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Original Research Article

Comparison of labetalol and nifedipine in control of blood pressure in severe pre-eclampsia in Dalhatu Araf Specialist Hospital

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ABSTRACT

Background: Severe preeclampsia and eclampsia are forms of hypertensive disorders of pregnancy that cause significant morbidity and mortality in the mother and foetus globally. The best drug for prompt lowering of blood pressure is required for a desirable outcome. This study was aimed determining the efficacy of intravenous labetalol compared with oral nifedipine in the immediate control of hypertension in severe pre-eclampsia.
Methods: Seventy-four women who fit the criteria for severe preeclampsia were randomly selected and recruited for the prospective comparative study. They were divided into two equal arms, one, receiving intravenous labetalol in precise, timed doses and the other, oral nifedipine in its own timed doses. The doses and time for effective blood pressure control were recorded in both arms and comparatively analyzed.
Results: The time taken to achieve targeted blood pressure of <150/100 mmHg in the intravenous labetalol group was (38.9±17.2 min) and in the oral nifedipine group was (37.1±17.2 min) with p value=0.302. The mean number of doses required to achieve this was (2.6±1.2 doses) and (2.3±1.0 doses) respectively with p value of 0.370. The mean cost of treatment per doses given for labetalol group was (NGN 3259.5±2294.4) and nifedipine group, was (NGN 3254.1±1440.4) with p value=0.990.
Conclusions: Both drugs were found to be equally efficacious in rapidity of controlling blood pressure in severe preeclampsia and both had similar cost effect per dose of drug.

Keywords: Labetalol, Nifedipine, Severe pre-eclampsia, Blood pressure, DASH

INTRODUCTION

Pre-eclampsia is a common complication of pregnancy and they are hypertensive disorders of pregnancy that cause significant morbidity and mortality in the mother and foetus both in developed and developing countries.[1,2] It is a pregnancy-specific condition characterized by the occurrence of hypertension and significant proteinuria after 20 weeks of gestation in a previously normotensive and non-proteinuric woman.[3,4] It is one of the leading causes of maternal and perinatal morbidity and mortality.[5-7] The major risk factors for the development of preeclampsia include a previous history of preeclampsia, chronic hypertension, pre-gestational diabetes mellitus, anti-phospholipid syndrome, and obesity, among others. While the cause of preeclampsia is still debated, clinical and pathological studies suggest that the placenta is central to the pathogenesis of this syndrome.[7]

The overall strategy in the treatment of hypertension in pregnancy with antihypertensives is to prevent maternal cerebrovascular and cardiac complications, while preserving the uteroplacental and foetal circulation and limiting medication toxicity to the foetus.[8] In severe

disease there may be red blood cell breakdown, a low blood platelet count, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances.[9,10] If left untreated, it may result in seizures at which point it is known as eclampsia.[10]

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.[1,2] Anti-hypertensives are commonly initiated for the control of severe hypertension in pregnancy (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg) as recommended by the National High Blood Pressure Education Program.[11,12] Various antihypertensive agents have been used for lowering blood pressure in severe pre-eclampsia, intravenous labetalol, oral nifedipine and intravenous hydralazine are the drugs most commonly used to control acute severe hypertension in women with pre-eclampsia.[11,12]

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 first line drug and has a better side effect profile but specific concern has been raised about the risk of neonatal bradycardia.[13,14]

Nifedipine is a calcium channel blocker that impedes the influx of calcium into vascular smooth muscle cells, causing vascular relaxation and decreasing Peripheral vascular resistance, reference.[14,15-19]

During pregnancy, the decision to choose one drug from amongst the pool of drugs depends on the obstetrician's experience with the particular drug, availability and cost. Hydralazine, labetalol and nifedipine have been generally recommended as first line for acute lowering of blood pressure without a consensus on which drug is superior, thus the rational for this study.[15] Both nifedipine and labetalol are used in management of acute severe hypertension in pregnancy but may differ in their efficacy and the total cost required for blood pressure control in the acute phase of the disease. Most of the available data on efficacy of labetalol and nifedipine in acute management of blood pressure in severe preeclampsia are from studies done in developed countries. Therefore, this study provides data comparing the efficacy of both drugs in the management of hypertension in severe pre-eclampsia in a resource-poor setting such as Lafia in North-Central Nigeria where this study was done.

METHODS

Study area

This is a hospital based study carried out in the maternity unit of Dalhatu Araf Specialist Hospital (DASH), Lafia, Nasarawa State. The hospital is located in Lafia, the state capital and it is the only tertiary institution that serves patients from the state and neighbouring states of Benue, Plateau, Taraba and the FCT.

Study population

The study population was pregnant women coming for antenatal care at the maternity unit of DASH with severe pre-eclampsia defined as systolic BP ≥160 mmHg and or diastolic BP ≥110 mmHg with significant proteinuria who met the criteria for the study.

Study design

A hospital based randomized clinical trial.

Inclusion criteria

Entry criteria were pregnancy more than 20 weeks and severe hypertension (systolic blood pressure of ≥160 mmHg and/or diastolic blood pressure of ≥110 mmHg) and proteinuria of >1+ as measured by dipstick in a clean catch midstream urine specimen.

Exclusion criteria

Those that declined consent, or had known allergy to nifedipine or labetalol or any other contraindication to the use of any of the drugs, those with chronic hypertension with superimposed preeclampsia on medications, patients who were on magnesium sulphate, multiple pregnancies, coexisting medical conditions like diabetes Mellitus, cardiac disease and sickle cell disease.

Sample size determination

The sample size for comparison groups was calculated using the formula given.

$$n = 2Z^2PQ/D^2$$

Here, n=minimum sample size, p value of 0.05 at confidence interval of 95%, Z=95% confidence interval using 1.96, P=prevalence of severe preeclampsia (1.2), Q=1.0-P, D=degree of accuracy desired, usually set at 0.05, and n=35.[16]

Adding 5% attrition rate, anticipated response rate 95%.

The selected sample size was 35/0.95=37.

Then each trial group was allocated 37 participants. The minimum sample size is at least 74 participants.

Sampling technique

Eligible consenting women with the diagnosis of severe pre-eclampsia seen at the antenatal clinic of DASH were recruited for the study. The women were randomly

assigned into one of the two treatment groups using a simple random technique.

Data collection and analysis

The procedure was explained to all subjects and a written consent obtained from each. The women were randomly divided into two groups. Group-A received oral nifedipine 20 mg tablets in the following order (20, 20, 20, 20, 20 mg) up to five doses every 20 minutes or until the target blood pressure of 150/100 mmHg was achieved. Group-B received intravenous labetalol 20 mg initially followed by 40mg in escalating doses (20, 40, 80, 80, 80 mg) up to five doses every 15 minutes or until the target blood pressure was achieved. Crossover treatment was effected when initial treatment regimen was unsuccessful. The median time taken to achieve the target blood pressure was recorded for both.

Blood pressure measurements were carried out by the researchers with the women sitting at a 45-degree angle and well rested. The same standard sphygmomanometer with appropriate cuff was used for all the women. The cuff applied around the upper arm at the level of the heart. The mercury sphygmomanometer was used for blood pressure measurement and the Korotkoff sound V (disappearance of the sound) was used to get the diastolic blood pressure because it is more reproducible than the fourth sound.[12,16,17] On each occasion, two blood pressure measurements were carried out four hours apart and the mean calculated and documented for each subject. Urine protein estimation was carried out using dipstick in clean catch mid-stream urine specimen.

Urine collection for urinalysis: each patient was given a labelled sterile urine sample bottle for urine collection after detailed explanation on collection of a mid-steam urine sample. Patients were counselled on the need to wash their hands and labia thoroughly with soap and water before taking the sample. One hand was used to expose the urethra while passing the first flow of the urine in to the toilet.

Patients were told to collect the middle part of the urine into the sterile bottle provided without interrupting urination. The bottle was covered immediately after sample collection without contamination by the patient. The appropriately labelled urine sample bottle handed over to the researchers for urine estimation for protein using Combi10 urinary strip. The entire urinary strip deepened into the urine sample for about 2 seconds and the degree of proteinuria assessed by matching the colour on the strip with the colour on the strip container.

Data was analyzed using statistical package software for social sciences (SPSS) version 25.0 Categorical variables were analyzed using Chi-square test and differences in continuous variables analyzed with Mann-Witney test. P value of less than 0.05 is considered statistical significance.

RESULTS

The mean age of participants for both groups is 25.4±5.4 years with majority, 43 (58.1%) between ages 21-31, 19 (25.7%) being less than age 20 and 12 (16.2%) in the age range 31-40 years. Mean weight of the participants was 73.4±9.5 kg (Table 1).

Table 1: Age distribution of participants in this study.

Categories	Frequencies	Percentage
Age (mean±SD)	25.4±5.4	
≤20	19	25.7
21-30	43	58.1
31-40	12	16.2

Table 2 showed the average parity of the participants is 1.3±1.5. Majority of the participants, 35 (47.3%) were nullipara, and the mean gestational age was 34.3±3.4 weeks with majority, 39 (52.7%) of the participants 34 weeks and beyond.

Table 2: Gestational age and parity of the study participants.

Categories	Frequencies	Percentage
Parity (mean±SD)	1.3±1.5	
0	35	47.3
1	9	12.2
2	15	20.3
3	9	12.2
4	4	5.4
5	1	1.4
7	1	1.4
Gestational age (weeks) (mean±SD)	34.3±3.4	
28–30	15	20.3
31–33	20	27.0
34 and above	39	52.7

Table 3 showed the average systolic blood pressure in both groups was compared showing mean 167.0±7.5 mmHg and 167.6±9.9 mmHg in the labetalol and nifedipine groups respectively with p value=0.792 showing no statistical difference. Similarly, average diastolic blood pressure (DBP) in both groups was compared revealing mean of 113.6±7.2 mmHg and 114.5±8.6 mmHg respectively with p value=0.649.

From Table 4, 11 (14.9%) of the entire patients enrolled in the study needed additional therapy. Seven patients representing 18.9% of participants in the IV labetalol group needed additional therapy while 4 (10.8%) of participants in the oral nifedipine group needed additional therapy. With Fisher's exact of 0.948 and p value=0.515 implied that the need for additional therapy was not associated with drug used.

Table 3: Comparison of the systolic blood pressure and diastolic blood pressure in the IV labetalol group and oral nifedipine group.

Variables	Labetalol n=37 (mean±SD)	Nifedipine n=37 (mean±SD)	P value
Systolic BP (mmHg)	167.0±7.5	167.6±9.9	0.792
Diastolic BP (mmHg)	113.6±7.2	114.5±8.6	0.649

Table 5 showed that in the IV labetalol group, the change in mean systolic blood pressure was 19.1±7.2 mmHg and in the oral nifedipine group, the mean systolic blood pressure was 19.9±9.1 mmHg with p value=0.692. The change in mean diastolic blood pressure in the IV labetalol group was 16.5±6.7 mmHg and in the oral nifedipine group, mean±SD of 16.4±6.4 mmHg with p value=0.929.

Table 6 showed that in the IV labetalol group, the mean cost of treatment per doses given was NGN 3259.5±2294.4 and in the oral nifedipine group, the mean cost of treatment per doses given was NGN 3254.1±1440.4 with p value=0.990. The mean doses required in the IV labetalol group was 2.6±1.2 doses and in the oral nifedipine group, the mean doses required was 2.3±1.0 doses with p value=0.370. The cost and the number of doses required in both drugs were not statistically significant.

Table 4: Comparison of the need for additional therapy between IV labetalol group and oral nifedipine group.

Need for additional therapy	IV labetalol (n=37) (%)	Oral nifedipine (n=37) (%)	Total (%)	Fisher's exact	P value
Yes	7 (18.9)	4 (10.8)	11 (14.9)		
No	30 (81.1)	33 (89.2)	63 (85.1)	0.948	0.515
Total	37 (100.0)	37 (100.0)	74 (100.0)		

Table 5: Comparison of the change in mean systolic and diastolic blood pressure in the IV labetalol group and oral nifedipine group.

Variables	Labetalol n=37 (mean±SD)	Nifedipine n=37 (mean±SD)	P value
Change in mean systolic blood pressure	19.1±7.2	19.9±9.1	0.692
Change in mean diastolic blood pressure	16.5±6.7	16.4±6.4	0.929
Weight	76.8±9.0	70.0±8.9	0.002

Table 6: Cost comparison of treatment per doses given.

Variables	IV labetalol n=37 (mean±SD)	Oral nifedipine n=37 (mean±SD)	P value
Cost of treatment per doses given	3259.5± 2294.4	3254.1± 1440.4	0.990
Doses required	2.6±1.2	2.3±1.0	0.370

Figure 1 showed the comparison of doses required and time taken to reduce blood pressure to <150/100 mmHg in both drugs. The mean time required were 38.9 minutes and 37.1 minutes for IV labetalol and oral nifedipine respectively with p value=0.302. The mean doses required to achieve this reduction were 2.6 and 2.3 doses respectively which were both not statistically significant.

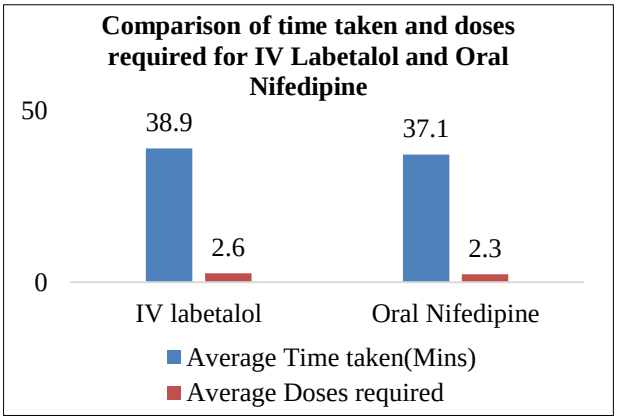

Figure 1: Comparison of time taken and dose required for both medications to achieve blood control.

DISCUSSION

This study showed that both intravenous labetalol and oral nifedipine are both equally efficacious in the control of hypertension in severe preeclampsia. The mean SBP in this study was 167.0±7.5 mmHg in the labetalol group and 167.6±9.9 mmHg in the nifedipine group with p value of 0.792. Similarly, the mean diastolic blood pressure (DBP) was 113.6±7.2 mmHg in the labetalol group and 114.5±8.6 mmHg in the oral nifedipine group with p value of 0.649. In this study the mean time taken to achieve targeted blood pressure of <150/100 mmHg in the iv labetalol group was 38.9±17.2 min and in the oral nifedipine group was 37.1±17.2 min with p value=0.302. The mean number of doses required to achieve targeted blood pressure were 2.6±1.2 doses and 2.3±1.0 doses respectively with p value of 0.370. This findings collaborates the study done by Swapan et al who found in their study the mean time

required to achieve target BP of 47.2±13.5 min in the labetalol group and 45.6±14.5 min in the nifedipine group with the 'p' value of 0.511.[20] Both group required two doses of each drug, 56% in the labetalol group and 62% in the nifedipine group to achieve the targeted blood pressure.[20] This was also similar to the study done by Raheem et al which showed that the median time taken to achieve target BP was 30 min (interquartile range 22.5 to 67.5 min) versus 45 min (IQR 30-60 min) for nifedipine and labetalol respectively (p=0.59).[21] In Raheem et al, average number of antihypertensive doses to achieve BP≤150/100 mmHg were two (1.5-4.5) in the nifedipine group, whereas three (2-4) in labetalol group as compared to two doses for both groups in this study.[21]

In this study 11(14.9%) of the entire patients enrolled in the study needed additional therapy. Seven patients representing 18.9% of participants in the IV labetalol group needed additional therapy while 4 (10.8%) of participants in the oral nifedipine group needed additional therapy with p value of 0.515. These collaborates the studies by Raheem et al in which 20% of patients in each group required crossover therapy and Swapan et al in which 12% and 14% of patients in the labetalol and nifedipine group respectively required crossover therapy.[20,21]

In Vermillion et al study, nifedipine took significantly less time (mean±SD, 25±13.6 minutes) in comparison to labetalol group (43.6±25.4 minutes; p=0.002) in achieving the target BP.[23] In many other studies like that conducted by Gavit et al, and Shekhar et al, showed that nifedipine took significantly less time in achieving the target BP which is at variance with this study where both similar time with no statistical difference.[18,24] Vermillion et al also found that the nifedipine group required significantly fewer doses (1.5±0.5 versus 2.5±1.5, p<0.001) to reach the blood pressure goal as against this study where in both labetalol and nifedipine the number of doses are similar.[23] These findings were in sharp contrast to our findings that showed no significant differences between the two groups. The reason for this disparity might be related to racial differences in the study population. There might also be the drug potency issues which will warrant more robust multi-centre studies in this our environment to find out what works best for us.

The cost of treatment per doses was compared for the labetalol and nifedipine group in this study. In the IV labetalol group, the mean cost of treatment per doses given was (NGN 3259.5±2294.4) and in the oral nifedipine group, the mean cost of treatment per doses given was (NGN 3254.1±1440.4) with p value=0.990. The mean doses required in the IV labetalol group was 2.6±1.2 doses and in the oral nifedipine group, the mean doses required was 2.3±1.0 doses with p value=0.370. There was no statistical significance difference in the cost of treatment per dose for both drugs. These findings were contrary to the study done by Chawla et al who found nifedipine to be cheaper.[22] The reason for this could be because of availability of instant release nifedipine in the study area.

The Cochrane review on drugs for the treatment of very high blood pressure in pregnancy concluded that until and unless better evidence is available the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug, and its adverse effects.[25] And our study clearly indicates that both intravenous labetalol and oral nifedipine are equally efficacious in controlling high blood pressure in severe preeclampsia with no significant difference in the cost of treatment.

CONCLUSION

In conclusion, the efficacy of intravenous labetalol and oral nifedipine were compared and both were found to be equally efficacious in rapidity of controlling blood pressure in severe preeclampsia and both had similar cost effect per dose of drug.

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