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MANAGEMENT OF ACUTE HYPERTENSION IN PREGNANCY- LABETALOL V/S HYDRAZINE

Gynecology

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ABSTRACT

Objective: To assess the safety, potency and effectiveness of intravenous hydralazine and labetalol for acutely lowering severe blood pressure in pregnancy and to compare maternal and perinatal outcome.

Method: In a prospective randomized study, women attending labor room and antenatal out patient department of Jawaharlal Nehru Medical College and Hospital during January 2014 to October 2015 were enrolled. The inclusion criteria were women with ≥24 weeks gestational age, blood pressure ≥160/110 mmHg with or without proteinuria and no concurrent anti-hypertensive therapy. Patients were randomized in two groups using simple randomized sampling, either receiving intravenous labetalol (Group A) or intravenous hydralazine (Group B) according to pre-decided protocol. The primary outcome was defined as lowering of blood pressure ≤ 160/110 mmHg taking into consideration the number of doses and time duration required to lower the blood pressure.

Result: Analysis elucidated a significant fall in systolic and diastolic blood pressure by both drugs (p value<0.05). The fall in both systolic and diastolic blood pressure was insignificant when compared between the two groups after 20 minutes. When measured at 40, 60 and 80 minutes the fall in systolic blood pressure was more significant in hydralazine group as compared to labetalol group. The fall in diastolic blood pressure remains almost equivalent at all intervals between both the groups

Conclusion: For women with severe blood pressure, both labetalol and hydralazine are equally effective in pregnancy.

KEYWORDS

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are one of the most common preventable multisystem medical complications seen during pregnancy. Its incidence is 5-10% (Williams 24 edition) and is responsible for 25% maternal deaths worldwide[1]. In management of hypertensive emergencies, three short acting antihypertensive agents namely hydralazine, labetalol and nifedipine are most commonly used, each having different advantages and disadvantages. Duley H et al have meta-analyzed 24 trials and compared different types of antihypertensive drugs used for women with severe hypertension during pregnancy[2]. This meta-analysis quotes 3 major trials namely Ash et al (1987), Harper et al (1991), and Vigil de Gracia et al (2006) comparing hydralazine and labetalol. They noticed lack of data comparison between the two drugs and have suggested for more studies to make reliable conclusions. Therefore we conducted a randomized clinical trial comparing hydralazine and labetalol for acute management of severe hypertension in pregnancy.

MATERIALS AND METHODS

In the present prospective randomized study, antenatal women with raised blood pressure attending the Department of Obstetrics and Gynecology at Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, India, were enrolled between January 1, 2014, and October 30, 2015. The inclusion criteria were: women with ≥24 weeks gestational age (calculated either by last missed period or by scan or by uterine size at first pre natal visit), blood pressure ≥160 mmHg systolic and/or 110 mmHg diastolic on two occasions at least 15 minutes apart, after rest, in the same arm in sitting or supine position (measurement of blood pressure was done by trained residents using mercury sphygmomanometer with arm at the level of the heart. The length of the cuff was 1.5 times circumference of the arm and the Korotkoff sound phase I and phase V was used for documenting systolic and diastolic blood pressure respectively), with or without proteinuria (using dipstick) or signs and symptoms of severe hypertension like headache, blurring of vision or epigastric pain and no concurrent anti- hypertensive therapy.

The exclusion criteria were severe bradycardia, cardiac failure, bronchial asthma, patients diagnosed with other causes of convulsions, known allergy to hydralazine or labetalol, diabetes and severe depression. The Ethical Committee of the Institution had approved the study and patients provided informed consent before the administration of anti-hypertensive drug.

After taking a thorough history, B.P measured and detailed examination done the diagnosis confirmed, the patients were randomly divided into two groups, Group A and B using simple randomized sampling. Participants were not told which group they had been assigned to, and investigators and data analysts were not masked to the group assignment.

Group A received a bolus dose 20mg of labetalol slowly by intravenous route over a period of 10 minutes. If SBP remained ≥160 mmHg and/or DBP ≥110 mmHg then bolus of 40mg was instituted. Blood pressure was recorded every 20 minutes to decide the next dosage. If blood pressure still remained ≥160 mmHg and/or DBP ≥110 mmHg then labetalol was administered as 80mg intravenous bolus, which could be repeated 3 times until the blood pressure was controlled. Maximum labetalol dosage delivered by intravenous route was 300 mg.

Group B were given hydralazine by intravenous route. It was reconstituted in 1ml of sterile water for injection. It was further diluted by dissolving with 19 ml of normal saline, total solution was 20 ml, and 5 ml of this solution was given slowly by i.v route over a period of 5 minutes. Blood pressure was recorded after 20 minutes. Further dose of hydralazine solution was given repeatedly every 20 minutes to a maximum of 20 ml (=20 mg), until the blood pressure was controlled. The reconstituted hydralazine was used within 24 hours.

All the patients in the two groups were questioned about the presence and absence of adverse reactions related to the use of medication with each dose. The blood pressure of all the patients was monitored every 20 minutes after each dose administration. After last i.v bolus of drugs, patients were monitored by trained obstetricians and gynecologists every 15 minutes within first 2 hours of for general condition, pulse rate, respiratory rate, blood pressure, cardio vascular system, chest, uterine contractions, fetal heart rate or other adverse effect. All the patients were subjected to routine antenatal investigations namely hemogram with platelet count, urine for albumin, HIV, HBsAg, VDRL, blood group, RFT, liver function test and coagulation profile. Bishops score, NST and biophysical profile were monitored whenever possible after patient stabilization and controlled B.P.

Primary outcome of the drug was measured by minimum number of doses required to decrease the systolic B.P <160 mmHg and diastolic <110 mmHg. Secondary outcome was recorded in terms of adverse effects related to the use of drugs like tachycardia, palpitation,

dizziness, flushing, gastrointestinal disturbance, maternal hypotension, bradycardia, and adverse effects on fetal heart rate, still birth, neonatal bradycardia and mode of delivery. Maternal outcome was recorded in terms of morbidity and mortality. Neonates were followed for gestational age at delivery, APGAR score at birth, birth weight, need of NICU admission.

Persistent hypertension, which needed the use of secondary anti-hypertensive was recorded. Severe persistent hypertension is defined when B.P was not lowered after the time period of maximum number of drug boluses that is 50 minutes after beginning administration of labetalol and 80 minutes after administration of hydralazine (Mabie et-al 1987). Patients were then administered additional antihypertensive drugs as per the hospital protocol if blood pressure was not controlled on any of these drugs. Patients were followed for their requirement of additional antihypertensive for maintenance of their blood pressure till discharge of the patients.

The mean data of the two groups were compared. SPSS (Statistical Package for Software for Social Sciences) version 21 (IBM, Armonk, NY, USA) was used for accurate analysis of the statistical data. Analysis of the categorical values was done using Chi-square test while continuous variables were analyzed using Mann-Whitney test. All significant tests were two tailed and p value < 0.05 was considered significant.

RESULTS

During the study period, there were 7065 deliveries, among which 693 women had hypertensive disease of pregnancy. 212 women were excluded in view of raised blood pressure prior to 24 weeks gestational age. 113 women were excluded because they had been already taking anti hypertensive therapy. 281 women had associated gestational diabetes. 2 women were excluded due to associated bronchial asthma. 12 patients were lost to follow up, thus, 73 patients were evaluated (Fig1.). There were 35 (47.9%) patients with severe pre eclampsia, 26 (35.6%) patients with eclampsia, 9 (12%) patients with gestational hypertension, 2 (2.7%) with HELLP syndrome. Among the study participants, 146 (70.2%) came from a rural background, 8 (3.8%) were literate and 55 (75.34%) were un-booked. Among the study participants, 35 were assigned to the hydralazine group and 38 were assigned to the labetalol group.

Among the patients included in analyses, those in each of the two groups were similar in terms of age, number of previous pregnancies, and length of pregnancy (Table 1).

Table 1. Baseline Characteristics [a]

Characteristic (on admission)	Hydralazine Group (n= 35)	Labetalol Group (n= 38)
Maternal age, y	25.1± 5.3	27.3± 5.1
Gravidity • Primigravida • Multigravida	 48.59% 51.42%	 39.47% 60.52%
Length of pregnancy, wk • <37 wk • >37 wk	 42.85% 57.14%	 50.0% 50.0%
Systolic blood pressure, mmHg	175.14±16.44	171.36±8.89
Diastolic blood pressure, mmHg	114.57±10.17	112.10±4.52
Mean arterial pressure, mmHg	134.76±12.26	131.85±5.97

[a] Values are given as mean ± SD or number (percentage)

In addition, systolic blood pressure, diastolic blood pressure, and mean arterial pressure on admission were similar in the two groups. The primary outcome of the study concluded fall in systolic and diastolic blood pressure in both the groups individually, which was significant (p value<0.05), when calculated after every 20 minute period for 100 minutes (Table 2 & 3).

Table 2. COMPARISON OF SYSTOLIC AND DIASTOLIC B.P IN LABETALOL GROUP

B.P.at respective time (min) S:systolic D:diastolic	Mean Blood Pressure (mmHg) (Sys/Dias)	Δ Mean Blood Pressure (Sys/Dias)	Standard deviation (Sys/Dias)	t value (Sys/Dias)	p value (Sys/Dias)
S_0; S_{20} D_0; D_{20}	171.37→168.42 112.11→108.95	2.947 3.157	6.303 4.463	2.883 4.418	.007 .000
S_0,S_{40} D_0; D_{40}	171.37→164.68 112.11→107.05	6.684 5.052	6.448 5.457	6.391 5.707	.000 .000
S_0;S_{60} D_0; D_{60}	171.37→159.26 112.11→102.11	12.105 10.000	9.111 7.682	8.190 8.024	.000 .000
S_0; S_{80} D_0; D_{80}	171.37→156.58 112.11→100.68	14.789 11.421	9.035 6.879	10.091 10.233	.000 .000
S_0; S_{100} D_0; D_{100}	171.37→153.53 112.11→97.68	17.631 13.526	9.774 7.717	11.120 10.805	.000 .000

Table 3. COMPARISON OF SYSTOLIC AND DIASTOLIC B.P IN HYDRALAZINE GROUP

B.P. at respective time (min) S:systolic D:diastolic	Mean Blood Pressure (mmHg) (Sys/Dias)	Δ Mean Blood Pressure (Sys/Dias)	Standard deviation (Sys/Dias)	t value (Sys/Dias)	p value (Sys/Dias)
S_0; S_{20} D_0; D_{20}	175.14→169.06 114.57→108.97	6.086 5.6	7.461 6.07	4.825 5.507	.000 .000
S_0,S_{40} D_0; D_{40}	175.14→163.49 114.57→104.69	11.657 9.88	11.906 7.48	5.792 7.816	.000 .000
S_0;S_{60} D_0; D_{60}	175.14→156.97 114.57→101.54	18.171 13.02	13.860 8.5	7.757 9.063	.000 .000
S_0; S_{80} D_0; D_{80}	175.14→153.60 114.57→98.86	21.543 15.714	16.030 9.395	7.951 9.895	.000 .000
S_0; S_{100} D_0; D_{100}	175.14→152.05 114.57→95.78	23.085 17.82	17.444 9.778	7.829 10.787	.000 .000

The fall in both systolic and diastolic blood pressure was insignificant when compared between the two groups after 20 minutes. When measured at 40, 60 and 80 minutes the fall in systolic blood pressure was more significant in hydralazine group as compared to labetalol group. The fall in diastolic blood pressure remains almost equivalent at all intervals between both the groups (Table 4).

Table 4. Unpaired t test

B.P. at respective time	Δ Mean Blood Pressure (labetalol group) n=38	Δ Mean Blood Pressure (hydralazine group) n=35	t value	p value
S_0→ S_{20} D_0→D_{20}	2.947± 6.303 3.157±4.463	6.086 ± 7.461 5.6 ± 6.07	1.946 1.969	0.055 0.052
S_0→S_{40} D_0→ D_{40}	6.684± 6.448 5.052±5.457	11.657 ± 11.906 9.88 ± 7.48	2.243 3.168	0.028 0.002
S_0→S_{60} D_0→D_{60}	12.105± 9.111 10.0±7.682	18.171 ± 13.860 13.02 ± 8.5	2.26 1.594	0.029 0.115
S_0→S_{80} D_0→D_{80}	14.789± 9.035 11.421±6.879	21.543 ±16.030 15.714 ± 9.395	2.24 2.239	0.028 0.028
S_0→ S_{100} D_0→ D_{100}	17.631± 9.774 13.526±7.717	23.085 ±17.444 17.82 ± 9.778	1.665 2.09	0.100 0.040

Table 5. Comparison between studies

Studies	Our study	Nombur et-al (2014)	Harper et-al (1991)	Vigil-De Gracia et-al (2006)	Pasquale et-al (2014)	Ashe et-al (1987)
Number of un booked patients	H: 27 (77.14%) L: 28 (73.68%)	H: 15 (23.8%) L: 21 (33.3%)	-N/A-	-N/A-	-N/A-	
Mean maternal age (yrs)	H: 25.114±5.38 L: 27.34±5.194	-N/A-	H: 25.9±6.3 L: 28.1±6.2	H: 29.9±6.4 L: 29.3±6.8	H: 26.3±7.1 L: 26.5±6.8	
Gravidity 1 ≥2	H: 17 (48.59%) L: 15 (39.57%) H: 18 (51.42%) L: 23 (60.52%)	H: 33 (52.4%) L: 37 (58.7%) H: 30(47.6%) L: 26(41.3%)	H: 9(60%) L: 10 (66.6%) H: 6 (40%) L: 5 (33.4%)	-N/A-	-N/A-	All primigravida
Mean Parity	H: 2.1 ± 1.27 L: 2.18 ± 1.29			H: 2.3±1.7 L: 1.9±1.3	H: 2 (1.4) L: 3 (1.7)	
Gestational Age (weeks) ≤37 >37	H: 15 (42.85%) L: 19 (50%) H: 20 (57.14%) L: 19 (50%)	H: 27(42.9%) L: 24 (38.1%) H: 36 (57.1%) L: 39 (61.9%)	(Mean) H: 31.2 ±3.2 L: 32.1±3.1	(Mean) H: 35.9±3.5 L: 35.3±4		(Mean) H: 38.3 L: 38.5
Distribution of HDP Severe preeclampsia Gestational Hypertension Ecclampsia	H: 15 (42.85%) L: 20 (52.63%) H: 5 (14.28%) L: 4 (10.52%) H: 14 (40%) L: 12 (31.75%)			H: 54 (54%) L: 57 (57%) H: 20 (20%) L: 17 (17%) H: 1 (1%) L: 2 (2%)	H: 97 (74.6%) L: 98 (74.8%) H: 2 (1.5%) L: 2 (1.5%)	
Mean systolic pressure (mmHg)	H: 175.14±16.44 L: 171.36±8.89	H: 170 L: 180			H: 170±13.8 L: 172±14.2	H: 167.14 ±14 L: 168±20
Mean diastolic pressure (mmHg)	H: 114.57±10.17 L: 112.10±4.52	H: 120 L: 100			H: 108±8.2 L: 107±7.7	H: 117±5 L: 118±8
Fall in SBP	After 20 minutes H: 6.086 ± 7.461 L: 2.947± 6.303	Over 20 minutes H: 10 L: 20				Over 25- 100 minutes H: 25 ± 17 L: 19±23
Fall in DBP	After 20 minutes H: 3.157±4.463 L: 5.6 ± 6.07	No significant difference between the groups (p-value=0.48).	No significant difference between the groups (p-value=0.052)			H: 19±16 L: 14±12
Total time needed to control BP (min)	H: 49.7±23.1 L: 32.1±13.8 p- <0.01	H: 40 L: 40 p-value=0.17				H: 55 L: 60
Change in Pulse rate	No significant change in both the groups (p=0.74)					H: Increase in pulse rate L: no change in pulse rate
Vaginal delivery	H: 17 (48.57%) L: 18 (47.36%)					
LSCS	H: 18 (51.54%) L: 20 (52.63%)		H: 60% L: 60%			H: 70% L: 60%
Birth weight	H: 2.2037±0.60 L: 2.2036±0.76 p-value=0.99	No significant difference between both the groups p-value=0.62	H: 1.89±0.96 L: 1.83±0.84	H: 2.677± .77 L: 2.646± .89		H: 2.4 L: 2.8

38 (52.05%) patients delivered vaginally and 35 (47.94%) delivered by cesarean section. The average birth weight in hydralazine group is 2.2037±0.60226 Kg and 2.2036±0.763Kg in labetalol group. It was observed that the incidence of nausea, headache, transient hypotension, tachycardia and hypoglycemia in newborn was observed in 2.6 % each in the labetalol group. Bradycardia was not observed in any patient as it was masked by the base line tachycardia. While the incidence of headache, palpitation and maternal tachycardia was 2.8% in hydralazine group. Incidence of nausea, flushing and fetal distress was found to be 5.7%, and headache was found to be more 8.5% in the hydralazine group. There were two fresh stillbirths, one in each group, but they were not due to the side effect of the drug. The stillbirths were result of abruption and had occurred before the start of the therapy. There were three neonatal deaths, two in hydralazine group and one in labetalol group. All deaths were due to prematurity. Overall the incidence of side effects, were found to be more common in the hydralazine group, although statistically it was not significant (p-value = 0.090). The side effects seen in both the groups were not of serious nature. There was no mortality in either group.

DISCUSSION

National High Blood Pressure Education Program (NHBPEP 2000, ACOG 2013) also recommends that antihypertensive therapy for treatment of hypertension in pregnancy should be started when SBP ≥160 mmHg or DBP ≥110 mmHg[3,4]. The objective of using any antihypertensive therapy is to bring smooth reduction in blood pressure to a level that is safe for both mother and baby. First line antihypertensive drugs, being used for emergent control are IV hydralazine or IV labetalol.

The time needed by labetalol is less but the action of hydralazine is more prolong. It can be explained by the fact that labetalol has a quicker onset of action, therefore it affects B.P early, whereas hydralazine has a delayed onset and prolong action. There were minor side effects in both the groups, which were not statistically different. There was no mortality in either group. As elicited in table 5, our findings collaborate with previous studies, Duley et-al (2007), Pasquale et al (2014), Nombur et al (2014) on the efficacy and safety of these drugs for the emergency management of severe hypertension in pregnancy[2,5,6].

CONCLUSION

Based on our results it is concluded that B.P in cases of severe hypertension of pregnancy is controlled equally by both hydralazine and labetalol in smooth, controlled and effective manner. Both drugs are quite potent and similar in safety profile for use in hypertensive disease of pregnancy. It was also noted that antihypertensive effect of labetalol was quicker, than hydralazine. We conclude that the choice of antihypertensive therapy for management of acute hypertension in pregnancy must be based on the availability of the drug, knowledge of side effects, costs and on the fact of experience and familiarity of the clinician with the drug. We suggest for further studies in larger number of patients with combined regimens of labetalol and hydralazine, utilizing the early onset of action of labetalol and sustained control of blood pressure by hydralazine.

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