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Original Research Article

Comparative study of intravenous hydralazine and labetalol in severe hypertensive disorders of pregnancy

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ABSTRACT

Background: Hypertensive disorders of pregnancy are among the most common medical complications of pregnancy and major cause of maternal, fetal and neonatal morbidity and mortality. The purpose of this study was to compare the efficacy and safety of intravenous hydralazine and labetalol for management of severe hypertensive disorders of pregnancy.
Methods: This prospective study was conducted among 100 women admitted with SBP ≥ 160 or DBP ≥ 110 mmHg or both. Patients were divided into 2 groups randomly: labetalol and hydralazine group.
Results: Majority of patients (38%) were in the age group of 21-25 years and primigravida (52%). There was more significant decrease in the systolic, diastolic and mean arterial blood pressure at the end of 15 and 30 minutes in labetalol group. Labetalol required fewer doses as compared to hydralazine to achieve the target blood pressure (average 1.95 versus 3.1). Total numbers of term deliveries were 19 (38%) in hydralazine group and 16 (32%) in labetalol group. Pre-term deliveries in hydralazine and labetalol group were 14 (28%) and 15 (30%) respectively. Headache was significantly more common in hydralazine treated patients than labetalol group.
Conclusions: Both hydralazine and labetalol were effective and well-tolerated in the treatment of severe hypertensive disorders of pregnancy. Labetalol may be preferred because it was more effective in lowering the systolic blood pressure, diastolic blood pressure and mean arterial pressure to achieve target levels with less number of doses.

Keywords: Hydralazine, Hypertensive disorders of pregnancy, Labetalol, Mean arterial blood pressures

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are the common medical disorders in pregnancy. It affects both expectant mother and fetus. The impact due to this disorder on maternal and neonatal mortality and morbidity is very high in India and other developing countries.[1] The incidence of pregnancy induced hypertension (PIH) in India is about 7-10%.[2] Hypertensive emergency is a condition of hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg or both) which is acute in onset, persistent for 15 minutes or more.[3]

There are various theories for the etiology of HDP which includes vasopressin onset, coagulation system activation, increased inflammatory response, abnormal trophoblast invasion and ischemia. Common pathophysiological changes seen are imbalance between vasoconstrictor thromboxane and vasodilator prostacyclin resulting in generalized vasospasm. This leads to endothelial damage resulting in release of vasoactive

substances which causes decreased intravascular volume and increased extravascular volume. The effects of this are placental insufficiency resulting in complications.[4-6]

A prompt control of blood pressure is of crucial importance to prevent sequel of disease. Parenteral labetalol and hydralazine has been used as first line drug for the treatment of acute severe hypertension.[7] Intravenous hydralazine, oral nifedipine and intravenous labetalol are used for the treatment of hypertensive crisis in pre-eclampsia since many decades.[8] These drugs are used alone or in combinations in routine obstetric practice. Duley et al, compared different antihypertensive drugs for very high blood pressure during pregnancy and concluded that, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug and its adverse.[9] Magnesium sulfate is the medication of choice for the prevention of eclamptic seizures in women with severe preeclampsia and for the treatment of women with eclamptic seizures.[10]

Hydralazine has been serving as anti-hypertensive since over 40 years. It acts as a vasodilator, decreases peripheral resistance and lowers blood pressure. The effects are of short duration and system reset itself to the blood pressure levels necessary to maintain pressure in kidney necessary for natriuresis. It is not used as primary drug because it elicits a reflex sympathetic stimulation of heart which would results in increased heart rate and cardiac output and risk of angina with myocardial infarction. A meta-analysis of clinical trials showed that maternal hypotension may be more common with parenteral hydralazine, which was also associated with an excess of caesarean sections, placental abruptions, and low Apgar scores (< 7) at five minutes.[11]

Labetalol is alpha-1 selective, nonselective beta-adrenergic blocker drug that causes a decrease in systemic arterial blood pressure and systemic vascular resistance without a substantial reduction in resting heart rate, cardiac output or stroke volume. Labetalol may be considered as first line drug, but there is a potential risk of fetal bradycardia. It has little placental transfer due to the poor lipid solubility.[12]

Hence, the aim of the present study is to compare two commonly used drug in India, i.e. IV hydralazine and IV labetalol in terms of efficacy, time and doses required to achieve desired level of blood pressure, safety profile and adverse effect of the drug, and also to observe the fetomaternal outcomes.

METHODS

The present study is a prospective study which was carried out in the department of obstetrics and gynaecology of Nalanda Medical College and Hospital, Patna from October 2015 to September 2017. The cases were selected from those admitted in labour room.

Inclusion criteria

- Age 16 to 35 years
- Patient with severe pre-eclampsia/eclampsia and blood pressure greater than or equal to 160/110 mmHg on at least two times after ten minutes of rest
- Single or multiple pregnancy
- Gestational age more than or equal to 24 weeks
- No contraindication to the use of labetalol or hydralazine.

Exclusion criteria

- Patient having history of allergy to labetalol or hydralazine, or other drugs of these groups.
- History of diabetes mellitus, bronchial asthma, cardiac disease, liver disease or hematological disorders.
- Patient previously diagnosed to have chronic hypertension.
- Maternal heart rate less than 60 or more than120 beats/min.

A total of 100 patients of severe preeclampsia/eclampsia with blood pressure ≥ 160/110 mmHg were included in study. Ethical clearance from the Institutional Human Ethics committee of Nalanda Medical College and Hospital, Patna was taken for the study. Also informed consent was taken from each patient.

Enrolled patients were randomly assigned to receive either intravenous labetalol (study Group A) or intravenous hydralazine (study Group B) until satisfactory BP control was achieved that is less than 150/100 mmHg.

Study Group A

A total 50 patients received 20 mg labetalol intravenous bolus over 2-4 minute followed by 40 mg 15 minutes later, then 80 mg every 15 minutes till the desired level of blood pressure was achieved or maximum of 5 doses.

Study Group B

A total 50 patients received 5 mg hydralazine intravenous bolus over 5 minute and repeated increasing by 5 mg every 15-minute interval until the desired effect was achieved or maximum 5 doses.

Maternal monitoring was done by record of pulse rate, respiratory rate, blood pressure and urine output every 15 minutes till the target blood pressure was achieved and thereafter for 24 hours. Fetal monitoring was done by intermittent fetal heart auscultation interval and cardiotocography when required. Labour events were monitored with the help of partograph.

Treatment was considered failure if blood pressure was not decreased below desired level even after increasing the dose to maximum, then additional antihypertensive agent was added and was managed conservatively. Patient was followed for 48 hours post-partum or until discharge. In case if patient developed hypotension (BP ≤ 90/60 mmHg), the trial was terminated and patient was treated with intravenous fluid bolus challenge. Injection $MgSO_4$ was given according to pritchard regimen to each patient.[13]

Statistical analysis

The data was inserted into Excel and then analyzed in the program STATA/SE version 13.0. The categorical data were presented as numbers (percent) and were compared among groups using Chi square test. A 'p' value of less than or equal to 0.05 was considered as statistically significant.

RESULTS

A total 100 patients of severe HDP enrolled in this study were equally divided into two groups to receive either intravenous labetalol (study Group A) or intravenous hydralazine (study Group B) until satisfactory BP control was achieved.

Age distribution

Maximum incidence of the preeclampsia in both groups were between 21 and 25 years (38%) followed by 26 to 30 year (27%). Overall mean age at presentation was 25.2 years.

Table 1: Gravidity distribution of patient.

Gravidity	Hydralazine group no. (%)	Labetalol group no. (%)	Total no. (%)
Primi gravid	24 (48)	28 (56)	52 (52)
Second gravid	9 (18)	8 (16)	17 (17)
Third gravid	6 (12)	5 (10)	11 (11)
Fourth gravid and above	11 (22)	9 (18)	20 (20)

Table 2: Gestational age distribution of patient.

Gestational age (week)	Hydralazine group no. (%)	Labetalol group no. (%)	Total no. (%)
24-28	2 (4)	3 (6)	5 (5)
29-32	8 (16)	7 (14)	15 (15)
33-35	14 (28)	16 (32)	30 (30)
> 35	26 (52)	24 (48)	50 (50)

Table 3: Response of drugs on blood pressure.

	Pre-treatment BP (mmHg)		Post-treatment BP (mmHg)	
	Hydralazine group	Labetalol group	Hydralazine group	Labetalol group
Mean SBP	172.44	173	136.66	137.36
Mean DBP	116.76	117.2	86.84	89.16
Mean MAP	134.09	135.52	103.14	104.88

BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure.

Gravidity distribution

The incidence of preeclampsia was maximum in primigravida i.e. in 52 (52%) patients. It was nearly similar in both study groups (48% in hydralazine versus 56% in labetalol group) (Table 1). 2nd maximum (20%) incidence was in fourth gravida or above and least in 3rd gravida (11%).

Rural/urban population distribution and socioeconomic status

A total 65% patients had rural background and 56% belonged to low socioeconomic status.

Gestational age distribution

Maximum number of cases (50%) had gestational age more than 35 weeks followed by 30% who belonged to 33-35 weeks. Only 5 cases had gestational age of 24-28 weeks. Overall mean gestational age was 35.2 weeks (Table 2).

Diagnostic features

A total 35% patients had only hypertension and proteinuria 3+, 13% of patients had visual symptoms and 5% of patients had HELLP syndrome (hemolysis, elevated liver enzymes and low platelets). Two still birth

was observed in patients having HELLP syndrome. Thrombocytopenia (platelet < 10^5/mm^3) was seen in 15% of patients.

Opthalmoscopic findings

There was normal ophthalmoscopic finding in maximum number of cases (62%). 25% (12 patients in hydralazine and 13 patients in labetalol group) cases had angiospasm. Retinal oedema was seen in 13% and there was no case with hemorrhage and exudates in any group.

Maternal serum uric acid: Maximum number (59%) of patients had serum uric acid level in between 4.6-6.0 mg% whereas 6% patients had serum uric acid level > 6.0 mg%.

Maternal haemoglobin (Hb)

Maximum number of patients (41%) had Hb between 6.1-8 gm% and 17% had Hb less than 6 gm%. 35% cases had Hb between 8.1-10 gm%. Only 7% patients had Hb more than 10 gm%.

Response of drugs on blood pressure

Pre-treatment mean systolic blood pressure (SBP) in the hydralazine group was 172.44 mmHg while in the labetalol group it was 173 mmHg (Table 3). Pre-treatment mean diastolic blood pressure (DBP) was 116.76 mmHg in the hydralazine group and 117.2 mmHg in the labetalol group. Hence, pre-treatment mean arterial pressure (mean MAP) in the former group was 134.09 mmHg and 135.52 mmHg in the later group.

After treatment, mean SBP in the hydralazine group was 136.66 mmHg while in the labetalol group it was 137.36 mmHg. The mean DBP after treatment was 86.84 mmHg in the hydralazine group and 89.16 mmHg in the labetalol group. Hence, the mean MAP in the former was 103.14 mmHg and 104.88 mmHg in the later group.

The mean fall in MAP in the hydralazine group was 30.95 mmHg and, in the labetalol, group was 30.64 mmHg which was statistically not significant. However, reduction of mean arterial blood pressure achieved within 15 minutes with labetalol was almost double that of hydralazine (17.72 mmHg versus 9.05 mmHg; $p < 0.05$) indicating the rapid onset of action of labetalol.

Dose required to achieve target blood pressure

A total 42% of patients achieved target blood pressure with first dose of labetalol whereas in hydralazine group only 16% patients achieved target blood pressure with first dose, indicating rapid lowering of blood pressure in labetalol group ($p = 0.00$) (Table 4). Average number of doses required in the labetalol group was 1.95 while in the hydralazine group it was 3.1 ($p = 0.04$). 4% patients in hydralazine group and 6% in labetalol group did not achieved the target blood pressure with maximum doses and were treated with nitroglycerine microdrip.

Table 4: Dose required to achieve target blood pressure.

No. of dose	Hydralazine group no. (%)	Labetalol group no. (%)
1st	8 (16)	19 (38)
2nd	14 (28)	13 (26)
3rd	11 (22)	9 (18)
4th	9 (18)	4 (8)
5th	6 (12)	2 (4)
Average dose	3.1	1.95
Alternative drug	2 (4)	3 (6)

Table 5: Side effect of drugs.

Side effect	Hydralazine group no. (%)	Labetalol group no. (%)
Headache	11 (22)	2 (4)
Palpitation	4 (8)	1 (2)
Nausea/vomiting	3 (6)	3 (6)
Epigastric pain	2 (4)	1 (2)
Dizziness	0 (0)	2 (4)
Maternal tachycardia	4 (8)	0 (0)
Hypotension	2 (4)	0 (0)
Fetal bradycardia	0 (0)	2 (4)

Side effects

Headache was seen in 11 (22%) patients of hydralazine group and only 2 (4%) patients in labetalol group had this side effect (Table 5). Palpitation was also more common in hydralazine (6% versus 2% in labetalol). Maternal tachycardia was seen in 4 (8%) patients of hydralazine while no patient in labetalol group had tachycardia. No fetal bradycardia was observed in hydralazine treated group while in 2 (4%) cases of labetalol group it was seen. Dizziness was seen only in labetalol group (4% cases). Hypotention was seen only in 2 cases of hydralazine group. There were no maternal deaths in any of the women studied.

Mode of delivery

In our study, maximum number of patients (41%) had induced vaginal delivery (Table 6). In hydralazine group, 15 (30%) patients had spontaneous vaginal delivery whereas 21 (42%) patients had induced vaginal delivery. Eleven (22%) patients underwent lower segment caesarean section (LSCS) and three patients had instrumental delivery. In labetalol group, 33 (66%) patient delivered vaginally among them 20 (40%) patients required some form of intervention. 13 (26%) required LSCS and four had instrumental delivery. The most common indication of LSCS in both the groups was fetal distress.

Table 6: Mode of delivery.

Mode of delivery	Hydralazine group no. (%)	Labetalol group no. (%)
Spontaneous vaginal	15 (30)	13 (26)
Induced vaginal	21 (42)	20 (40)
Instrumental	3 (6)	4 (8)
LSCS	11 (22)	13 (26)

LSCS: Lower segment caesarean section.

Perinatal outcome

There were no significant differences in the fetal outcome in both the groups (P > 0.05) (Table 7). Total numbers of term deliveries were 19 (38%) in hydralazine group and 16 (32%) in labetalol group. Pre-term deliveries in hydralazine and labetalol group were 14 (28%) and 15 (30%) respectively. Intrauterine growth retardation was 11 (22%) and 12 (24%) in hydralazine and labetalol group respectively whereas still birth was almost similar i.e. 6 (12%) and 7 (14%) respectively. Low Apgar (< 7) score at 1 min in hydralazine and labetalol group was found in 3 (6%) and 1 (2%) new-borns respectively. However, low Apgar score at 5 min were seen in equal new-born in both study groups i.e. 2 (4%).

Table 7: Fetal outcome.

Perinatal outcome	Hydralazine group no. (%)	Labetalol group no. (%)
Term delivery	19 (38)	16 (32)
Preterm delivery	14 (28)	15 (30)
IUGR	11 (22)	12 (24)
Still birth	6 (12)	7 (14)
Apgar score (< 7) at		
1 min	3 (6)	1 (2)
5 min	2 (4)	2 (4)
Birth weight (gm)		
1500-2000	16 (32)	17 (34)
2001-2500	24 (48)	23 (46)
2501-3000	8 (16)	9 (18)
3001-3500	2 (4)	1 (2)

In both study groups, maximum numbers of new-born had their birth weight between 2001-2500 gm, 24 (48%) in hydralazine group and 23 (46%) in labetalol group. 33 (16 in hydralazine versus 17 in labetalol group) patients had new-born of weight between 1500-2000 gm either due to intrauterine growth retardation or prematurity. Only three patients had new-born of weight more than 3 kg. No patient in either group had new-born with body weight either less than 1500 gm or more than 3500 gm. The mean birth weight of both groups was 2.1 kg.

DISCUSSION

Hypertensive disorder of pregnancy is one of the direct causes of maternal mortality and morbidity globally. It is responsible for 31% of maternal deaths in India.[14] Therefore, controlling hypertension in pregnancy prevents complications both in mother and fetus.

Hydralazine has been serving as anti-hypertensive since over 40 years. However, it is not used as primary drug because it elicits a reflex sympathetic stimulation of heart which would results in increased heart rate and cardiac output and risk of angina with myocardial infarction.[11] Labetalol may be considered as first line drug, but there is a potential risk of fetal bradycardia.[12]

The purpose of this study was to compare the efficacy and safety of intravenous hydralazine and labetalol for management of severe pre-eclampsia. For this study, pregnant women fulfilling inclusion criteria were enrolled. Base line characteristics of patients were analyzed together in two treatment groups. Whereas efficacy, maternal and neonatal out comes were analyzed separately in two treatment groups.

In our study, maximum incidence of the preeclampsia was between 21 and 25 years (38%) followed by 26 to 30 year (27%). 52% patients were primigravida and 20% were fourth gravida or above (Table 1). Maximum patients (56%) belonged to low socioeconomic status and 65% had rural background. Nombur LI et al, found maximum cases (37.30%) of severe preeclampsia in the age group of 25 to 29 years. They also found that majority of women (71.42%) are from urban area and are likely to utilize the facility for antenatal care may be responsible for this finding.[15] Prakash J et al, reported that 57% patients were primigravida and 43% were multigravida.[16] This support the fact that preeclampsia is more common among primigravidae. A population-based cohort study concluded that low socioeconomic status is a strong risk factor for preeclampsia.[17] Mean gestational age in this study was 35.2 weeks. Maximum number of cases (50%) had gestational age more than 35 weeks followed by 30% who belonged to 33-35 weeks (Table 2). Nombur LI et al, also found majority (59.52%) of cases had gestational age more than 35 weeks.[15] Khan A et al. showed that mean gestational age in labetalol group was 33.23 weeks and in hydralazine group was 32.97 weeks.[18]

A total 5% of patients in this study had HELLP syndrome and thrombocytopenia was seen in 15% of patients. Prakash J et al, reported thrombocytopenia in 18% and HELLP syndrome in 7.5% of pre-eclamptic patients.[16] Study by Rahim et al, concluded that platelet count is a very important investigation for antenatal mother having PIH as it directly related to maternal and perinatal outcome.[19] Ophthalmoscopic finding was normal in maximum number of cases (62%) in our study. 25% cases had angiospasm and retinal oedema was seen in 13% cases. In Bakhda RN study, normal fundus seen in 49% cases, arterial attenuation in 16.33%, arterio venous crossing changes along with retinal edema in 21.67%, hemorrhages and exudates in 11.67%, papilledema in 0.33% and retinal detachment in 1%.[20]

Higher maternal serum uric acid is associated with poor perinatal outcome. In our study, 59% of patients had serum uric acid level in between 4.6-6.0 mg% whereas 6% had > 6.0 mg%. Patel T study also concluded that there is increased risk of an Apgar score < 7 by 6.0 fold, intrauterine fetal death (IUFD) by 20 fold, intrauterine growth retardation (IUGR) by 4.0 fold, eclampsia by 4.2 fold and cesarean section by 3.4 fold in patients with a uric acid level 6 mg/dl as compared to those with a level of < 6 mg/dl.[21] Also, severe anemia has been found to be a major risk factor for preeclampsia and eclampsia.[22]

In this study (Table 3), mean fall in MAP in the hydralazine group was 30.95 mmHg and in the labetalol group was 30.64 mmHg which was statistically not significant. However, reduction of mean arterial blood pressure achieved within 15 minutes with labetalol was almost double that of hydralazine (17.72 mmHg versus 9.05 mmHg; P < 0.05) indicating the rapid onset of action of labetalol. Khan A et al, study found that mean fall in MAP in labetalol group was 29.10±7.21 mmHg and that in the hydralazine group was 25.05±10.15 mmHg, which was statistically significant with the P-value being 0.046.[18] In a study conducted by Mable WC et al, authors found hydralazine lowered mean arterial pressure more than labetalol, that is 13.3 versus 11.2 mmHg.[23] Trivedi Swati et al, in their analysis, did not found statistical difference in MABP between the hydralazine and labetalol groups but overall effects of both the drugs were comparable.[24]

In our study (Table 4), labetalol had statically significant rapid blood pressure lowering effect than hydralazine (P = 0.00). This finding corresponds to that of Khan A et al, study.[18] Average number of doses required to achieve target blood pressure in the labetalol group was 1.95 and in the hydralazine group it was 3.1 (P = 0.04) while in Khan A et al, study average number of doses required in the labetalol group was 1.59 and 1.90 in hydralazine group.[18]

In our study (Table 5), headache, palpitation and hypotension was more common in hydralazine group. Maternal tachycardia was seen in 8% patients of hydralazine group while fetal bradycardia observed in 4% cases of hydralazine treated group only. There were no maternal deaths in any of the women studied. Khan A et al, study showed that patients in hydralazine group had headache and tachycardia more often as compare to labetalol group. Side effects like maternal hypotension, nausea, vomiting, adverse fetal heart rate recording was not noted significantly in either group.[18] Gracia VD et al. found that hypotension and bradycardia were significantly more frequent in the labetalol than hydralazine group.[12]

In our study (Table 6), maximum number of patients (41%) had induced vaginal delivery, 28% spontaneous vaginal delivery, 24% underwent lower segment caesarean section (LSCS) and 7% had instrumental delivery. The most common indication of LSCS in both the groups was fetal distress. Nombur LI et al, found that over 90% of the women in both groups had normal delivery without complications.[15]

In present study, there were no significant differences in the fetal outcome in both the groups (Table 7). Pre-term deliveries in hydralazine and labetalol group were 28% and 30% respectively. Intrauterine growth retardation was 22% and 24% in hydralazine and labetalol group respectively whereas still birth was almost similar i.e. 12% and 14% respectively. Nabanita D et al and Nombur LI et al, also had findings similar to this study.[15,25] However, Magee LA et al, found more cases of stillbirth in hydralazine group than labetalol group.[11] In our study, low Apgar (< 7) score at 1 min in hydralazine and labetalol group was found in 6% and 2% newborns respectively. However, low Apgar score at 5 min were seen in 4% of newborn in both study groups. Magee LA et al, showed that hydralazine was associated with more low Apgar scores at one minute than labetalol (67% versus 15%) but the incidence of low Apgar scores at five minutes did not differ between groups.[11]

The mean birth weight of newborn in both groups was 2.1 kg in our study. Maximum numbers of newborn (Table 7) had their birth weight between 2001-2500 gm (48% in hydralazine group and 46% in labetalol group). 33% newborn had weight between 1500-2000 gm which may be due to intrauterine growth retardation or prematurity. No patient in either group had newborn with body weight either less than 1500 gm or more than 3500 gm. Nombur LI et al, study had maximum numbers of newborn (51.58%) with birth weight between 2.5-3.9 kg followed by 37.30% newborn between 1.5-2.4 kg.[15]

CONCLUSION

We found that both intravenous hydralazine and labetalol are effective and well-tolerated in the treatment of severe HDP. Intravenous labetalol may be preferred because it is more effective in lowering blood pressure to achieve target levels with less number of doses. Also, the availability and cost of the drug are important requirement for use of particular drug.

However, poor neonatal outcome especially, neonatal mortality rate emphasizes the need for patient education, education of primary health care personal, prompt diagnosis of high-risk patients, timely referral to tertiary care centre, regular antenatal care (ANC) attendance, improved prenatal care, prompt treatment of elevated BP at the earliest.

The baseline characteristics and pre-treatment risk factors of the study may be useful in diagnosing high risk patients. Outcome of this study is useful to the practicing obstetricians in choosing an appropriate antihypertensive agent as well as in formulating the guidelines for treatment of hypertensive disorders in pregnancy.

Further, well designed randomized control trials are desired to identify long term effects of these agents in prenatally exposed children.

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