THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (September–October 2018) 68(5):376–381
https://doi.org/10.1007/s13224-017-1053-9

ORIGINAL ARTICLE

# Comparison of Efficacy and Safety of Intravenous Labetalol Versus Hydralazine for Management of Severe Hypertension in Pregnancy

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Received: 5 May 2017 / Accepted: 12 September 2017 / Published online: 10 October 2017


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## Abstract

*Background* There is no consensus about the better intravenous drug between Hydralazine and Labetalol to control hypertension in cases of severe hypertension in pregnancy. Both drugs have their own advantages and disadvantages.

*Methods* This is a prospective randomized controlled trial comparing the efficacy and safety of intravenous Labetalol versus Hydralazine for management of severe hypertension in pregnancy. A total of 152 eligible subjects were randomised in two groups consisting 76 subjects each by envelope method. Both the groups were comparable with respect to systolic, diastolic and mean arterial blood pressure at admission. One group received Labetalol and the other Hydralazine. The number of drug doses, the time taken to achieve target blood pressure and side-effects were noted.

*Results* With a single dose, Labetalol (81.5%) was able to achieve target blood pressure in a significantly higher number of cases as compared to Hydralazine (69.5%). Labetalol could help in achieving the target blood pressure faster than Hydralazine. The incidence of maternal adverse

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effects was comparable between the groups. Fetal outcome was comparable in both groups.

*Conclusion* Hydralazine and Labetalol both were found to be equally efficacious in reducing blood pressure in cases of severe hypertension in pregnancy. Labetalol achieved the target blood pressure faster than Hydralazine. The adverse effects of both the drugs were comparable.

**Keywords** Severe hypertension in pregnancy · Hydralazine · Labetalol

## Introduction

Hypertensive disorders of pregnancy are one of the most common medical disorders of pregnancy. They affect 10–15% of all pregnancies and cause significant maternal, fetal and neonatal morbidity and mortality [1]. Pregnant women with severe hypertension (systolic blood pressure $\geq$ 160 mmHg or diastolic $\geq$ 110 mmHg or both) are the most vulnerable group for maternal and fetal complications. The majority of these maternal deaths are related to cerebral hemorrhage that is secondary to poorly controlled hypertension. The ultimate cure for preeclampsia and eclampsia is the delivery of the baby. However, maternal and perinatal deaths are significantly reduced with appropriate treatment. There is general consensus in guidelines that acute management should be instituted for severe hypertension and that blood pressure should be lowered to systolic $<$ 160 mmHg and diastolic $<$ 110 mmHg. Although treatment of hypertension does not strike at the basic disorder, it may still benefit the mother and fetus.

There are many studies [2–4] and meta-analysis [5] on the subject, but there is no definitive consensus or recommendation of great power regarding which is the best antihypertensive to achieve short-term success in controlling a hypertensive crisis in pregnancy. The aim of antihypertensive therapy is to lower blood pressure quickly but safely, avoiding maternal and fetal complications.

Three short-acting antihypertensive agents: Hydralazine, Labetalol and Nifedipine (orally administered) are commonly used to control blood pressure in women with severe hypertension in pregnancy. All three agents have their pros and cons. The purpose of this study was to compare the efficacy and safety of the two intravenous drugs: Hydralazine and Labetalol in management of severe hypertension in pregnancy.

Hydralazine is a peripheral vasodilator that activates potassium channel causing potassium efflux, so decreased potassium prevents calcium-mediated smooth muscle contraction. But the vasodilatation requires nitric oxide from the endothelium. This drug is placed in US FDA Pregnancy Category C. The onset of action is 10–20 min with duration of action ranging from 3 h to 8 h. Precautionary fluid management with crystalloid 500 ml before or at the same time as first dose is advised since immediate hypotension can occur with IV Hydralazine.

Labetalol is a mixed alpha-/beta-adrenergic antagonist. The alpha-blocking action is selective to alpha 1 receptor, while the beta action is non-selective. Beta-blocking action doubles when the drug is given parenterally. By blocking adrenergic stimulation of beta-1 receptors in myocardium and alpha-1 receptors of vascular smooth muscles it reduces systemic arterial blood pressure and systemic vascular resistance without altering resting heart rate, cardiac output or stroke volume, apparently because of its combined alpha- and beta-adrenergic activity. This is classified under Pregnancy Category C of US FDA. The onset of action after reaching blood is 5 min with duration ranging from 3 h to 6 h. The maximum IV dose is 300 mg.

## Subjects and Methods

This randomized controlled trial was carried out at Department of Obstetrics and Gynecology, Medical College and SSG Hospital, Baroda, during 1-year period from December 1, 2015 to November 30, 2016 after approval from the Institutional Ethics Committee For Human Research (IECHR).

Sample size calculation: For sample size calculation, we considered meta-analysis done by Magee et al. [2]. They found a rate of persistent severe hypertension of 3.8% in the Hydralazine group and 13.5% in the Labetalol group. With an error rate of 20% and power of 80% the sample size was calculated as 152 (76 in each group).

Inclusion criteria for the study were subjects with singleton pregnancy $>$ 28 weeks of gestation with severe hypertension (systolic blood pressure of 160 mmHg or more and or diastolic blood pressure of 110 mmHg or more).

Subjects with eclampsia, multiple pregnancy, medical disorders like asthma, cardiac failure, heart block, cardiac arrhythmias and known allergy to Hydralazine and Labetalol were excluded from the study.

The eligible subjects and their relatives were given a patient information sheet, and patients were enrolled in the study after obtaining a written informed consent to participate in the study. Baseline characteristics like gestational age at presentation, blood pressure at admission and other obstetric data were noted. After careful history and general examination, standard mercury sphygmomanometer with appropriately sized cuff was used to measure the blood pressure. The first and fifth Korotkoff sounds were used to record systolic and diastolic blood pressure, respectively. The blood pressure was measured with patient

in left lateral recumbent position with the patient's arm at the level of the heart for all measurements.

Enrolled patients were allocated to one of the two therapeutic regimens using envelope method. Randomization was performed using sealed envelopes indicating their medication. One group of patients received Hydralazine, and the other group was given Labetalol. The desired end point was systolic blood pressure 140–150 mm Hg and diastolic blood pressure 90–100 mm Hg. This was to prevent repeated prolonged exposure of the patient to severe systolic hypertension with subsequent loss of cerebral vasculature auto-regulation. After initial stabilization, the BP was monitored closely and maintenance therapy was instituted with the same drug as needed. In case the primary drug was not able to control the hypertension as desired, Nifedipine 10 mg orally was added. The drugs were administered as per the study protocol given below. In this study, we did not give the maximum permissible dose of the drugs.

Hydralazine group: In this group, the subjects received Hydralazine 5 mg intravenously over 2 min. Blood pressure was measured after 20 min and if either BP threshold was still found to be high, Hydralazine 10 mg was administered slowly intravenously over 2 min. After 20 min, if BP was still higher than the threshold, oral Nifedipine 10 mg was administered and BP monitoring was continued. If BP was below threshold, BP monitoring was continued. If the BP was still high, a physician reference was sought and further medications were continued as per their advice.

Labetalol group: In this group, the subjects received Labetalol 20 mg intravenously over 2 min. Blood pressure was measured after 10 min and if either BP threshold was still found to be high, Labetalol 40 mg was administered slowly intravenously over 2 min. After 10 min, if BP was still higher than the threshold, Labetalol 80 mg was administered and BP monitoring was continued. After 10 min, if BP was still higher than the threshold, oral Nifedipine 10 mg was administered and BP monitoring was continued. If BP was below threshold, BP monitoring was continued. If the BP was still high, a physician reference was sought and further medications were continued as per their advice.

Management of severe preeclampsia included termination of pregnancy using induction of labor and preventing seizures, all women received magnesium sulfate as a 4-g intravenous loading dose over 10 min and 10 g intramuscularly (5 g in each buttocks). Maintenance dose 5 g intramuscularly in alternate buttocks was administered every 4 h until 24 h after delivery.

The fetal heart rate was recorded every 10 min during the loading infusion. Fetal heart rate was monitored using cardiotocography at every 30-min interval. The rest of the obstetric management was similar for both groups of patients.

## Data Collection

Participant data including demographic characteristics like age, parity, a detailed medical and obstetric history, labor course and outcomes were collected and entered in excel sheet. Primary outcome measures studied were the number of doses and time taken to achieve target blood pressure. Secondary outcome measures studied were persistent severe hypertension, requirement of additional drug, convulsions after drug administration, mode of delivery, maternal hypotension ($< 90$ mm Hg systolic BP), maternal tachycardia ($> 120$ bpm), maternal complications like headache, nausea, vomiting, epigastric pain, visual disturbances, dizziness, fetal heart rate abnormalities, incidence of fresh stillbirth, abnormal APGAR scores: 1 min APGAR $< 7$ and/or 5 min APGAR $< 7$ and incidence of NICU admission.

## Data Analysis

Data was analyzed using SPSS (Statistical package software for social sciences) version 16.0. $\chi^2$ test was used to analyze categorical variables, and unpaired $t$ test was used to analyze continuous variables. Fisher exact test was used to compare the maternal and fetal outcomes. $P$ value of less than 0.05 was accepted as indicating statistical significance.

## Results

Both the groups were comparable as regards age distribution, parity and gestational age. Forty-eight (63.2%) out of 76 women delivered normally in the Hydralazine group as compared to 55 (72.3%) in the Labetalol group. Twenty-eight (36.8%) in the Hydralazine group and 21 (27.7%) in the Labetalol group underwent cesarean section. The difference was statistically insignificant ($P$ value by $\chi^2$ test $= 0.22$). Indications for LSCS were fetal distress, pathological cardiotocography findings, cephalopelvic disproportion, non-progression of labor and breech presentation in primigravida.

Table 1 indicates that mean systolic blood pressure was $169.6 \pm 11.71$ in Hydralazine group and $172.3 \pm 12.6$ in Labetalol group, which was comparable for both groups. Mean diastolic blood pressure in Hydralazine group was $105.6 \pm 8.38$ mm Hg, and in Labetalol group mean was $104.6 \pm 8.23$ mm Hg. The difference was statistically

**Table 1** Blood pressure values at the time of admission

| Blood pressure in mm hg | Hydralazine group $n = 76$ (%) | Labetalol group $n = 76$ (%) | $P$ value (unpaired $t$ test) |
|---|---|---|---|
| Systolic blood pressure | | | |
| 160–180 | 71 (93.4) | 66 (86.8) | |
| 181–200 | 4 (5.3) | 9 (11.9) | |
| > 201 | 1 (1.3) | 1 (1.3) | |
| Mean ± SD | 169.6 ± 11.7 | 172.3 ± 12.6 | 0.17 |
| Diastolic blood pressure | | | |
| 80–100 | 39 (51.3) | 44 (57.8) | |
| 101–110 | 29 (38.2) | 23 (30.3) | |
| 111–120 | 7 (9.2) | 9 (11.9) | |
| > 120 | 1 (1.3) | – | |
| Mean ± SD | 105.6 ± 8.36 | 104.6 ± 8.23 | 0.45 |
| Mean arterial pressure | | | |
| 110–120 | 28 (36.8) | 19 (25) | |
| 121–130 | 28 (36.8) | 43 (56.6) | |
| 131–140 | 16 (21) | 7 (9.2) | |
| > 140 | 4 (5.4) | 7 (9.2) | |
| Mean ± SD | 126.94 ± 7.99 | 127.15 ± 8.15 | 0.8 |

**Table 2** Number of drug doses required

| Number of doses | Hydralazine group $n = 76$ (%) | Labetalol group $n = 76$ (%) | $P$ value ($\chi^2$ test) |
|---|---|---|---|
| 1 | 53 (69.7) | 62 (81.5) | 0.04 |
| 2 | 23 (30.3) | 12 (15.8) | |
| 3 | – | 2 (2.7) | |

insignificant ($P$ value = 0.45). The difference in the mean arterial blood pressure between the two groups was statistically insignificant ($P$ value = 0.8).

Table 2 shows that 69.7% subjects in Hydralazine group and 81.5% in Labetalol group required only one dose to lower the blood pressure to desired level; the difference was statistically significant. ($P$ value = 0.04). Thus, in this study, with a single dose, Labetalol was able to achieve target blood pressure in a significantly higher number of cases as compared to Hydralazine. Fourteen out of 76 subjects (18.5%) receiving Labetalol and 23 out of 76 subjects (30.3%) receiving Hydralazine required a second or a third dose of the drug. On comparison by the $\chi^2$ test, the $P$ value ($\chi^2 > 2.894$) was 0.0889, which was statistically significant.

Table 3 indicates that Labetalol achieved the target blood pressure faster than Hydralazine.

Table 4 indicates that the incidence of adverse effects like headache, nausea, vomiting and visual disturbances in the subjects was minimal and comparable between the groups. There were no maternal deaths in any of the women studied.

**Table 3** Time taken to achieve target blood pressure (140/90 mm hg)

| Time in minutes | Hydralazine group $n = 76$ (%) | Labetalol group $n = 76$ (%) | $P$ value (unpaired $t$ test) |
|---|---|---|---|
| 10 | 1 (1.3) | 62 (81.5) | |
| 20 | 52 (68.3) | 12 (15.8) | |
| 40 | 21 (27.7) | – | |
| 50 | 2 (2.7) | 2 (2.7) | |
| Mean ± SD (95% ci) | 26.32 ± 9.78 (24.08–28.55) | 12.63 ± 7.19 (10.99–14.27) | < 0.0001 |

Table 5 indicates that the fetal outcome was comparable in both the groups.

## Discussion

Earlier meta-analysis [6, 7] suggested that parenteral Hydralazine may be associated with a higher risk of maternal hypotension, and less persistent hypertension as compared to Labetalol. Especially, the use of Hydralazine in continuous infusion was associated with more episodes of hypotension than Labetalol and was associated with higher maternal adverse effects like headache, palpitations, tachycardia and flushing [2]. These results made clinicians to believe that Labetalol was a safer option in hypertensive crisis and the use of Hydralazine was very limited. The maternal hypotension associated with Hydralazine in the earlier studies made Labetalol a preferable option.

**Table 4** Maternal complications

| | Hydralazine group $n = 76$ (%) | Labetalol group $n = 76$ (%) | $P$ value (comparison of proportion) | Fisher's exact test |
|---|---|---|---|---|
| Headache | 2 (2.7) | 3 (3.9) | 0.97 | 1 (NS) |
| Nausea | 2 (2.7) | – | | 1 (NS) |
| Vomiting | – | 2 (2.7) | | 0.49 (NS) |
| Visual disturbances | 1 (1.3) | – | | 1 (NS) |
| Additional drug required | 2 (2.7) | 2 (2.7) | | 1 (NS) |
| Persistent hypertension | 2 (2.7) | 3 (3.9) | 0.97 | 1 (NS) |
| Convulsion after drug administration | 3 (3.9) | 1 (1.3) | 0.62 | 0.61 (NS) |
| Maternal hypotension | 1 (1.3) | – | | 1 (NS) |
| Maternal tachycardia | – | 1 (1.3) | | 1 (NS) |

**Table 5** Fetal complications

| | Hydralazine group $n = 76$ (%) | Labetalol group $n = 76$ (%) | $P$ value (comparison of proportion) | Fisher's exact test |
|---|---|---|---|---|
| 1 min APGAR score $< 7$ | 7 (9.7) | 8 (11.1) | 0.57 | 0.79 (NS) |
| 5 min APGAR score $< 7$ | – | 1 (1.4) | | 1 (NS) |
| Fetal heart abnormalities | 21 (29.1) | 12 (16.6) | 0.11 | 011 (NS) |
| Fresh stillbirth | 4 (5.2) | 3 (3.9) | 0.99 | 1 (NS) |
| NICU admission | 31 (43) | 35 (48.6) | 0.61 | 0.62 (NS) |

However, recent studies suggested that both the drugs have a similar efficacy in controlling hypertensive crisis in patients with hypertension in pregnancy. The number of cases with persistent hypertension and maternal hypotension were also similar, as well as the adverse effects [3, 4].

In a similar study by Delgado De Pasquale [3], the analysis of the primary outcome (antihypertensive efficacy) found no statistical differences in systolic, diastolic and mean blood pressure between the Hydralazine and Labetalol groups. A total of six cases (4.6%) in the Hydralazine group and two cases (1.5%) in the Labetalol group ($p = 0.085$) developed persistent hypertension. Although this difference was not statistically significant, they did observe a trend of persistent hypertension with the use of Hydralazine. In our study, we found the incidence of persistent hypertension similar in both groups. The frequency of other adverse reactions showed no statistically significant difference between groups. In this study, the incidence of persistent hypertension requiring additional drug was similar in both the groups.

In a recent study by Sharma [4], 69 women received Hydralazine and 31 women received Labetalol during the study period. The incidence of hypotension ($\geq$ 30% reduction in systolic BP) was similar between the Labetalol (10%) and Hydralazine (11%) groups ($p = 0.98$). No women experienced post-treatment systolic BP $< 90$ mmHg. In our study, only one subject in the Hydralazine group and none in the Labetalol experienced hypotension. No association was observed between fetal heart rate category change and drug used. No women required emergent delivery for fetal indications.

A meta-analysis conducted by Duley et al. [5] found insufficient data for reliable conclusions about the comparative effects of these two antihypertensive agents. They concluded that until better evidence is available, the choice of antihypertensive should depend on what is known about adverse drug effects and how familiar the clinician is with a particular drug.

A comparative study of Hydralazine and Labetalol was carried out by Nombur et al. [8]. This randomized clinical trial for the treatment of severe preeclampsia using either Hydralazine or Labetalol demonstrated that both drugs remain effective. Contrary to our study, the time to achieve control and the required number of doses were not statistically different between the two groups. The difference in the number of women in both groups that had persistent hypertension was not statistically significant. There was no maternal hypotension in both groups. Headache was significantly more frequent in patients given Hydralazine than following Labetalol use in this study. The difference was statistically significant (25.4% vs. 3.2%, respectively, $p = 0.01$). There were no significant differences observed in fetal outcome between the two arms of study.

A comparative study of IV Labetalol and IV Hydralazine on mean arterial blood pressure changes in pregnant women with hypertensive emergency by Swati et al. [9] showed no significant difference between the changes in the mean arterial blood pressure after giving drugs; concluding that both the drugs were equally effective in management of severe hypertension in pregnancy.

In a systematic review [10] of the antihypertensives for severe hypertension in pregnancy, 11 studies with 608

participants met inclusion criteria. Five studies compared Hydralazine to Labetalol, three studies compared Hydralazine to Nifedipine, and three compared Labetalol to Nifedipine. Time to achieve target BP was shorter with Nifedipine than Hydralazine (two studies, 176 participants, standard difference in means 0.357; 95% CI, 0.059, 0.656). Two additional studies with a total of 110 participants compared Nifedipine to Labetalol, but data could not be combined via meta-analysis. Both found shorter time to achieve target BP with Nifedipine, although this difference was significant in only one study. They found no significant differences in any other outcomes including treatment failure, mode of delivery, eclampsia, hypotension, fetal heart rate abnormalities, NICU admission, or maternal or perinatal mortality. The reviewers concluded that Nifedipine is associated with a shorter time to achieve target BP as compared to either Hydralazine or Labetalol. There are no other differences in maternal or fetal outcomes to suggest superiority of one agent over the others.

## Conclusions

Hydralazine as well as Labetalol were found to be equally efficacious in reducing blood pressure in cases of severe hypertension in pregnancy. Labetalol achieved the target blood pressure faster than Hydralazine. The adverse effects of both the drugs were comparable.

### Compliance with Ethical Standards

**Conflict of interest** Dr Purvi Patel, Dr Deepika Koli, Dr nandita Maitra, Dr Tosha Sheth and Dr Palak Vaishnav have no conflict of interest.

**Informed Consent** Informed written consent was obtained from all participants of the study.

**Ethical Approval** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008 (5).

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