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Labetalol versus Hydralazine in the Management of Severe Pre-Eclampsia at Tertiary Hospitals in a Low-Resource Setting: A Randomised Controlled Trial

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Abstract

Objective: Intravenous labetalol and hydralazine are both considered first-line medications for the management of acute-onset, severe hypertension in pregnant and postpartum women. The study compared the efficacy and safety profile of intravenous labetalol and hydralazine in the control hypertension in severe pre-eclampsia. **Materials and Methods:** One hundred patients who presented with severe pre-eclampsia were randomized into two study groups. The fifty patients in each arm of the study received either intravenous labetalol or intravenous hydralazine for the control of blood pressure. **Results:** The mean age of the labetalol subjects was 28.6 ± 5.47 years while that of their hydralazine counterparts was 29.12 ± 5.77 years. The majority of respondents in both groups were primigravidae (76% vs. 78%) (P = 0.813). The number of doses of drug needed to significantly lower the mean systolic blood pressure was slightly lower in the labetalol group (2 doses) compared to the hydralazine group (5 doses) ($t = 0.803^{Y}$, P = 0.977). The incidence of headaches which were the commonest complaints was comparable in both groups 8% and 10% of respondents respectively (P > 0.05). **Conclusion:** Although both intravenous labetalol and hydralazine are useful in patients with severe pre-eclampsia, the response to labetalol was better with comparable side effects.

Keywords

Blood Pressure, Hydralazine, Labetalol, Low-Resource Setting Severe

Pre-Eclampsia, Side Effects

1. Introduction

Pre-eclampsia is a multi-systemic syndrome characterized by elevated blood pressure of ≥140/90 mmHg obtained on two separate occasions at least 4 hours apart with significant proteinuria in the second half of pregnancy, labour and puerperium in a previously normotensive and non-proteinuric woman [1].

Pre-eclampsia complicates between 3% - 14% of pregnancies worldwide severe pre-eclampsia accounts for approximately 25% of all cases of pre-eclampsia and 5% - 8% of pregnancies in the United States [2]. In Nigeria, pre-eclampsia complicates 6% - 8% of all pregnancies [3] and a prevalence of 9.7% has been reported in Ibadan [4]. In general, about 5% - 10% of women develop this condition during their first pregnancies while it is seen in 7% of women in subsequent pregnancies [5].

Although this disease is primarily associated with hypertension and proteinuria, the multi-systemic consequences affect both the mother and the foetus [6]. The World Health Organization (WHO) has estimated that worldwide, approximately 63,000 women die from hypertensive diseases during pregnancy each year with 98% of these occurring in developing countries [7]. There is a need for frequent assessment of maternal and foetal well-being and monitoring of disease progression, so as to prevent the occurrence of these complications [8].

Hypertension in pregnancy could either be mild or severe based on the blood pressure and/or the occurrence of both clinical and laboratory abnormalities [9]. The delivery of the woman is the cure for this disease and the principles of management of severe disease include control of blood pressure, prevention of fits and delivery by the most expedient route [10]. In the acute control of blood pressure in severe hypertension in pregnancy, it is important to maintain blood pressure below 160/110 mmHg, so as to prevent the complications associated with maternal hypertension and loss of cerebral autoregulation [11]. The antihypertensive agents used for the acute control of blood pressure are few and most of these drugs can precipitate foetal distress [12] [13].

Intravenous labetalol and hydralazine are both considered first-line medications for the management of acute-onset, severe hypertension in pregnant and postpartum women [14]. Hydralazine is widely used especially in low-resource settings due to the fact that it is cheaper and readily available. However, it is now less emphasized because of its side effects, especially tremor, nausea, hypotension and reflex tachycardia and the fact that it may be less well tolerated than labetalol [15]. The alternative drug is labetalol, its major drawback is beta-adrenoceptor blockade leading to neonatal bradycardia, hypotension and hypoglycaemia. Respiratory distress and apnoea have also been reported in newborns and are usually mild and resolve within 48 hours [16] [17].

2. Materials and Methods

This was a randomized controlled study comparing the effectiveness of Labetalol and Hydralazine for blood pressure control in severe pre-eclamptic women and the side effects following the use of either drug during a period of three months (Sept-November 2014). Ethical clearance for this study was obtained from the ethical review board of the Federal Teaching Hospital, Ido-Ekiti, Ekiti State, Nigeria.

A hundred women who satisfied the inclusion criterion were recruited. They were randomized into two groups of fifty each with the aid of computer-generated random numbers. Exclusion criteria included postpartum severe pre-eclampsia, mild pre-eclampsia, eclampsia, chronic renal disease, chronic hypertension and other cardiovascular diseases. Others are asthmatics, gestational diabetics and known drug reactions or hypersensitivity to drugs used in the research.

A hundred women were recruited based on the minimum calculated sample size of 45 patients on each arm of the study and deliberate over-sampling of 10%. The subjects who fulfilled the inclusion criteria were recruited after detailed history and physical examination had been conducted.

At admission, each patient was stabilized and assessed for delivery, intravenous access was secured and blood samples were taken for necessary investigations such as electrolyte, urea and creatinine, full blood count, liver function tests, prothrombin time, and partial thromboplastin time in Kaolin. Magnesium sulfate was given for seizure prophylaxis.

Consent for study participation was taken and the patient was assigned a sequential study number. One of the investigators assigned (O.T) of the study opened the corresponding numbered envelope for the purpose of allocation into the labetalol or hydralazine study arm.

Participants in the labetalol group received 25 mg as the initial intravenous (IV) bolus, administered slowly over 5 min. Thirty minutes from start of administration of the first dose, the blood pressure was then measured and if systolic blood pressure (SBP) persisted ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 110 mmHg, the dose was doubled (50 mg). After 30 min the blood pressure was still not controlled, a third dose of 75 mg was given and this dose was to be repeated two more times if the blood pressure remained uncontrolled (*i.e.* a total of 5 doses of IV labetalol adding up to 300 mg, the maximum daily dose).

The hydralazine group received 5 mg as an initial IV bolus administered over five minutes. After 30 min from start of administration of the first dose, blood pressure was measured and if SBP was ≥160 mmHg and/or DBP ≥ 110 mmHg, the 5 mg dose was to be repeated up to a maximum daily dose of 40 mg (*i.e.* a total of 8 doses) unless the blood pressure became controlled (SBP < 160 mmHg and DBP < 110 mmHg).

When the maximum dose of either labetalol or hydralazine had been reached without an adequate control of the blood pressure (SBP < 160 mmHg and DBP < 110 mmHg), this was to be noted and managed according to our protocol. All

new episodes of hypertensive crisis in either group were also to be recorded.

Regardless of the group, the presence or absence of adverse reactions related to the use of the medication with each dose was ascertained from all participants.

The primary outcome was the efficacy of the medication, described as the minimum number of doses of labetalol or hydralazine required to obtain an adequate control of the blood pressure (systolic blood pressure < 160 mmHg and diastolic blood pressure < 110 mmHg). The proportion of patients whose systolic blood pressure remained ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg after completing the maximum recommended dose of either antihypertensive was to be noted. Secondary outcome measures were the occurrence of side effects of labetalol or hydralazine on the mother and fetus.

Data Analysis

A structured profoma was used to obtain relevant data from each patient. Data obtained from the subjects included biodata, gestational ages at booking (or first visit to antenatal clinic) and admission, blood pressure readings at booking (or first antenatal if unbooked at admission and the degree or severity of proteinuria were recorded in the profoma.

The generated database was analyzed with Statistical Package for Social Sciences (SPSS) for Windows software version 17 manufactured by Chicago: SPSS Inc. in 2008. Categorical variables were expressed as absolute numbers and percentages while continuous variables were presented as means with standard deviations and the differences analyzed with the *t*-test. The level of significance was set at $P \leq 0.05$.

3. Results

The important socio-demographic characteristics were similar in both groups, and the clinical and obstetrics parameters are similar (Table 1 and Table 2).

The respondents in the labetalol arm needed not more than two doses of intravenous labetalol to bring down the SBP from 180.76 ± 14.31 mmHgto 147.27 ± 4.67 mmHg as against those in the hydralazine arm where some respondents needed up to five doses of intravenous labetalol to lower the SBP from 179.00 ± 19.40 mmHg to 150.00 ± 0.00 mmHg. It was also shown that the reduction in SBP in the labetalol group after the first and second doses of the drug was statistically significant than the hydralazine group (P = 0.0001, P = 0.010) respectively (Table 3).

Table 4 showed the similarity in the diastolic blood pressure (DBP) between the labetalol and hydralazine groups on admission into the hospital (122.40 ± 15.63 mmHg vs 121.00 ± 17.85 mmHg), the difference was not statistically significant (P = 0.677). The table also showed that respondents needed up to five doses of intravenous labetalol to lower the DBP from 121.00 ± 17.85 mmHg to 106.00 ± 0.00 mmHg. It was also shown that the reduction in DBP in the labetalol group after the first and second doses of the drug was statistically more significant than the hydralazine group (P = 0.001, P = 0.005) respectively.

Table 1. Socio-demographic characteristics of respondents.

	Labetalol	Hydralazine	Test	P-value
Maternal Age (Years)	Frequency (%)	Frequency (%)		
<20	3 (6.0)	5 (10.0)	1.785[Y]	−0.168
21 - 25	13 (26.0)	7 (14.0)		
26 - 30	17 (34.0)	16 (32.0)		
Above 30	17 (34.0)	22 (44.0)		
Total	50 (100.0)	50 (100.0)		
Mean ± SD	28.6 ± 5.47	29.12 ± 5.77	−0.462	0.645
Educational Level				
None	6 (12.0)	5 (10.0)	1.188	0.756
Primary Education	11 (22.0)	15 (30.0)		
Secondary	20 (40.0)	16 (32.0)		
Tertiary	13 (26.0)	14 (28.0)		
Total	50 (100.0)	50 (100.0)		
Marital Status				
Married	37 (74.0)	41 (82.0)	1.805	0.406
Single	6 (12.0)	6 (12.0)		
Separated	7 (14.0)	3 (6.0)		
Total	50 (100.0)	50 (100.0)		
Religion				
Islam	12 (24.0)	13 (26.0)	0.053	0.818
Christianity	38 (76.0)	37 (74.0)		
Total	50 (100.0)	50 (100.0)		
Ethnicity				
Igbira	7 (14.0)	6 (12.0)	0.568[Y]	0.988
Yoruba	33 (66.0)	32 (64.0)		
Igbo	4 (8.0)	6 (12.0)		
Urhobo	1 (2.0)	1 (2.0)		
Fulani	2 (4.0)	3 (6.0)		
Bini	3 (6.0)	2 (4.0)		
Total	50 (100.0)	50 (100.0)		

Table 2. Clinical characteristics of the respondents.

	Labetalol	Hydralazine	T-test	P-value
Maternal Weight (Kg)	74.63 ± 9.07	76.76 ± 8.12	−1.232	0.221
Pulse Rate (Beats/min)	77.82 ± 13.14	81.2 ± 5.44	−1.681	0.096
Respiratory Rate (cycle/min)	20.76 ± 2.18	21.31 ± 2.69	−1.147	0.254

Continued

Gestational Age at Admission	38.42 ± 1.34	37.90 ± 1.50	−1.826	0.071
Gestational Age at Booking/ First Antenatal Visit	18.8 ± 5.4	19.76 ± 6.20	−0.583	0.562
Booking Status	(%)	(%)		
Booked	15 (30)	19 (38)	0.713*	0.398
Unbooked	35 (70)	31 (62)		
Total	50 (100.0)	50 (100.0)		
Gravidity				
Primigravidae	38 (76.0)	39 (78.0)	0.056*	0.813
Multigravidae	12 (24.0)	11 (22.0)		
Total	50 (100.0)	50 (100.0)		

*Chi-square test used.

Table 3. Systolic blood pressure (SBP) on admission and following administration of antihypertensives.

SBP (mmHg)	Labetalol	Hydralazine	T-test	P-value
On Admission	180.76 ± 14.31	179.00 ± 19.40	0.459	0.064
After First Dose	154.92 ± 11.98	166.04 ±13.72	−4.315	0.0001
After Second Dose	147.27 ± 4.67	158.37 ± 13.29	−2.307	0.010
After Third Dose		156.73 ± 10.33		
After Fourth Dose		153.66 ± 6.62		
After Fifth Dose		150.00 ± 0.00		

Table 4. Diastolic blood pressure (DBP) on admission and following administration of antihypertensives.

DBP (mmHg)	Labetalol	Hydralazine	T-test	P-value
On Admission	122.40 ± 15.63	121.00 ± 17.85	0.417	0.677
After First Dose	100.52 ± 14.49	110.92 ± 14.85	−3.543	0.001
After Second Dose	94.00 ± 5.65	106.22 ± 13.36	−2.938	0.005
After Third Dose		103.68 ± 14.22		
After Fourth Dose		118.33 ± 17.22		
After Fifth Dose		106.00 ± 0.00		

The changes in the mean arterial blood pressure also followed the trend as the systolic and diastolic values, the number of doses needed to significantly lower the blood pressure and the changes after the first 2 doses. It was also shown that the reduction in MAP in the labetalol group after the first and second doses of the drug was statistically more significant than the hydralazine group ($P < 0.05$).

In this study as shown in **Table 5**, patients were noticed to have side effects

Table 5. Side effects profile of the antihypertensives among respondents.

Side effect	Labetalol	Hydralazine	Test	P-value
Headache	4 (8.0)	5 (10.0)		
Dizziness	3 (6.0)	2 (4.0)		
Nausea	1 (2.0)	1 (2.0)		
Vomiting	2 (4.0)	3 (6.0)	0.803[Y]	0.977
Palpitations	1 (2.0)	3 (6.0)		
None	39 (78%)	36 (72.0)		
Total	50 (100.0)	50 (100.0)		

such as headaches, dizziness, nausea, vomiting and palpitations. Headaches were the commonest complaint in both groups accounting for 8% and 10% of respondents respectively. No side effect of the drug was seen in 78% of the labetalol group and 72% of the hydralazine group.

4. Discussion

Hypertension in pregnancy contributes significantly towards the maternal and perinatal morbidity and mortality in developed as well as developing countries of the world.

Acute control of blood pressure with parenteral fast acting antihypertensive remains one of the principles of management of patients with severe pre-eclampsia so as to reduce the incidence of complications. Intravenous labetalol and hydralazine are both considered first line medications for the management of acute-onset, severe hypertension in pregnant and postpartum women [18].

Both labetalol and hydralazine groups were similar with respect to age, gravidity, baseline systolic blood pressure, diastolic blood pressure and mean arterial pressure. Similar observations were noted in randomised controlled trial of hydralazine and labetalol for the treatment of severe hypertensive disorders of pregnancy [19].

It was shown that after two doses, all patients who had intravenous labetalol had adequate systolic, diastolic and mean arterial blood pressure control when compared with the patients in the hydralazine arm where up to five doses of intravenous hydralazine were needed, in some, to achieve good blood pressure control. the above findings were different in a study carried out by Mabie *et al.* [20] where he randomised sixty peripartum patients in a 2:1 ratio to receive either labetalol or hydralazine, labetalol in dose range 20 - 80 mg or hydralazine 5 mg (max. 4 doses) were given until diastolic BP was 100 mmHg. There were four treatment failures in labetalol group (N40) and none in hydralazine group (N20). Hydralzine lowered mean arterial pressure more than the labetalol.

American College of Obstetricians and Gynecologists recommends parenteral labetalol and hydralazine as first line drug for the treatment of acute severe hypertension [21]. Hydralazine has been serving as antihypertensive for over 40 years.

It acts as a vasodilator, decreases peripheral resistance and lowers blood pressure. The effects are of short duration and system reset to the blood pressure levels necessary to maintain pressure in kidney necessary for natriuresis.

Labetalol is a non-selective beta-blocker and postsynaptic alpha-1 blocking agent. Labetalol may be considered as first line drug but there is a potential risk of fetal bradycardia. Nombus in his study demonstrated Labetalol and Hydralazine effective and rapid antihypertensive agents in hypertension crises. The time taken to lower blood pressure and the number of doses for the drugs are similar in Numba's study [22]. A study from Delgado De Rasquel also reported similar findings [23].

In a study conducted by Mable *et al.*, authors found Hydralazine lowered mean arterial pressure more than Labetalol which is 13.3 versus 11.2 mmHg [20]. A study by Ashe *et al.* showed comparable results [24].

Contrary to the above findings in the current study the blood pressure reduction with Labetalol was significant with P-value < 0.05. In the Cochrane review meta-analysis data from the two drugs was not significant to decide superiority of one drug over the other.

In this study, patients were observed for side effects of labetalol and hydralazine such as headaches, dizziness, nausea, vomiting and palpitations. There was no adverse drug reaction, such as respiratory distress or cardiovascular depression noted. The side effects of the intravenous anti-hypertensives were comparable in both groups. Most of the patients in both groups complained of headaches (labetalol 8%, hydralazine 10%) after administration of the drugs. It was however difficult to know if the headache was due to the disease process or a side effect of the drug. This finding is consistent with the study done by Samuel *et al.* using intravenous labetalol and hydralazine showing a similar frequency of adverse effects in both groups. Previous studies by Gonzalez *et al.* [25] showed that intravenous labetalol was safe and not associated with any major side effects.

5. Conclusion

The treatment of severe pre-eclampsia using either labetalol or hydralazine is quite effective although the response to labetalol is better as shown in this study. Studies reporting the efficacy of hydralazine and labetalol as anti-hypertensive mostly favored the null hypothesis demonstrating no superiority of one drug over another in achieving blood pressure reduction. A well-designed, randomized controlled trial with an adequate sample size will help to determine better drugs for the control of hypertension, particularly in the context of our pregnant population.

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Conflicts of Interest

There authors declare no conflicts of interest.

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