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ORIGINAL ARTICLE

Comparative Study of Efficacy and Safety of Intravenous Labetalol and Intravenous Hydralazine in managing Hypertensive Emergencies in Pregnancy

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ABSTRACT

Objectives: Evaluation of efficacy and safety of intravenous labetalol and intravenous hydralazine in managing hypertensive emergency in pregnancy.

Study design: An open, randomized comparison of intravenous labetatol *vs* intravenous hydralazine was conducted in 100 pregnant women presenting with hypertensive emergency during pregnancy.

Materials and methods: Inclusion criteria: Women with severe hypertension in pregnancy at 34 weeks of gestation or more, i.e., systolic BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg with or without proteinuria either in labor or not in labor.

Results: The antihypertensive efficacy of both the drugs was found to be comparable. The primary outcome in terms of BP control was achieved in both the groups. There were four treatment failures in labetalol group and none in hydralazine group. No significant difference was observed in maternal and fetal outcomes. Palpitation and tachycardia occurred significantly more often in patients treated with hydralazine. Bradycardia was significantly more frequent in labetalol group. The neonatal outcomes were similar per group.

Conclusion: The randomized clinical trial showed that labetalol and hydralazine fulfil the criteria required for an antihypertensive drug to treat severe hypertension in pregnancy. Hydralazine has its side effects like palpitation, headache, oliguria, dizziness, muscle cramps, and nasal congestion, which mimic symptoms of deteriorating pre-eclampsia. Labetalol has a better side effect profile, but specific concerns have been raised about the risk of neonatal bradycardia.

Keywords: Hydralazine, Hypertensive emergency, Labetalol, Pregnancy.

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INTRODUCTION

Hypertensive disorder may complicate in about 3 to 10% of all pregnancies with variable incidence in the world. Overall, they complicate 5 to 10% of pregnancies in India. Various antihypertensive agents have been used for lowering blood pressure (BP) in severe hypertension of pregnancy. The use of these drugs has led to a reduction in the maternal mortality rate by preventing complications, such as pulmonary edema, abruptio placentae, convulsions, and cerebrovascular accidents.[1]

Labetalol hydrochloride is an antihypertensive agent, available for both oral and intravenous use, that produces nonselective beta-blockade and postsynaptic alpha-1 blockade. It produces dose-dependant decrease in BP by decreasing periphereal vascular resistance without causing reflex tachycardia. Labetalol does not reduce cerebral blood flow and uteroplacental blood flow. American Congress of Obstetrician and Gynaecologists (ACOG) currently recommends labetalol as one of the first-line antihypertensive medications in pre-eclampsia.

Hydralazine is a direct acting smooth muscle relaxant used to treat hypertension by acting as a vasodilator primarily in arteries and arterioles. By relaxing vascular smooth muscle, vasodilation acts to decrease peripheral resistance, thereby lowering BP and decreasing after load.[2] The most common adverse effect of hydralazine is unpredictable hypotension at times associated with placental abruption and low Apgar score (<7) at 5 minutes.

This study has been contemplated to evaluate the efficacy and safety of two commonly used drugs for the treatment of hypertensive emergency in pregnancy, i.e., intravenous labetalol *vs* intravenous hydralazine. This study also reviewed the fetomaternal outcome with the use of both the drugs. The search for an ideal antihypertensive in severe hypertension in pregnancy continues.

MATERIALS AND METHODS

In our department, the study was conducted during the period from October 2013 to September 2015. Total antenatal patients registered were 8,487, out of which 1,984 patients presented with hypertension in pregnancy. Out of these patients we selected 100 patients for our study with severe hypertension after ruling out the exclusion criteria. Informed consent was obtained from all the patients. Ethical committee permission was taken from the college. Severe hypertension in pregnancy was defined as a systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg or more (Korotkoff phase IV sound) which had not settled after 2 hours of bed rest. No other therapy, such as administration of diuretics or volume expansion, was used.

Women at 34 weeks of gestation or more having severe hypertension on admission who had not received previous hypotensive therapy, who had no signs and symptoms of imminent eclampsia were included in the trial. Patients with the history of asthma, diabetes mellitus, or cardiac disease were excluded. Patients included in the trial were randomly allocated into one of two groups.

There were 50 patients in the labetalol group (group I) and 50 patients in the hydralazine group (group II). Labetalol or hydralazine was used according to the ACOG guidelines (2002).[3,4]

Hydralazine: 5 to 10 mg doses intravenously every 15 to 20 minutes until the BP is lower than 150/100 mm Hg. Maximum dose 40 mg.

Labetalol: 20 mg intravenous bolus dose followed by 40 mg if not effective within 10 minutes then 80 mg every 10 minutes until BP lower than 150/100 mm Hg or maximum total dose of 220 mg. If in either group the diastolic pressure was not effectively lowered to the desired level after 60 minutes at the maximum dose it was regarded as a failure of the drug.

During the trial of the drug, the BP was recorded every 10 minutes using a mercury syphygmomanometer. The maternal pulse rate was also measured at 10 minutes intervals by digital palpation of the left radial artery. The uterine activity and fetal heart rate were recorded continuously, before, during, and after the administration of either drug by cardiotocographic machine. The Apgar scores were recorded at 1 and 5 minutes after delivery. Platelet count, fundus examination, liver function test, kidney function test were performed before and 48 hours after the study in all patients. A record of side effects headache, palpitation, nausea, vomiting, hot flushes, or any other untoward complaints was made. Data collected on infants of mothers who received either of the drug antepartum included gestational age, birth weight, heart rate, blood glucose, septicemia, admission to neonatal intensive care unit, need for ventilator, and any other neonatal complication.

Data was analyzed by Student's "t" test (either paired or independent) with significance levels taken at ($p < 0.05$).

RESULTS

There were no differences in the clinical characteristics of the two treatment groups as shown in Table 1.

Out of the 50 patient in group I (labetalol), 46 patients responded with a decrease in both systolic and diastolic BP (Table 2). The mean time of the maximum response was 26.1 ± 9.2 minutes. Four patients did not achieve a satisfactory reduction in BP even after giving the maximum dose of 220 mg.

Of the 50 patients in group II (dihydralazine), all patients responded with decrease in both systolic and diastolic BP. The mean time taken to achieve maximum response was 16.87 ± 4.47 minutes ($p < 0.05$). Eclamptic convulsions or hypotensive episodes did not complicate either treatment regimen.

Systolic BP in mm Hg before and after treatment was 184.4 ± 7.57 and 144.51 ± 11.933 in labetalol group and 184.4 ± 7.02 and 141.44 ± 12.38 in hydralazine group. This comparison was not significant as ($p > 0.05$). Diastolic BP in mm Hg before and after treatment was 127.2 ± 9.90 and 105.57 ± 13.28 in labetalol group and 128.0 ± 7.07 and 105.58 ± 12.07 in hydralazine group. This comparison was not significant ($p > 0.05$) (Table 2).

Table 1: Patient profile

	Group I	*Group II*	
	Labetalol n = 50	*Hydralazine n = 50*	*Mean ± SD*
Age (years)			
<25	33	35	24.10 ± 2.33
25–30	17	15	
Gestational age (weeks)			
32–34			
≥34	21	19	
	29	31	
			34.2 ± 0.98

Table 2: Distribution of patients showing the number of doses required in the two groups

	Group I		*Group II*		
	Labetalol		*Hydralazine*		
	No.	*%*	*No.*	*%*	*p-value*
1 dose	15	30	42	84	0.32
2 doses	19	38	7	14	0.007
3 doses	10	20	1	2	1.67
4 doses	6	12	0	0	2.1

There was no significant difference between the two groups with respect to mean maternal gestational ages, birth weight, and mode of delivery. Twenty patients from labetalol group and 24 patients from hydralazine group delivered vaginally ($p > 0.05$). Twenty-nine patients from labetalol group and 24 patients from hydralazine group had lower segment ceserean section ($p > 0.05$). One patient from labetalol group and two patients from hydralazine group had instrumental delivery.

In group I (labetalol group), six patients developed HELLP syndrome and in group II (hydralazine group), eight patients developed partial HELLP syndrome. Two patients in labetalol group and five in hydralazine group had abruptio placentae (Table 3).

There were two cases of bradycardia in labetalol group and none in hydralazine group. There were four patients with tachycardia in hydralazine group and none in labetalol group ($p < 0.05$). Fetal bradycardia was seen more in labetalol group. In hydralazine group palpitation, headache, oliguria, dizziness, muscle cramps, nasal congestion was more common. In labetalol group scalp tingling, tiredness were more common (Table 4).

In our study the mean birth weight of labetalol and hydralazine group was 2810 ± 8.51 and 2639.95 ± 10.10 gm respectively ($p > 0.05$). The fetal outcome parameters in both the groups were comparable. In labetalol group, there was one stillborn. There were five neonatal admission in labetalol group and six in hydralazine group ($p < 0.05$). There were no significant difference for prematurity, respiratory distress syndrome, need for ventilator, septicemia, hypotension, hypoglycemia in both the groups .

There was a tendency to lower Apgar score at 1 and 5 minutes in hydralazine group ($p > 0.81$). The mean Apgar score of labetalol group was 5.99 ± 3.08 and 8.61 ± 3.10 at 1 and 5 minutes. In hydralazine group mean Apgar score was 5.52 ± 3.09 and 7.26 ± 3.15 at 1 and 5 minutes respectively.

Table 3: Maternal complications

	Group I Labetalol		*Group II Hydralazine*	
Complications	*No.*	*%*	*No.*	*%*
HELLP syndrome (Deranged LFT)	6	12	8	16
Abruptio placenta	2	4	5	10
Mean ± SD	8.0 ± 6.68	10.25 ± 7.54		
p-value	> 0.05			

Table 4: Side effects of the drugs

	Labetalol	*Hydralazine*
	No.	*No.*
Bradycardia (<60 bpm)	2	0
Tachycardia (>120 bpm)	0	4
Flushing	0	3
Headache	1	5
Palpitation	0	3
Fetal bradycardia	2	0
Fetal distress	4	3
Oliguria	3	3
Scalp tingling	2	0
Nasal congestion	0	2
Tiredness	1	0
Muscle cramps	0	1
Mean ± SD	1.78 ± 1.53	2.61 ± 2.7

DISCUSSION

The main object of this study was to compare the hypotensive agents labetalol and hydralazine in the emergency treatment of severe preeclampsia in primigravidae. Hydralazine, a peripheral vasodilator, is the most commonly used agent in hypertensive crisis of pregnancy, but its use has certain disadvantages: (1) It causes a reflex tachycardia; (2) some patients may be unusually sensitive to hydralazine because of a reduced capacity to metabolize the drug resulting in profound hypotension; and (3) drug interactions with other hypotensive agents, viz diazoxide, have been reported.[5]

Labetalol's hypotensive effects are mediated by its ability to act both as an alpha and beta adrenoreceptor blocking agent, and it is reported to lower BP without causing a reflex tachycardia or reducing cardiac output.[6] Neither drug caused a precipitous fall in blood pressure, a complication recognised in previous studies using bolus dose of antihypertensives, particularly hydralazine.[7]

Other studies have indicated that labetalol has little or no effect on pulse rate and this was supported by our result (Table 5). The alpha-blocking action of labetalol ablates the bradycardiac effects of its beta-blocking component. In our study a marked rise in mean pulse rate occurred after hydralazine administration (Table 5). There is a significant statistical difference in the pulse rate between the two study groups, illustrating the reflex tachycardia which is one of the troublesome side effects of hydralazine limiting its use in certain hypertensive patients.

In our study, there were four treatment failures in labetalol group and none in hydralazine group. In a study by Mabie et al,[7] there were four treatment failures in the labetalol group and none in hydralazine group. Hydralazine had a quicker onset of action than labetalol.[5]

Mabie et al[7] observed that the average mean arterial pressure decreased from a maximum of 137.4 ± 9.9 to a minimum of 111.9 ± 9.5 mm Hg in labetalol group and from 139.9 ± 8.9 to 106.6 ± 12.5 mm Hg in hydralazine group. In

Table 5: Blood pressure and hemodynamic parameters before and after treatment

Blood pressure mm Hg	*Group I Labetalol*	*Group II Hydralazine*	*p-value*
1 Systolic blood pressure before treatment			
160–180	44	48	>0.05
>181	56	52	
	(184.4±7.57)	(184.4±7.02)	
2 Diastolic blood pressure before treatment			
110–130	64	60	>0.05
>131	36	40	
	(127.2±9.90)	(128.0±7.07)	
3 Systolic blood pressure after treatment			
110–140	62	72	>0.05
>141	38	28	
	(144.51±11.93)	(141.44±12.38)	
4 Diastolic blood pressure after treatment			
90–110	88	96	>0.05
>111	12	4	
	(105.57±13.28)	(105.58±12.07)	
5 Mean arterial pressure before treatment	(127.2±9.90)	(128.0±7.07)	>0.05
6 Mean arterial pressure after treatment	(105.57±13.27)	(105.58±12.07)	>0.05
7 Pulse (beat/min) before treatment	88±10	86±10	>0.05
8 Pulse (beat/min) after treatment	82±11	101±16	>0.05
9 Platelet count per liter			
Before treatment	$192\pm24\times10^9$	$203\pm27\times10^9$	>0.05
After treatment	$196\pm23\times10^9$	$211\pm32\times10^9$	

a study by Ashe et al,[8] the average mean arterial pressure decreased from a maximum of 103.8±8 to minimum of 102±3.5 mm Hg in labetalol group and from 99.7±13 to 98±8 mm Hg in hydralazine group. The results of both these studies were comparable to our study.

CONCLUSION

In conclusion, our study shows that both labetalol and hydralazine were effective in the emergency treatment of severe hypertension of pregnancy. Hydralazine began to work more quickly and lowered BP to greater degree but it was accompanied with side effect of reflex tachycardia. Labetalol was better tolerated by mother and fetus and had a better side effect profile. In a few patients where labetalol is contraindicated or patient is resistant, hydralazine definitely has a role.

Therefore, the choice between two drugs should be based on criteria, such as respective contraindications, cost, availability, and clinician's experience. Although further studies are needed on present evidence, it is suggested that labetalol is a useful agent in the armamentarium of hypertensive drugs for the management of severe hypertension of pregnancy.

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