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A Comparison of Hydralazine and Labetalol in the Management of Severe Preeclampsia

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Abstract

The burden of pre-eclampsia and eclampsia is the rationale behind the research. There is paucity of prospective study on this subject in Nigeria. Therefore there was a need for a prospective study that may provide concrete data and firm conclusion on this subject. Furthermore, there was also a need for a study among pregnant women in the Federal capital territory, with a rapidly increasing heterogeneous population. Recently Labetalol was introduced in the obstetrics unit, of the University of Abuja Teaching Hospital but hydralazine has been in use for the management of severe pre-eclampsia in the hospital. Therefore, there was a need to compare the safety and efficacy of these drugs for acutely lowering blood pressure in severe pre-eclampsia in this unit.

Keywords: Hydralazine; Labetalol; Severe pre-eclampsia

Introduction

Pre-eclampsia is a common complication of pregnancy. Pre-eclampsia and eclampsia are hypertensive disorders of pregnancy that cause significant morbidity and mortality in the mother and fetus both in developed and developing countries [1]. In Nigeria, they are listed as one of the top three causes of maternal mortality [2-6]. The ultimate cure for pre-eclampsia and eclampsia is the delivery of the baby. However, maternal and perinatal deaths are significantly reduced with appropriate treatment [1].

The most commonly used threshold for treatment of hypertension in pregnancy is severe hypertension (Systolic Blood Pressure ≥ 160 mmHg or Diastolic Blood Pressure ≥ 110 mmHg) as recommended by the National High Blood Pressure Education Program [7,8]. Various antihypertensive agents have been used for lowering blood pressure in severe pre-eclampsia.

Hydralazine is a peripheral vasodilator, and the most frequently used intravenous antihypertensive for women with severe hypertension in pregnancy [8]. However, its side effects are common and mimic symptoms of deteriorating pre-eclampsia for example headache, nausea and vomiting [9].

Labetalol is a non-selective beta-blocker and a post-synaptic alpha-1 blocking agent. Intravenous Labetalol is also used for treatment of severe hypertension in pregnancy as a first line drug and has a better side effect profile but specific concerns have been raised about the risk of neonatal bradycardia [10].

Intravenous hydralazine, oral nifedipine and oral or intravenous Labetalol are the drugs most commonly used to control acute severe hypertension in women with pre-eclampsia [8,11-13]. Nifedipine is not currently recommended for acute severe hypertension in pregnancy by the American College of Obstetricians and Gynaecologists [14]. The reason for this may be uncertainty that exists about how safe it is for the mother.[10]

Recently, a Cochrane systematic review considered the effectiveness of antihypertensives for treatment of severe hypertension during pregnancy and concluded that there is no evidence that one antihypertensive agent is preferable to the others for improving outcome for women with very high blood pressure during pregnancy, and their babies [15]. The purpose of this study was to compare the efficacy and safety of intravenous hydralazine and intravenous Labetalol for management of severe pre-eclampsia.

Materials and Methods

This was a randomised clinical trial to compare the efficacy and safety of intravenous hydralazine and labetalol for the management of severe preeclampsia.

Entry criteria were pregnancy more than 20weeks and severe hypertension (systolic blood pressure of 160mmHg or more and /or diastolic blood pressure of 110mmHg or more) and Proteinuria of at least 1+ as measured by dipstick in a catheter specimen urine sample.

Those who did not consent, contraindication or known allergy to hydralazine or labetalol were excluded.

Standard mercury sphygmomanometer with appropriately sized cuff was used. The first and fifth Korotkoff sounds were recorded for 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.

The sample size for comparison groups was calculated using the formula [16] $n= 2Z^2 PQ/D^2$

n= minimum sample size, Z= 95% confidence interval using 1.96

P= Prevalence of severe preeclampsia (2.0) [17], Q= 1.0-P

D = degree of accuracy desired, usually set at 0.05.

n = 60. Adding 5% attrition rate, anticipated response rate 95%.

The selected sample size was 60/0.95 = 63. Then each trial group was allocated 63 participants. The minimum sample size was 126 participants.

Enrolled patients were randomly allocated to one of the two

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therapeutic regimens. Randomisation was performed using computer-generated list by means of sequentially numbered, opaque, sealed envelopes indicating their medication. One group of patients received hydralazine and the other group received labetalol (Table 1) [8,18,19].

The desired end point Systolic Blood Pressure 130-140 mmHg and Diastolic Blood Pressure 80-100 mmHg

Management of severe preeclampsia included preventing seizures, all women initially received magnesium sulphate as a 4 g intravenous loading dose over 10 minutes and 10 g intramuscularly (5g in each buttocks). Maintenance dose 5 g intramuscularly in alternate buttocks was administered every 4 hours until 24 hours after delivery.

Data was analysed using SPSS (Statistical package software for social sciences) version 16.0. Chi-square test was used to analyse categorical variables and differences in continuous variables were analysed using Mann-Witney test. P-value of less than 0.05 was accepted as indicating statistical significance.

The ethical clearance was obtained from the Research Ethics Committee of the University of Abuja Teaching Hospital and informed consent for participation was obtained for all patients.

Results

A total of 126women met the inclusion criteria, agreed to participate and were randomized. The demographic variables were similar between women in both arm of the study (Table 3).

The time to achieve blood pressure control and the number of doses of each drug needed to achieve such control is presented in Table 3. An average of 40 minutes was required in both groups to achieve blood pressure control while 77.7% and 81.0% of women in Hydralazine and Labetalol group respectively needed a maximum of 3 doses of their respective drugs to achieve control. The timing to achieve control and the required number of doses was not statistically different between the 2 groups (Table 3). A combination of hydralazine and Labetalol were used in 3 (4.8%) and 2 (3.2%) patients for Hydralazine and Labetalol groups respectively, because of persistent severe hypertension (P=0.94).

Table 4 showed number of repeat courses of administrations to achieve blood pressure control. There was no significant difference observed in rebound hypertension and need for subsequent repeat administration of the Hydralazine and Labetalol in either group (P=1.0).

Maternal complications and outcome were summarised in Table 5. Headache was significantly more frequent in patients given hydralazine than following Labetalol use. The difference was statistically significant (25.4% vs. 3.2% respectively, p = 0.01). Eclampsia occurred after the loading dose of magnesium sulphate and 2 doses of hydralazine while none in the labetalol group. There was no difference demonstrated in the maternal outcome between the 2 groups, as over 90% in each group delivered without complication. There were no maternal deaths in any of the women studied.

The fetal outcome is shown in Table 6. The respective fresh stillbirth of 4 and 2 among the Hydralazine and Labetalol groups were those women that had Abruptio placentae. Three and 2 of the stillbirths occurred before commencement of treatment in hydralazine and labetalol group respectively. A woman that had abruptio placenta during the treatment with 3 doses of hydralazine had a stillbirth while none had stillbirth during treatment with labetalol. There were no significant differences observed in fetal outcome between the 2 arms of the study.

Figures 1 and 2 shows median systolic and diastolic blood pressure control with respect to Hydralazine and Labetalol. There was a similar control in both groups.

Discussion

This randomized clinical trial for the treatment of severe preeclampsia using either Hydralazine or Labetalol demonstrated that both drugs remain effective rapid antihypertensive agents in such hypertensive emergencies as severe preeclampsia. This finding collaborate earlier studies including Cochrane review on the efficacy of either drugs in hypertensive crisis in pregnancy [10,15,20].Majority of

Drug	Treatment
Hydralazine	5mg as a slow bolus dose administered intravenously and repeated 10mg every 20-minutes until the desired effect was achieved up to a maximum of 5 doses
Labetalol	20mg intravenous bolus dose followed by 40mg if not effective within 10-minutes followed by 80mg every 10-minutes up to a maximum dose of 300mg (5 doses)

Table 1: Treatment of severe preeclampsia [8,18,19].

Parameter	Hydralazine No	(%)	Labetalol No	(%)	P – value
Maternal age (Years)					
<20	5	(7.9)	8	(12.7)	
20-24	13	(20.6)	8	(12.7)	
25-29	26	(41.3)	21	(33.3)	
30-34	16	(25.4)	22	(34.9)	0.61
35-39	1	(1.6)	1	(1.6)	
≥40	2	(3.2)	3	(4.8)	
Total	63	(100.0)	63	(100.0)	
Parity					
Nulliparous	33	(52.4)	37	(58.7)	
Multiparous	30	(47.6)	26	(41.3)	0.47
Total	63	(100.0)	63	(100.0)	
Gestational Age					
<37weeks (Preterm)	27	(42.9)	24	(38.1)	
> 37weeks (Term)	36	(57.1)	39	(61.9)	0.58
Total	63	(100.0)	63	(100.0)	
Booking status					
Unbooked	15	(23.8)	21	(33.3)	
Booked	48	(76.2)	42	(66.7)	0.23
Total	63	(100.0)	63	(100.0)	

Over 80% of women in each group were in the age bracket of 20 – 34 years and more than half were Nulliparous in both groups. Majority delivered at term and were booked patients.

Table 2: Demographic characteristic of women enrolled.

Variables	Hydralazine		Labetalol	p- value
Time to BP control (mins)				
Median (IQR)	40 (30, 50)		40 (30, 60)	0.17
No. of Doses to BP Control	No	(%)	No (%)	
Single	30	(47.6)	33 (52.4)	
2 – 3	19	(30.1)	18 (28.6)	
4 – 5	11	(17.5)	10 (15.8)	0.94
Persistent severe hypertension	3	(4.8)	2 (3.2)	
Total	63	(100.0)	63 (100.0)	

The Blood pressure control was achieved within 40 minutes in both groups. There was no significant difference between the numbers of doses required to achieve control in both groups. Interquartile range (IQR).

Table 3: Time to achieve blood pressure control and Number of doses required.

Repeats	Hydralazine	(%)	Labetalol	(%)	P value
None	57	(90.5)	58	(92.1)	
1	5	(7.9)	4	(6.3)	1.0
2 or more	1	(1.6)	1	(1.6)	
Total	63	(100.0)	63	(100.0)	

Majority of women had control with the loading doses of Hydralazine and Labetalol.

Table 4: Repeat courses of administration to achieve blood pressure control.

Complication	Hydralazine No	(%)	Labetalol No(%)		P – value
Headache	16	(25.4)	2 (3.2)		0.01
Nausea / Vomiting	1	(1.6)	1 (1.6)		
Epigastric Pain	2	(3.2)	1 (1.6)		
Visual disturbances	3	(4.8)	4(6.4)		
Dizziness	2	(3.2)	2(3.2)		
None	39	(61.9)	53(84.1)		
Outcome					
Normal delivery	57	(90.5)	60	(95.2)	
Placenta Abruptio	5	(7.9)	2	(3.2)	
Eclampsia	1	(1.6)	0	(0.0)	0.35
HELLP Syndrome	0	(0.0)	1	(1.6)	
Total	63	(100.0)	63	(100.0)	

Headache was significantly more frequent in patients given hydralazine. Over 90% of the women in both groups had normal delivery without complications.

Table 5: Maternal complications and Outcome.

Fetal outcome	Hydralazine No	(%)	Labetalol No	(%)	P – value
Fresh stillbirth	4	(6.3)	2(3.2)		
Fetal distress	4	(6.3)	5(7.9)		
1 min APGAR < 7	3	(4.8)	2 (3.2)		0.91
5 min APGAR < 7	2	(3.2)	4(6.3)		
Admission into SCBU	10	(15.9)	11 (17.5)		
No Admission to SCBU	40	(63.5)	39 (61.9)		
Fetal Birth weight					
Very low birth weight (1.0-1.4kg)	6	(9.5)	8	(12.7)	
Low birth weight (1.5–2.4kg)	26	(41.3)	21	(33.3)	0.62
Normal birth weight (2.5–3.9kg)	31	(49.2)	34	(54.0)	
Total	63	(100.0)	63	(100.0)	

Most of the babies were discharge to their mothers at delivery, without admission to Special Care Baby Unit (SCBU) in both groups of women. The Apgar scores were similar in both arm of the study. The recorded very low and Low birth weight were not statistically different between both groups.

Table 6: Fetal outcome.

the patients in both arms of the study were nulliparous. This supported the fact that Preeclampsia is more common among primigravidae [17].The preponderance of preeclampsia at advanced maternal age of greater than 35 year [21] was however not supported in this research work where over 80% of women in both group were aged between 20 – 34years. It is probable that recruitment with majority of participants in the lower age group may have bias the outcome of this study in contrast to previous workers [21]. A community based study where a wider age distribution of the participants may be feasible may corroborate the earlier reports of previous study [21]. It has also been shown in previous report that severe preeclampsia was more likely to occur among unbooked patient who may not have had the benefit of early diagnosis and monitoring in antenatal clinic [17]. The finding from this study runs contrary to this assertion as more patients in both arms of the study were booked. Perhaps, the fact that majority of women attending this institution are from urban area and are likely to utilise the facility for antenatal care may be responsible for this finding.

The average time taken to achieve desired blood pressure control was similar for both drugs. Also similar doses were required for blood pressure control in both groups. This finding perhaps forms the basis of accepting the null hypothesis in this study that demonstrated no superiority of one over the other in achieving fast blood pressure control. This finding was in keeping with previous studies [10,20]. The difference in the number of women in both groups that had persistent hypertension was however not statistically significant just as was earlier reported by previous workers [10,20]. There was no maternal hypotension in both groups. The absence of maternal hypotension and the relative success and safety profile observed in this study has earlier been reported by other workers using the same agents [10,15,20,22-24].

Those who had fresh stillbirths in Hydralazine and Labetalol group were patients managed for abruptio placentae. These deaths were more likely to be the complication from the abruptio placenta than from the effect of either the Hydralazine or Labetalol administration. This is because 3 and 2 of the stillbirths occurred before commencement of treatment in hydralazine and labetalol group respectively. There were no significant differences in the fetal outcome in both groups, further collaborating the finding of non-superiority of these drugs over one another.

Headache was significantly more frequent in patients given hydralazine compared to Labetalol. Vigil-De Gracia et al reported a rather higher frequency of maternal tachycardia and palpitations with the use of hydralazine compared to the use of labetalol, but no statistically significant difference in frequency of headache among their study groups [10]. Other researchers had reported similar adverse maternal side effects with either hydralazine or Labetalol [20].

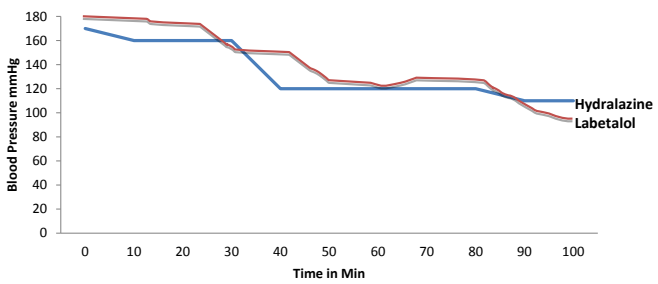

Figure 1: Median Systolic Blood Pressure control in Hydralazine and Labetalol Groups.

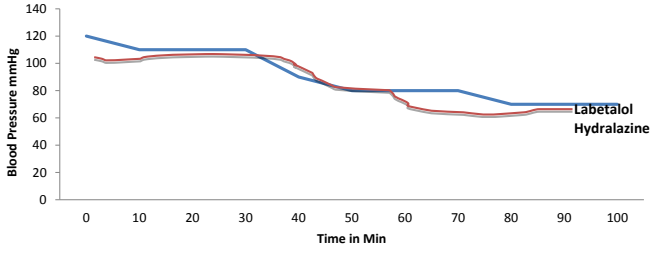

Figure 2: Median Diastolic Blood Pressure control in Hydralazine and Labetalol Groups.

In a meta-analysis conducted by Duley et al. [15] they 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. Our findings in this study may have added to the existing knowledge on the subject matter.

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