevent intracerebral hemorrhage, hypertensive encephalopathy and other target organ damage [7,8]. It also presents an increased risk of complications for the foetus, including prematurity, low birth weight, NICU involvement and even fetal death [8-10].

In addition to the risk they present to the pregnancy, hypertensive disorders of pregnancy have been linked to future high blood pressure and cardiovascular disease in women [11].

The obstetrician should aim not just for the diagnosis, but also the prevention of complications of hypertensive disorders. It is imperative to treat severe hypertension in pregnancy, mandating hospitalization. It is common practice to stabilise severe maternal hypertension prior to delivery by labour induction or caesarean section to avoid dangerous fluctuations or exacerbations of blood pressure during labour or anaesthesia [12]. Hence speedy but safe blood pressure control will allow the definitive treatment of delivery of the baby to be carried with minimum delay in many cases of severe hypertension in pregnancy. During this period the maternal and fetal conditions are monitored along with control of hypertension by antihypertensive drugs.

The most commonly used antihypertensive agents for hypertensive emergencies in pregnancy are Nifedipine, Labetalol and Hydralazine. The 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 this agent as first line drug when compared with Labetalol and Nifedipine [13] and is also not widely used in the India. Hence the aim of the present study is to compare the two most commonly used drug in India i.e. Oral Nifedpine and Intravenous (IV) Labetalol in terms of efficacy, time required and doses required to achieve target blood pressure, adverse effects, and the maternal and fetal outcome.

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 also transient neuromuscular weakness when used concomitant with magnesium sulphate [14].

Intravenous (IV) Labetolol is considered to control severe hypertension in pregnancy. Its advantages includes 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 [14].

Since the literature of comparison of efficacy of these two drugs is sparse, this study was undertaken to compare the efficacy of oral Nifedipine and IV Labetalol in the treatment of hypertensive emergencies of pregnancy and prevention of further complications.

ISSN: 0975-8585

MATERIALS AND METHODS

The study got ethical approval by Institutional review board of Sri Siddhartha medical college, Agalkote, Tumkur, Karnataka on 0ctober 2012.

The subjects for the study had got selected from pregnant women with a systolic BP ≥160 mm of Hg and/or diastolic BP ≥110 mm of Hg who came to labour room or OPD have been admitted to Sri Siddhartha Medical College and Hospital, Tumkur from 1st October 2012 to 30th March 2014 were included in trial. It is a randomised controlled trial. Assignment of the participants to the two groups was done by allotting the subjects alternatively to Oral Nifedipine and IV Labetalol.

Gestation age more than or equal to 28weeks, Pregnant women with a systolic BP of more than 160mm Hg or more and diastolic BP of 110mm Hg or more, maternal heart rate > 60 and < 120 beats per minute were included in this study.Patient with history of heart rhythm abnormality and/ or heart failure, exposure to either study medication within 24hrs of enrolment, asthma or allergic disorders with predisposition to bronchospasm, severe Hepatic/ Renal impairment, secondary hypertension and hypovolaemic shock were excluded.

Sample size calculation

In the trial conducted by Vermillion et al [15], indicated that patients receiving oral nifedipine, more rapidly achieved the therapeutic blood pressure goal in 25.0 ± 13.6 minutes (mean ± SD), as compared with 43.6 ± 25.4 minutes, in women receiving labetalol (P = 0.002). The nifedipine group also required significantly fewer doses (1.5 ± 0.5 versus 2.5 ± 1.5; P < 0.001) to reach the blood pressure goal.

Using these results as guidance data, sample size of 30 to each group, was calculated where oral nifedipine required an average of 25 min (x1=25) to reduce blood pressure and IV labetalol required 43.6 min (x2=43.6) to reduce blood pressure. Level of significance was taken as 5% (Zα=1.96) and the power of test was taken as 80% (Zβ=0.84). An additional 10% is added for lose to follow up cases. . Informed consent was obtained from enrolled patient, a signature or left had thumb impression from the consented subject was obtained after reading the informed consent document.

Method of data collection

The patients were administered either Oral Nifedipine or IV Labetalol based on the randomization. Patients randomized to Oral Nifedipine received 10 mg initially, with repeated doses of 10 mg every 15 minutes for up to a maximum of 5 doses, or until the target blood pressure systolic ≤150 mmHg & diastolic ≤100 mmHg were achieved. Nifedipine was never given sublingually.

Patients randomized to intravenous Labetalol, received 20 mg initially, followed by escalating doses of 40 mg, 80 mg, & then 80 mg every 15 minutes until the therapeutic goal blood pressure systolic ≤150 mmHg & diastolic ≤100 mmHg was achieved, or for a maximum of five doses. Inj labetalol was infused at a slow rate over 2-5 minutes.

The dosing regimens for each study medication correspond with the regimens from two previous clinical trials [16,17].

Participants were rested in bed in a semi recumbent position, vital signs were recorded. Blood pressure measurement done by a mercury sphygmomanometer in the right arm. The measurement of blood pressure was continued quarter-hourly for at least 60 minutes or longer until target blood pressure was achieved. Once blood pressure was ≤150/100 mmHg, no further trial medication was given unless there were two consecutive blood pressure readings ≥160/110 mmHg, in which case the trial medication was restarted.

If the therapeutic goal blood pressure was not achieved after 5 doses, crossover of the trial medication was done. If clinically significant maternal hypotension occurred, intravenous fluid bolus challenge or intravenous ephedrine was given. Investigations included complete hemogram, platelet count, blood urea,

serum creatinine, serum uric acid, liver function test, fundoscopy, NST, ultrasound and Doppler in some cases. Those patients with impending eclampsia were given magnesium sulphate (MgSO4).

The primary outcome of our study was the time interval required to achieve the therapeutic goal of systolic blood pressure of ≤150 mmHg & diastolic ≤100 mmHg. Secondary outcomes analyzed included, number of drug doses administered, adverse effects of the drugs, maternal outcome, and perinatal outcome.

Statistical Analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumption on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random. Cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS AND OBSERVTIONS

The randomized sixty pregnant women with hypertensive disorders were divided into two groups of thirty each, one is oral Nifedipine group (Group N) & other is IV Labetalol group (Group L). All participants were started on their allocated treatment. Table 1 shows the baseline characteristics of the participants stratified according to their randomisation. All baseline characteristics were similar across the groups.

Table 1: Characteristics of participants randomised to oral nifedipine or intravenous labetalol for acute blood pressure control in hypertensive emergencies in pregnancy

Characteristics	Oral Nifedipine (n=30)	IV Labetalol(n=30)	P value
Age in years(Mean +SD	23.73±4.57	23.80±3.09	0.947
Primi	60%	56.7%	0.947
Gestational age(Mean ± SD)	36.10±2.22	35.40±3.27	0.335
Previous history of PIH	20%	30%	0.371
Proteinuria#	73.3%	86.2%	0.661
Systolic BP (mm Hg)##	171.40±13.39	172.13±15.28	0.844
Diastolic BP(mm Hg)##	110.87±9.26	112.80±13.13	0.512
Distribution of hypertensive disorders A. Gestational hypertension	26.7	17.2	0.383
B. Severe preeclampsia	93.3	75.9	0.080+
C. Eclampsia	10.0	6.9	1.000
D. Chronic hypertension	3.3	0.0	1.000
E. Chronic hypertension superimposed with preeclampsia	0.0	3.4	1.000

#Proteinuria by urine dipstick at randomisation: proteinuria is considered to be present if dipstick analysis is at least 1+.
##Systolic and diastolic blood pressure at randomisation prior to starting treatment.
+ Suggestive significance (P value: 0.05<P<0.10),* Moderately significant (P value: 0.01<P < 0.05) and ** Strongly significant (P value: P<0.01)

ISSN: 0975-8585

There was no statically difference in the complete blood count, liver function and renal function parameters of the two groups (data not shown).

Table 2: primary and secondary outcomes of randomised trial of oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies in pregnancy

Primary outcome	Oral Nifedipine (n=30)	IV Labetalol (n=30)	P value
Time (minutes) taken to achieve blood pressure ≤150/100 mmHg	14.00±6.87	25.17±12.76	0.014*
Secondary outcome			
Number of doses required to achieve target BP	1.87±0.63	2.53±0.97	0.158
Maternal complications(%)			
Hypotension	0.0	0.0	1.000
Palpitation	33.3	6.0	0.32
Nausea and vomiting sweating	30.0	13.8	0.133
Sweating and flushing	0.0	0.0	1.000
Chest pain	6.7	0.0	0.492
Head ache	33.3	6.9	0.12
Fetal tachycardia	6.9	10.0	1.000
Other complications	16.7	6.9	0.424
• HELLP Syndrome	3.3	0.0	1.000
• Renal failure	3.3	0.0	1.000
• Eclampsia	10.0	6.9	1.000

+ Suggestive significance (P value: 0.05<P<0.10),* Moderately significant (P value: 0.01<P < 0.05) and ** Strongly significant (P value: P<0.01)
. *- Fischer's Exact test used for statistical analysis.

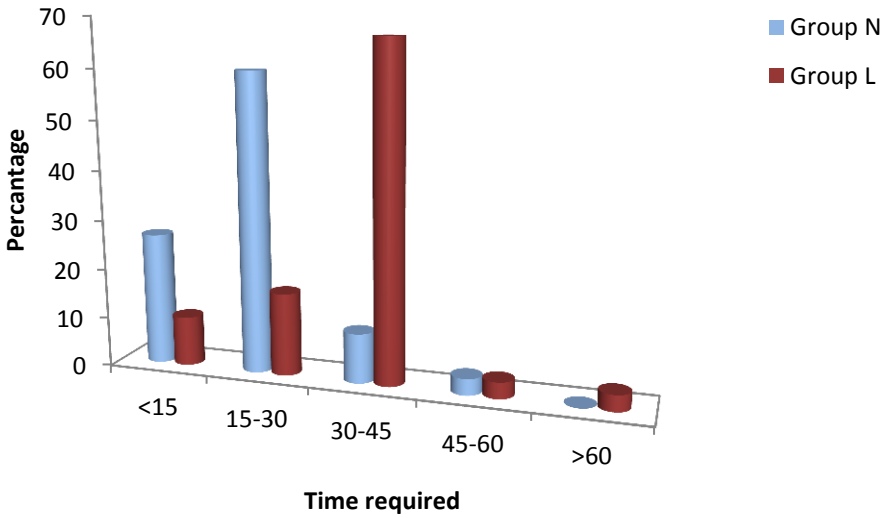

Figure 1: Time required achieving target BP

Outcomes stratified according to randomisation are shown on Table 2.For the primary outcome of time to achieve target blood pressure, there was significant differences in the time take to reduce the blood pressure to the target level. On an average the target blood pressure in the Nifedipine group was achieved in 14± 6.87 minutes and the time for achieving the target blood pressure in the Labetalol group was 25.17±12.76 minutes. The p-value obtained was <0.05, which indicates that difference in the time between the two groups was moderately significant (Figure 1). On an average the Nifedipine group required 1.87±0.63 doses to bring about the desired action and the Labetalol group required 2.53±0.97 doses to bring about the same action. P

ISSN: 0975-8585

value is 0.158 which indicates that there was no significant difference in the number of drugs required to get the desired action (Figure 2). In our study only one case treated with IV Labetalol required crossover of regimen. This patient treated with 2 doses of oral Nifedipine achieved target BP. In our study, overshoot of hypertension was observed in 3 patients treated with oral Nifedipine and none with IV Labetalol. In our study 2 patients treated with IV Labetalol had continued pregnancy. First patient had continued for 22 hours and second patient for 72 hours after the treatment with Labetalol regimen. The second patient was lost to follow up.

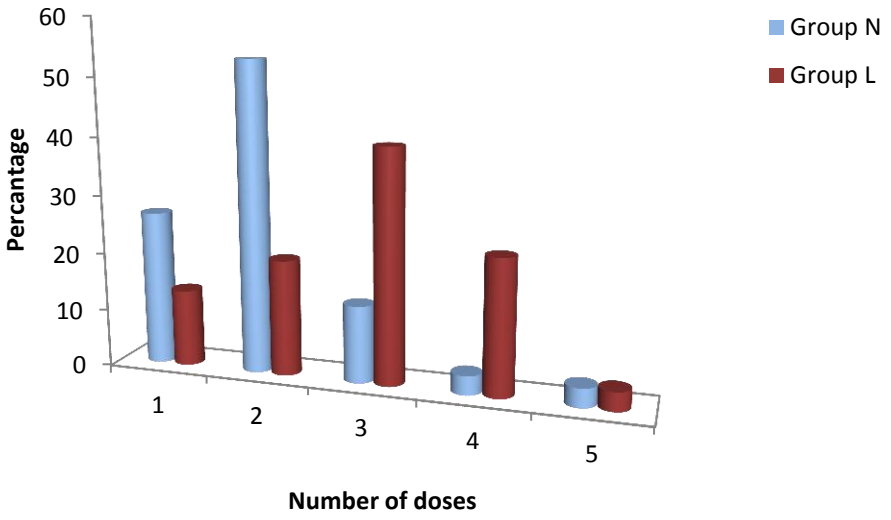

Figure 2: Number of doses required to achieve target BP

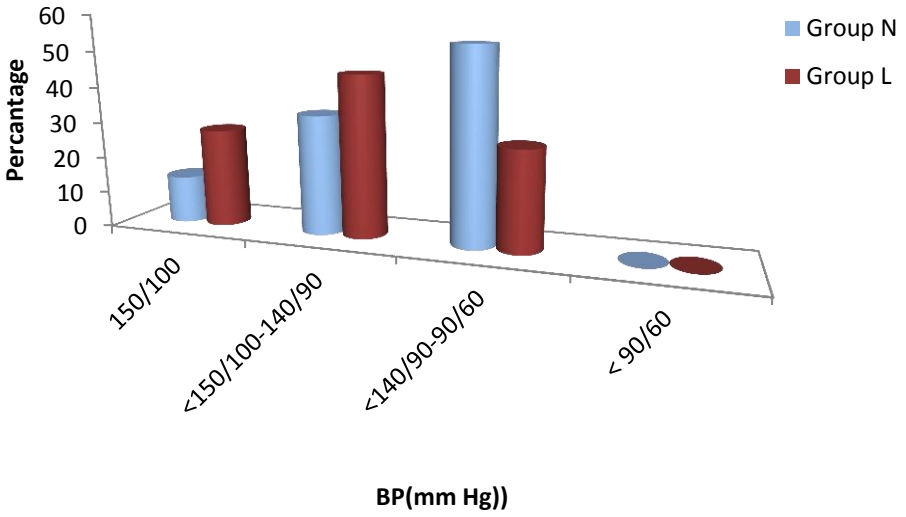

Figure 3: Blood pressure (mm Hg) in two groups studied after treatment

There were no incidences of hypotension in either of the study groups. The various side effects that would arise from the study drugs were noted and were not statistically significant though in Group N, number of patients with palpitation and headache were more compared to Group L. There was no significant difference in other recorded pregnancy and neonatal outcomes. Additionally there were no significant differences in both the study groups regarding the fetal heart rate abnormality, 5-minutes Apgar scores of <7 & NICCU admission (Table no 3).

Table 3: Neonatal outcome of randomised trial of oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies in pregnancy			
Neonatal outcome	Group N (n=30)	Group L (n=29)	P Value
Gestational age (in weeks)	36.23±2.47	35.55±3.05	0.349
Birth weight (kg)	2.17±0.52	2.13±0.66	0.771
APGAR score 5'	8.13±0.90	7.97±0.82	0.458
NICU admission(%)	33.3	48.3	0.243
Neonatal mortality	00(n=30)	1(n=29)	0.492
+ Suggestive significance (P value: 0.05<P<0.10),* Moderately significant (P value: 0.01<P < 0.05) and ** Strongly significant (P value: P<0.01) Statistical analysis done by Chi square test.			

The complications encountered during the study period were studied. The complications were attributed to severe preeclampsia and were not related to the study drugs. Eclampsia recorded in this study occurred prior to admission. There were no incidences of eclampsia after therapy was started. 3 patients (n=30, 3.3%) in the Nifedipine group and 2 patients (n=29, 6.9%) in the Labetalol group had eclampsia. There was 1 (3.3%) case of HELLP syndrome and 1 case of renal failure (n=30, 3.3%) in the Nifedipine group. Complications were treated promptly and there were no maternal mortality in our study period.

DISCUSSION

A total of 60 patients were included in the trial of which, 30 patients were randomized to Nifedipine and 30 patients to Labetalol. Of the 30 patients who were randomized to IV Labetalol one patient was lost to follow up after 3days of expectant management. During the trial all enrolled patients were in ante-partum period. In our study, data indicates that both oral Nifedipine and intravenous labetalol regimens are effective in controlling severe hypertension in pregnancy with the target blood pressure achieved in100% of cases in nifedipe group and 80% of cases with Labetalol group within five doses of commencing treatment. One participant who was treated with an intravenous Labetalol, needed crossover treatment with oral Nifedipine.

In our trial, in Nifedipine group, the mean systolic blood pressure before treatment was 171.40 ±13.30mm Hg and in Labetalol group it was 172.13±1 5.28 mm Hg. The diastolic blood pressure before treatment was 110.87 ± 9.26 mm Hg in Nifedipine and in Labetalol group it was 112.80 ± 13.13 mm Hg. We set a target blood pressure of $\leq$150/100 mmHg for our patients, with the dosing regimen to be stopped once the goal is achieved, and with maintenance therapy typically starting 2 hours later. This target blood pressure is in keeping with Saibai's [18] suggestion to keep systolic blood pressure between 140 and 155 mmHg and diastolic blood pressure between 90 and 105 mmHg in severe pre-eclampsia.

Many studies have shown that both Nifedipine and Labetalol can be used successfully in treating hypertensive crisis. The present study reveals that oral Nifedipine reduces the blood pressure at a significantly faster rate than IV Labetalol. The average duration to control blood pressure in the Nifedipine group was 14.00$\pm$6.87 minutes where as Labetalol takes about 25.17$\pm$12.76 minutes. This indicates that both Nifedipine and Labetalol can be used to lower blood pressure but Nifedipine does so, at a significantly faster rate. The p-Value was 0.014 calculated using Fisher Exact test. This result is echoed by two of the randomized controlled study done by Raheem et al [16] and Dhali. B et al [19] comparing these two drugs. In these studies target BP to be achieved is similar to our study. They had similar results wherein both Nifedipine and Labetalol are effective in the management of acute hypertensive emergencies in pregnancies but Nifedipine reduced blood pressure in a significantly shorter duration when compared to the Labetalol group.

The mean dosage required to reduce blood pressure was 1.87$\pm$0.63 for the Nifedipine group and 2.53$\pm$0.97for the Labetalol group achieve the same effect. The p-value is calculated using the Fisher Exact test. The p-value obtained was 0.158 which indicates that the test is not significant. Though it was statistically not significant, Nifedipine required fewer doses than IV Labetalol to achieve therapeutic goal. A randomized controlled trial done by Raheem et al [16] and Dhali B et al [19], on the same drugs had similar results where a significantly smaller dose was required by Nifedipine to control blood pressure.

The principal finding of Vermillion et al [15] was 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. Patients receiving oral Nifedipine more rapidly achieved the therapeutic blood pressure goal in 25.0 ±13.6 minutes (mean ± SD) as compared with 43.6 ± 25.4 minutes in those receiving Labetalol (*P* = .002). The Nifedipine group also required significantly fewer doses (1.5 ± 0.5 vs 2.5 ± 1.5; *P* < .001) to reach the blood pressure goal. Vermillion's drug regimen used higher oral Nifedipine doses (10 mg initially, then 20 mg for a further four doses, as required; we used a flat 10 mg Nifedipine dose throughout, as this is our longstanding standard regimen and an intravenous Labetalol regimen of 20, 40, 80, 80 and 80 mg, as required which is identical to our regimen.

At enrolment, Vermillion's subjects had potentially higher initial systolic blood pressure (>170 versus >160 mmHg), but had potentially lower diastolic pressure (>105 versus >110 mmHg), compared with our blood pressure inclusion criteria [15]. Vermillion's target systolic blood pressure was higher but the diastolic blood pressure was similar to ours (<160 and <100 versus <150 and <100 mmHg), indicating a more difficult to achieve blood pressure target in our trial.

Though our study is comparable to vermillion et al and Raheem et al studies in pre-treatment BP, no studies clearly mentions about the fall in BP after treatment. All the studies done comparing efficacy of oral Nifedipine and IV Labetalol have given importance about time taken and doses required to achieve target BP, but fails to mention mean fall in BP after treatment. Both Nifedipine and Labetalol significantly reduced the systolic and diastolic BP (Figure no 3).

In all the similar studies [15, 16, 19] there was no blood pressure fall <90/60 mmHg. Raheem et al [16]. in his study mentioned lowest SBP recorded is 130mm Hg and DBP is 64 mmHg. In the study lowest SBP is 110 mmHg and DBP is 72 mmHg.

Magnesium sulphate infusion as seizure prophylaxis is commonly used in women with severe pre-eclampsia, as supported by favourable data from the Magpie trial [20]. There are case reports [21] of severe hypotension, neuromuscular blockade and symptomatic hypocalcaemia when Nifedipine was used concurrently with magnesium sulphate infusion in hypertensive pregnancies. Of the eight women in our study with overlapping exposure to Nifedipine and magnesium sulphate, none had a significant adverse event which is similar to study by Raheem et al [16].

In studies by Vermillion et al [15], Dhali B et al [19], participants included antepartum, postpartum and many were managed expectantly after treatment whereas in the trial by Raheem included only antepartum cases before the start of regimen and more than two-thirds of the subjects had their delivery expedited very shortly after achieving blood pressure control.

In our study, all the patients at enrolment were in antepartum period. Most of all the patients had their delivery expedited very shortly after achieving blood pressure control except one case treated with IV Labetalol and this case was lost to follow up after 3 days of treatment.

Our trial also indicated that there was no statistically significant adverse maternal outcome or neonate outcome due to use of these antihypertensive agents but attributed to severe preeclampsia.

CONCLUSION

A hypertensive disorder of pregnancy is one of the life threatening complications encountered in obstetrics. Management of hypertension in pregnancy is a challenging task, because drastic reduction leads to uteroplacental insufficiency and intra uterine fetal death, and continuation of pregnancy with severe hypertension leads to life threatening complications to the mother. Therefore there is a need for an ideal antihypertensive agent for effective reduction of severe hypertension in pregnancy.

The present study compares the efficacy of oral Nifedipine and IV Labetalol in reaching the therapeutic goal. Oral Nifedipine achieved the target blood pressure more rapidly and with fewer doses than Labetalol. Nifedipine is also cheaper, easier to store and easier to administer as it is given orally. IV Labetalol is more effective in sustaining therapeutic level than oral Nifedipine. IV Labetalol is more expensive, needs to be stored at a lower temperature and needs slow IV administration.

Thus the present study concludes that both oral Nifedipine and IV Labetalol are ultimately effective in controlling blood pressure in cases of Hypertensive emergencies of pregnancy, however individualisation is required.

ACKNOWLEDGEMENT

We thank the staffs and postgraduates of the department of obstetrics & gynaecology, Sri Siddhartha Medical College, Tumkur, for their help in recruiting patients and assistance in completing this study.

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