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Intravenous Hydrallazine or Intravenous Labetalol in Severe Hypertension in Pregnancy: A Randomized Clinical Trial

Abstract

Background: Hypertensive disorder of pregnancy is one of the direct causes of maternal mortality and morbidity globally. Prompt Blood pressure control is key to successful outcome.

Objective: To compare the efficacy of intravenous labetalol and hydrallazine in lowering severe hypertension in pregnancy.

Study Design: A randomized clinical trial; conducted in the University of Port Harcourt Teaching Hospital, Nigeria. Sixty Pregnant women with severe hypertension of ≥160mmHg/≥110mmHg were randomized into 2 groups by simple balloting. In Group A, 30 women received intravenous hydrallazine 10mg slowly and repeated every 20 minutes until systolic blood pressure was ≤150mmHg and/or diastolic blood pressure was ≤100mmHg. In Group B 30 women received intravenous labetalol in escalating doses of 20, 40, 80 and 80mg every 20 minutes until systolic blood pressure was ≤150mmHg and/or diastolic blood pressure was ≤100mmHg.

Results: Intravenous hydrallazine required 28.00±3.65 minutes while intravenous labetalol required 75.27 ± 21.66 minutes to achieve the target blood pressure (p=0.00). The number of doses required to achieve the target blood pressure was 1.33+/-0.54 for hydrallazine and 3.0± 1.57 for labetalol (p=0.00). There was no severe perinatal morbidity or adverse maternal effects in the two groups.

Conclusion: This study shows that intravenous hydrallazine acts faster than intravenous labetalol in reducing blood pressure in pregnant women with severe hypertension without any increase in adverse effects. Hydrallazine is therefore suggested as a drug of first choice in severe hypertension in pregnancy in our population.

Keywords: Hydrallazine, Labetalol, Severe Hypertension, Pregnancy

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Mmom Chigozirim Faith, Ogu RN, Orazulike NC, Uzoigwe SA

Department of Obstetrics and Gynaecology, University of Port Harcourt Teaching Hospital, Nigeria

Correspondence: Mmom, Chigozirim Faith, Senior Registrar, Department of Obstetrics and Gynaecology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria, Email mmomfaith@yahoo.com, faithmmom@gmail.com

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Background

Hypertension is the most common medical condition complicating pregnancy.[1-4] Globally, about 5-8% of pregnancies are complicated by hypertension.[3,4] It is a leading cause of maternal mortality and morbidity in the United Kingdom (UK), Canada, the United States of America (USA), and the developing world,[2-7] and the leading cause of maternal mortality and morbidity in Port Harcourt,[8] In addition, for every woman who dies from hypertensive disorder in pregnancy approximately 20 others suffer severe morbidity.[9]

Sustained rise in blood pressure places the pregnant woman at increased risk of placental abruption, cerebrovascular accident, cardiac arrest, acute kidney injury, maternal and perinatal mortalities.[2-6] In order to avert these complications, rapid-acting antihypertensive agents are usually administered in severe hypertension. The aim of treatment is to quickly bring about a smooth reduction in BP to levels that are safe for both mother and baby. Once blood pressure is controlled in many cases, a decision will be made to deliver the baby fairly soon particularly if the pregnancy is at or near term. However, in extreme prematurity with good blood pressure control, and in the absence of any other complications, the pregnancy may be continued with the hope that this will improve the baby's outcome.[10]

During pregnancy, the decision to choose one drug from amongst the pool of drugs depends on his experience with a particular drug, availability and cost. Hydrallazine, Labetalol and Nifedipine have been generally recommended as first line for acute lowering of blood pressure without a consensus on which drug is superior.[11] There has been no clinical data specific to choice of antihypertensive agents in the management of severe hypertension amongst pregnant women in Nigeria and clinicians in Nigeria had based their practice on studies done in Europe and America. This study sought to provide that missing evidence-based data for the choice of either labetalol or hydrallazine in the management of severe hypertension in pregnant women in Nigeria.

Method

This was a single blind randomized clinical trial for emergency control of severe hypertension among pregnant women in the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, South-South Nigeria. The Maternity Unit (Labour Ward) has a delivery rate of 3000-3500 per year. The trial was conducted in the labour ward of the department of Obstetrics and Gynaecology of the UPTH, Port Harcourt. The recruitment took place from April 2014 to September, 2015 after obtaining approval from the UPTH ethical committee.

Inclusion criteria

Pregnant women with severe hypertension (defined as systolic

blood pressure of ≥160mmHg or diastolic blood pressures of ≥110mmHg, aged between 18 and 45 years, gestational age of 28 weeks or more, live fetus with normal fetal heart rate and a maternal heart rate of >60 beats per minute but <120 beats per minute were enrolled. On the other hand, women with known allergy to either hydrallazine or labetalol, refusal of the patient to participate in the study, atrial-ventricular heart block or history of heart failure, bronchial asthma, exposure to antihypertensive agent within 24 hours prior to presentation, non pregnancy related hypertension (diagnosed cases of chronic hypertension or secondary hypertension) were excluded from the study.

The randomization sequence was done by balloting. Women picked from a bag containing 60 sealed envelopes labeled as A or B. Women that picked 'A', received intravenous hydrallazine (Mack- hydrallazine Hydrochloride 20mg/2ml, India) and those that picked 'B' were given intravenous labetalol (labet 50mg/10ml, Bangladesh). Blood pressure was rechecked every 10 minutes. The dose was repeated at 20 minutes when the desired blood pressure of ≤150/100mmHg was not achieved. Maximum number of 5 doses was allowed. If control was not achieved, the drug was said to have failed and a combination with oral nifedipine or intravenous labetalol was given.

Similarly, women randomized to group B received bolus doses of intravenous labetalol 20mg slowly while blood pressure check was done every 10 minutes. This was repeated in incremental doses of 40mg and 80mg to a maximum of 5 doses if the desired blood pressure was not attained, a combination with oral nifedipine or intravenous hydrallazine was given.

During the course of treatment, intermittent fetal heart rate monitoring was performed using the hand-held Doppler (Huntleigh Healthcare Ltd, UK). At the end of the trial protocol, the participants were made to complete the questionnaire concerning side effects during the trial period. Those whose blood pressure were un controllable had emergency caesarean delivery while those with controlled blood pressure remote from term were transferred to the antenatal ward for a conservative care.

Sample Size Determination

Sample size determination for this study was done using the values from previous studies,[12-16] and assuming a p value of 0.05, at 95% confidence interval and power of the study at 90%, and allowing for 10% attrition and possible skewed distribution that might require non-parametric testing, thirty women were randomized in each group.

Collection/Analysis of Data

All measurements and participant's bio-data were recorded in the data collection forms. Baseline data included age, parity, gestational age, family history of hypertension, prior use of antihypertensive drugs, systolic BP at enrollment, diastolic BP at enrollment, pulse rate at enrollment, pulse rate at the end of study, use of magnesium sulphate, use of antenatal corticosteroids, systolic BP ≥160mmHg after treatment, diastolic BP of ≥110mmHg after treatment, Primary outcome for each group and the secondary outcomes.

The data were entered and analyzed using SPSS version 19.0. Analysis was based on intention-to treat. Student t-test was used to analyze normally distributed data. Categorical data sets were analyzed with Fisher exact test. All tests were two-sided and $p< 0.05$ was considered significant.

Results

Sixty women were randomized into intravenous labetalol or intravenous hydrallazine (30 women in each group). Table 1 shows the baseline characteristics of the both study groups at presentation and it reflects uniformity in the study population for the two groups. Table 2 shows the primary outcome of the study which indicates that It took about 28.00+/- 3.64 minutes to reach a target blood pressure of 150/100mmHg for patients randomized to intravenous hydrallazine as compared to 75.27±21.66 minutes for those in the labetalol group to achieve the target blood pressure (p=0.00).

Table 1 baseline characteristics of subjects

	Labetalol Group	Hydrallazine Group	p value
Age (years)	30.80 ± 4.382	29.43 ± 4.216	0.776
Parity	0.93 ± 0.907	0.97 ± 0.850	0.252
Gestational Age (weeks)	37.40 ± 1.429	38.83 ± 1.262	0.473
Systolic BP at Enrollment	185.00 ± 20.299 mmHg	178.73 ± 17.573 mmHg	0.154
Diastolic BP at Enrollment	120.00 ± 17.617 mmHg	114.40 ± 11.631 mmHg	0.069
Pulse rate at Enrollment	90.2 ± 9.102 /minute	86.20 ± 7.867/minute	0.681
Fetal heart rate	146.37 ±8.938 beats/minute	141.33 ± 7.189 beats/minute	0.295

Table 2 Primary outcome

Outcome	Labetalol	Hydrallazine	P value
Time to reach target Blood Pressure (minutes)	75.27±21.66	28.00 ± 3.648	0.00
No of doses required	3± 1.57	1.33 ± 0.54	0.00
Failure rate	40%	13.3%	0.00

Intravenous hydrallazine also required fewer doses (1.33 ±0.54) than intravenous labetalol (3±1.57) to achieve the target blood pressure. Similarly, 4 patients in the intravenous hydrallazine and 12 patients in the labetalol group had persistent hypertension despite 5 doses of the assigned antihypertensive agent, representing 13.33% and 40.0% failure rate respectively. Fifteen patients in the labetalol group and 18 from the hydrallazine group received magnesium sulphate for seizure prophylaxis. Five 5 patients in the labetalol group and 6 in the hydrallazine group got intramuscular corticosteroids to enhance lung maturity as they were less than 34 weeks of gestational age.

Table 3 shows mode of delivery. In the labetalol group, 15 patients had emergency caesarean section and 3 had vaginal delivery. Whereas, in the intravenous hydrallazine group, 10 patients had emergency caesarean section and 12 had vaginal delivery. The rest continued on conservative management as they achieved blood pressure control and were transferred to the antenatal ward because they were remote.

Table 4 shows adverse maternal and fetal outcome for the two groups. One minute APGAR scores <7 were seen in 5 babies in labetalol and 6 in intravenous hydrallazine group. Five minute APGAR scores < 7 were one in each group. Two neonates in the labetalol group and 3 in the hydrallazine group had early neonatal deaths.

There was no case of hypotension (defined as systolic BP<90mmHg or a diastolic BP <60mmHg or both). Two patients each in both groups had headache while nausea occurred in 1 patient in the labetalol group and 2 in the hydrallazine group. On the other hand, 3 patients from the hydrallazine group complained of dizziness while none was observed in the labetalol group.

Table 3 Mode of delivery

	Labetalol	Hydrallazine
Emergency Caesarean Section	15	10
Vaginal Delivery	3	12
P Value	0.45	0.58

Table 4 Adverse maternal and fetal outcome

	Labetalol	Hydrallazine	P value
Dizziness	0	3	0.78
Headache	2	2	0.54
Nausea	1	2	0.44
Maternal Hypotension	0	0	0.54
1 minute APGAR Scores less than 7	5	6	0.88
5 minute APGAR Scores less than 7	1	1	0.45
Early neonatal death	2	3	0.77

Discussion

This study showed that intravenous hydrallazine acts faster than intravenous labetalol in controlling blood pressure in severe hypertension of pregnancy. Intravenous hydrallazine also required fewer doses to achieve a safe blood pressure level when compared with intravenous labetalol. The mean time to achieve target blood pressure obtained from this study is comparable to other studies comparing hydrallazine with other antihypertensive agents.[13-14]

On the other hand, it took an average of 75 minutes and 3 doses to achieve the target blood pressure in the labetalol group with a 40% failure rate compared with the 13.33% failure rate in the hydrallazine group. This defeats the purpose of rapid blood pressure reduction in hypertensive emergency. These findings are not in agreement with other studies on intravenous labetalol where intravenous labetalol was adjudged to have met the criteria as a first line antihypertensive with a mean time between 43.6 minutes - 60 minutes.[15-19]

The reason for this disparity might be related to racial differences in the study population as beta blockers have been found to be less effective in controlling hypertension amongst blacks.[20-21] Our study population was predominantly black. There might also be the drug potency issues in the tropics which will warrant more robust multi-centre studies in this our environment to find out what works best for us. Caesarean section rate was higher with the labetalol group in this study. This is not surprising as failure to achieve control usually result in delivery by the fastest and safest means available and in our environment, it is caesarean section. In the same vein, vaginal delivery was more in the hydrallazine group compared with the labetalol group as those who had effective blood pressure control were allowed to achieve vaginal delivery.

Dizziness and nausea were more in the hydrallazine group, but headache occurred equally in both groups and there was no case of hypotension. This finding is in keeping with the documented side effects of hydrallazine by past studies.[22-25] These side effects were not serious enough to warrant discontinuation of the drug. It was also said that these side effects of dizziness, headache, and nausea mimic features of worsening preeclampsia/eclampsia[18,19,23,26] and as a result preferred labetalol. These same side effects have also been documented with labetalol use,[27] which made a later Cochrane review to state that no one drug is better than the other thus urging clinicians to individualize their patients using their clinical experience and availability of the said drug.[23] The adverse perinatal outcome noted in this study might not be related to the antihypertensive drugs used in the study as those babies were delivered preterm and might have suffered from other complications related to prematurity.

This study takes its strength from the fact that it was a randomized clinical trial. There was no difference in the baseline characteristics of the participants. However, it was not blinded due to logistic constraints and as a result the individual bias of the researchers may not have been completely eliminated.

Conclusion

This study therefore concluded that intravenous hydrallazine acts faster than intravenous labetalol in reducing blood pressure in pregnant women with severe hypertension in Nigeria, and has a tolerable side effects profile.

Recommendations

Hydrallazine is therefore suggested as a drug of first choice in severe hypertension in pregnancy in Nigeria. More multi-centre studies are therefore suggested to have a generalizable conclusion and also to find other suitable alternatives to intravenous hydrallazine and labetalol.

Acknowledgments

None.

Conflicts of interest

None.

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