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Original Research Article

Hydralazine versus Labetalol for acute control of blood pressure in patients with severe pre-eclampsia: a randomized controlled trial

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ABSTRACT

Background: Authors sought to compare the effectively of intravenous hydralazine and intravenous labetalol in controlling acute rise in blood pressure in patients with severe preeclampsia.
Methods: In this double-blind randomized controlled trial, all pregnant women with sustained increase in blood pressure (BP) of 160 mmHg systolic or 110 mmHg diastolic or higher were randomized to receive intravenous (IV) hydralazine 5 mg (max. 4 doses) or IV labetalol in escalating doses of 20mg, 40mg, 80mg, 80mg to achieve target blood pressure of 150 mmHg systolic and 100 mmHg diastolic or lower. The primary objective of the study was to assess the time taken to control blood pressure. Secondary agendas were the number of repeat doses required and other side effect profile.
Results: In the study duration of September 2015 to September 2017, authors enrolled 60 participants for our trial. The median time taken to achieve the target blood pressure was 22.4 minutes in both the groups. Close to half of the participants did not require repeat doses (46.66% with labetalol and 50% with hydralazine). No serious maternal or foetal side effects were noted during the study. Statistical tests were performed using SPSS for Windows version 22.
Conclusions: As operated in the study, the efficacy of hydralazine and labetalol to control the acute rise in blood pressure is similar.

Keywords: Hydralazine, Labetalol, Severe preeclampsia

INTRODUCTION

The hypertensive disorders of pregnancy are one of the leading causes of maternal and perinatal mortality and morbidity worldwide.[1] During pregnancy it can be complicated by severe rise in blood pressure, incidence of which is approximately 15% of pregnancies.[2,3] In India, incidence ranges from 6-8%.[4-6] The American College of Obstetrics and Gynaecology (ACOG) defines systolic blood pressure (BP) ≥160 mmHg or diastolic BP ≥110 mmHg as one of the features of severe pre-eclampsia. Hydralazine, Labetalol and Nifedipine, alone and in combinations have been used to treat severe hypertension in pregnancy and have been recommended as first line alternative drugs for the same by various authorities like Royal College of Obstetrics and Gynaecology (RCOG), ACOG and Cochrane review. Labetalol has been widely studied with other anti-hypertensive agents and its safety in pregnancy is well established. On the other hand, hydralazine, despite being a popular anti-hypertensive agent, raised concerns regarding its use in women with severe pre-eclampsia.[7] From 1982 through 2017 a PubMed database search of trials comparing hydralazine and labetalol for blood pressure control in women with severe preeclampsia using key words "severe preeclampsia", "hydralazine", and "labetalol" revealed

only 3 randomized controlled trials which compared the efficacy of hydralazine and labetalol in controlling blood pressure in women with severe preeclampsia. Hence, in the era of evidence- based medicine, there is a paucity of good quality evidence for the use of commonly used anti-hypertensive agents namely hydralazine and labetalol for acute blood pressure control in women with severe preeclampsia.

Therefore, authors planned this study with the objective to compare the safety and efficacy of intravenous labetalol and intravenous hydralazine in pregnant women with severe hypertension.

METHODS

Authors conducted a double blinded, randomized controlled trial between September 2015 to September 2017, in the department of Obstetrics and Gynaecol in Bharati Hospital, Pune to compare the efficacy and safety of intravenous hydralazine and labetalol for the acute lowering of blood pressure in women with severe preeclampsia. All pregnant women attending the antenatal clinic during the study period were screened.

Inclusion criteria

- Women with pregnancy of more than 20 weeks with severe hypertension and proteinuria (at least +1 on dipstick).

Severe Hypertension was defined as per the guidelines by National High Blood Pressure Education Program (NHBPEP): sustained high blood pressure: systolic ≥ 160 mmHg or more and /or diastolic ≥ 110 mmHg or more8.

Authors considered sustained high blood pressure when high values were recorded at two consecutive intervals 20 minutes apart. Written consent was obtained from each patient enrolled for the study. The study was approved by the institutional ethical committee of the Bharati Vidyapeeth Deemed University Medical College and hospital, Pune. Those who did not provide the consent, had contraindication to any of the study drugs or had other systemic diseases like asthma, cardiac disease, diabetes mellitus or renal disease were excluded from the trial.

Enrolment of participants, assessing eligibility and obtaining consent was carried out by one of the authors. Both the study investigators and the patients were blinded to the study treatment in the two groups respectively.

Randomization sequence was computer generated in a block of 10. The sequences were kept in opaque sealed envelope and were handed over to the clinical trial coordinator at the time of enrolment that administered, monitored and maintained the dose as per the protocol throughout the study period. Investigators were kept blinded to the treatment groups through pre-filled colourless intravenous study solution (Labetalol or Hydralazine in 10 ml syringe) by the coordinators in both groups.

Doing such, one group received intravenous hydralazine 5 mg initial IV bolus in not less than 5 minutes to a maximum of 20 mg and intravenous labetalol 20 mg IV bolus to a maximum of 220 mg to the other group till the target blood pressure was achieved. Sequential blood pressure recordings were obtained while the intravenous drugs were used until their maximum dose was reached or the desired blood pressure recordings (150 mmHg systolic and 100 mmHg for diastolic or lower) were achieved. Blood pressure was measured with single trained observer with LED sphygmomanometer in the left lateral recumbent position. The duration of the drug to achieve the expected blood pressure was calculated along with the need for repeat doses and their side effects. Once the blood pressure was controlled to the expected range further antihypertensive drug was initiated as per the provider's convenience. If in either of the groups, the blood pressure was not effectively lowered after 60 minutes or once the maximum dose of the drug was reached it was considered as failure.

Neonatal morbidity in terms of birth weight, 1- and 5-minute APGAR scores, NICU stay and the indication of the stay were considered. Continuous foetal heart rate monitoring was done during the course of treatment. Delivery of the new born was carried out as per the standard practice considering it to be the definitive treatment for severe pre-eclampsia.

Sample size calculations were based on a previous study by Mabie et al, whose results revealed that women who received labetalol achieved target BP in ± 33.1minutes (mean ± standard deviation) as compared to 75.8 ±30.6 minutes in patients who received hydralazine. Authors assumed mean difference of 25 mmHg with Standard deviation of 30 mmHg.[9] With alpha value of 0.05 and 80% power. Authors calculated sample size of 25 participants in each group. Allowing for attrition and possible skewed distributions that might require non-parametric testing, authors planned to randomize a total of 60 women (30 in each group).

Statistical analysis

Data was collected on a predesigned and pretested questionnaire and entered in Microsoft Xcel spread sheet. Baseline parametric data was expressed as the proportion, mean ± standard deviation and median with interquartile range. The differences in the groups were analyzed using chi-square test, unpaired t-test or Mann-Whitney test as appropriate. Fishers exact test was used as and when required. Paired t-test was used to compare the changes before and after the intervention. All statistical tests were performed using SPSS for Windows version 22 (SPSS Inc., Chicago, IL.

RESULTS

A total of 60 women were enrolled into the study. Participants in group 1 (labetalol) were akin to group 2 (hydralazine) on grounds of gravidity, gestational age, baseline SBP and DBP as shown in Table 1.

Table 1: Baseline characteristics.

Characteristics	Group 1 (Labetalol) (n=30)	Group 2 (Hydralazine) (n=30)	P value
Maternal age (years) (mean)	24.1±3.5	23.2± 2.5	0.26
Gravidity (1,2,3,4,5)	16 (53.3%)	16 (53.3%)	0.46
	5 (16.7%)	10 (33.3%)	
	5 (16.7%)	2 (6.7%)	
	2 (6.7%)	1 (3.3%)	
	2 (6.7%)	1 (3.3%)	
Gestational age (weeks) (mean)	32.9±3.2	33.9±2.6	0.20
SBP on enrollment (mmHg)	171.3±17.9	172.1±12.9	0.86
DBP on enrollment (mmHg)	115.7±7.7	118.3±7.7	0.19
Pulse rate at enrollment (bmp)	83.5±4.9	85.5±4.2	0.11

On analysing the primary outcome of the study (efficacy and safety of the anti-hypertensive drugs), statistically significant difference in SBP (add mean ± SD of drug 1 v/s drug 2) and DBP (add mean ± SD of drug1 v/s drug 2) readings were noted after 30 minutes of injecting the respective drugs though the median time taken to control the blood pressure was almost the same in both the groups (22.5 minutes) (interquartile range 25th- 75th percentile) (Figure 1).

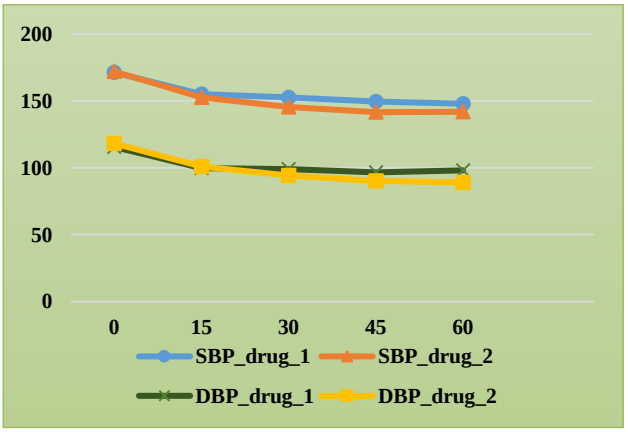

Figure 2: Profiles of mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) during treatment.

In group 2, a total number of 18 patients (60%), who received hydralazine, developed tachycardia after the 1st dose. Tachycardia persisted till 30 minutes in all these participants. By the next reading, at 45 minutes, tachycardia was relieved in 6 of these cases but continued for the rest. By the end of 60 minutes, only 9 participants (30%) persisted with tachycardia (Figure 2).

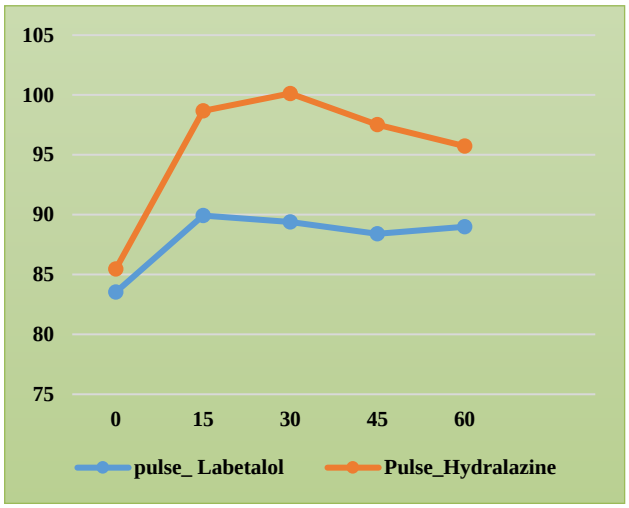

Figure 2: Mean pulse rate measurements with both Hydralazine and Labetalol during the study

Of these, 2 had reached the maximum dose of the drug, one required a repeat dose and the rest did not require any repeat dose of the drug. Maximum dose of the study drugs was reached in total 9 cases, out of which 8 were the ones who were given labetalol and 1 was from the group who received hydralazine. Close to half of the participants in each group (46.665 in group 1 and 50 % in group 2) did not require even a single repeat dose of the respective drugs to control blood pressure. This shows efficacy of both the drugs and not specific to any one drug. The failure rate with labetalol was 23.33% and with hydralazine was 3.33%. Mean birth weight in both the study groups were noted as a secondary outcome. No statistically significant outcome was noted from this data (Table 2). Of all the NICU admissions within the study 8 in each group were due to RDS. There was no foetal heart rate abnormality noted during the study.

Table 2: Mean birth weights.

Group 1	Mean Birth Weight	P value
Group 1	1.63 ± 0.66 kg	0.18
Group 2	1.86 ± 0.65 kg	

DISCUSSION

Authors conducted this double blind randomized controlled trial with the sole aim to compare the two most widely used anti-hypertensive drugs (hydralazine and labetalol) for the treatment of severe hypertension in pregnancy. In present study, authors found that the time taken to achieve the target blood pressure in pregnant

women with labetalol and hydralazine was the same. Though this is an insignificant finding of present study, it still warrants attention as a drug's efficacy is also determined by the time taken to control blood pressure and not just by its ability to reduce blood pressure. This finding of ours is at odds with the findings of Mabie et al, who found that the time taken to achieve maximum decrease in blood pressure was statistically significant between these two drugs. This can be explained by the fact that Mabie et at used different dosages of labetalol in their study.[9]

Sudden hypotension is a well-known side effect of hydralazine. However, no such event was encountered in present study.[8] There were eight failures with labetalol and one with hydralazine and the difference was statistically significant, whereas in the study by Mabie et al, the difference in the failure rates was insignificant. Failures were further managed with a change in anti-hypertensive treatment as per the choice of the care giver. There was no effect on the maternal heart rate with the use of labetalol. However, authors noted tachycardia with hydralazine in almost three forth of the patients. None of these required any supportive treatment for the same. No arrhythmia was noted, complicating drug- induced tachycardia. No pulse rate changes were noted with labetalol and this difference in the pulse rate was a highly significant finding of present study and is supported by a study done by Ashe et al. This study signifies a worrisome side effect, reflex tachycardia, of the drug hydralazine, which may limit its use in pregnant women. No significant side effects of labetalol were noted during the study. The mean weight of the new-borns in both the groups was almost similar.

CONCLUSION

The use of Hydralazine in severe pre-eclampsia has been less extensively studied as compared to control the blood pressure to other available anti-hypertensive drugs due to its tendency to cause reflex tachycardia thereby making it a less ideal anti-hypertensive drug for use in pregnancy. But this study differs in opinion. The drug needs larger trials to make a significant impact of its use as no study clearly explains the superiority of one drug over the other and hence leaves the choice of the anti-hypertensive drug on the clinician's experience and comfort. In our opinion, both Hydralazine and Labetalol are comparable drugs in spite of the fact that hydralazine shows better control of blood pressure its known side effect profile is unnerving. Hence, the use of both the drugs in patients with severe pre-eclampsia must argument the Obstetrician's armamentarium.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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