Original Article

FREQUENCY OF INTRAUTERINE GROWTH RETARDATION IN GESTATIONAL HYPERTENSION IN PRIMIGRAVIDA TREATED WITH NIFEDIPINE VERSUS LABETALOL

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ABSTRACT

Background: It is estimated that about 6-8% of pregnancies are complicated by hypertensive pregnancy disorders, which cause the severe mother and fetal morbidity and death. The incidence of gestational hypertension is 6.3% worldwide. To treat hypertensive problems during pregnancy, several different medications have been employed.

Objective: The objective of this study was to assess the frequency of intrauterine growth retardation in gestational hypertension in primary gravida treated with nifedipine versus labetalol.

Material and Methods: This study was a randomized controlled trial carried out at Obstetrics and Gynecology department, Unit-III, Sir Ganga Ram Hospital, Lahore for six months from 26/09/2017 to 25/03/2018. In Group A patients were treated with Nifedipine whereas in Group B patients were treated with Labetalol. Within 30 minutes after delivery, a qualified operating room staff member assessed the newborn birth weight using weighing equipment that was set to zero before usage. By using IBM SPSS version 23, all the data was analyzed.

Results: Mean birth weight was lower significantly in patients in the labetalol group in comparison to the nifedipine group (2.3±0.3 Kg vs. 2.6±0.3 Kg with a p-value of less than 0.01). The frequency of IUGR was higher significantly in patients of the labetalol group in comparison to nifedipine (22.4% vs. 6.9% with a p-value of 0.018).

Conclusion: Nifedipine was found superior to labetalol in the treatment of patients with hypertensive disorder of pregnancy as its use was associated with significantly higher mean neonatal birth weight and significantly lower frequency of IUGR which recommends its routine use in future practice.

Key Words: Pregnancy, Intrauterine Growth Retardation, Hypertension

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INTRODUCTION

It is estimated that about 6-8% of pregnancies are complicated by hypertensive pregnancy disorders, which cause the severe mother and fetal morbidity and death.[1] Incidence of gestational hypertension is 6.3% worldwide.[2] The incidence of gestational hypertension is higher in Pakistan (10-12%).[3]The established risk factors for gestational hypertension include maternal age more than 35, body mass index greater than 24 and pregnancy complicated by gestational diabetes mellitus and renal diseases.[4]

Placental abruption, pulmonary oedema, renal impairment, elevated liver enzyme, uncontrolled blood pressure, thrombocytopenia, impaired coagulation profile, and maternal death are the known complications of gestational hypertension.[5] Labetalol, methyldopa, nifedipine, glycerol trinitrate, and other beta blockers are the

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drugs commonly used to treat this condition.[6] Because labetalol is more often used to treat gestational hypertension and is more efficient as compared to methyldopa and nifedipine at lowering blood pressure in people with gestational hypertension.[7]

Historically, methyldopa has been the medicine of choice for treating hypertension in pregnant women due to its efficacy and safety both for the mother and foetus as an anti-hypertensive agent, despite its slower onset of action and lower efficacy as a hypotensive drug. For the long-term management of hypertension during pregnancy, it remains the medicine of choice.[8] In comparison to other anti-hypertensive medications, labetalol provides excellent blood pressure management.[9] The availability of injectable and oral labetalol, as well as the fact that it begins working faster than methyldopa, are both advantages.[10-12] Nifedipine has long been regarded as a second-line medication even though its effectiveness has been well established.[13] This is due to its simple accessibility, quick commencement of the action, simplicity in oral administration, and adequate decrease in blood pressure. The choice of nifedipine over labetalol was recommended in current research that indicated labetalol usage was more often associated with intrauterine growth retardation.[14]

Giannubilo et al. in 2012 in a randomized controlled trial showed that the frequency of intrauterine growth retardation (IUGR) in gestational hypertension treated with nifedipine is lower as compared to those treated with labetalol (15.5% vs. 38.8%; $p<0.05$) respectively.[15] The results of this randomized controlled trial showed that the use of labetalol is associated with a higher frequency of IUGR as compared to nifedipine. Labetalol is routinely used as a preferable choice in patients with gestational hypertension.[16] There is no other local as well as international published data present on this topic. Repeating this research in the local population is necessary since it will enable us to choose the best anti-hypertensive drugs for these Patients.

MATERIAL AND METHODS

This study was a randomized controlled trial carried out at Obstetrics and Gynecology department, Unit-III, Sir Ganga Ram Hospital, Lahore. The study duration was six months from 26/09/2017 to 25/03/2018 after synopsis approval. The sample size was 116 cases (58 cases in each group), calculated by using 80% test power confidence interval of 95% and taking the projected frequency of IUGR among patients of gestational hypertension treated with nifedipine vs. labetalol to be 15.5% vs. 38.8% respectively.[15] The selection of participants was done by consecutive Non-Probability sampling. The inclusion criteria in our study were primary gravid patients with ages in the range of 18-35 years suffering gestational hypertension and patients willing to take part in our study whereas the criteria for exclusion were all the patients who were multipara as per history and clinical record, patients with twin pregnancy or having fetal anomaly (as per obstetric ultrasound), patients having liver disorder (bilirubin ≥1.2mg/dl) or renal disorder (serum creatinine ≥1.2mg/dl) as per history and clinical record, patients having anemia (hemoglobin ≤9g/dl) as per clinical record and patients having cardiac disorder (ejection fraction ≤40%) or diabetes (fasting blood glucose level ≥110mg/dl) based on history and clinical record. The study was explained, after taking approval from the ethical and research committee to all the patients from the outpatient department of Gynae Unit-Ill, Sir Ganga Ram Hospital, Lahore, and then informed consent was signed. By employing the lottery method, patients were randomized into two groups. In Group A patients were treated with Nifedipine whereas in Group B patients were treated with Labetalol. Nifedipine 20 mg or labetalol 100 mg (was given according to the group in which the patient was assigned) orally given twice daily to 12 hours apart and continuation of the same drug without overlaps with other medications until delivery. Within 30 minutes after delivery, a qualified operating room staff member assessed the newborn birth weight using

weighing equipment that was set to zero before usage. Infants were classified as having intrauterine growth retardation if their birth weight was below the 10th percentile for their gestational age.[17] All the data was recorded by using proper Performa. By using IBM SPSS version 23, all the data was analyzed. Numerical variables; age, BMI, duration of therapy, and neonatal birth weight have been presented by mean ±SD. Nominal variables; like intrauterine growth retardation have been presented as frequency and percentage. Chi-square test was applied for comparison of the frequency of intrauterine growth retardation amongst the study groups by considering a value of $p \leq 0.05$ as statistically significant. Stratification of data was done concerning age, BMI, and therapy duration to determine effect modifiers. Post-stratification chi-square test was employed by considering a p-value of ≤0.05 as significant statistically.

RESULTS

In the current research, a total of 116 patients (58 in each group) were enrolled. The overall mean (SD) age, BMI, and treatment duration were 25.6±4.4 years, 28.0±3.8 Kg/m^{2,} and 16.2±2.5 weeks respectively. In the current study, the mean age (SD) in group A was 25.8 (4.0) years while the mean age (SD) in the group was 25.3 (4.8) years. In group A, 31 (53.4%) patients were in the age group 18-26 years and 27 (46.6%) in the age group 27-35 years while in group B, 34 (58.6%) patients were in the age group 18-26 years and 24 (41.4%) in the age group 27-35 years (p=0.575). In groups A and B the mean BMI was 28.2±3.9 Kg/m^2 and 27.9±3.7 Kg/m^2 respectively. In group A based on BMI, the number of patients in 20-25, 25-30 and 30-35 Kg/m^2 were 18 (31.0%),20 (34.5%) and 20 (34.5%) respectively while in group B, the number of patients in 20-25, 25-30 and 30-35 Kg/m^2 were 18 (31.0%), 22 (38.0%) and 18 (31.0%) respectively (p=0.905). In group A, the mean treatment duration was 16.2±2.2 weeks while in group B it was 16.2±2.2 weeks. Based on treatment duration, the number of patients in a range of 13-17 weeks and 18-22 weeks was 41 (70.7%) and 17 (29.3%) respectively while in group B the number of patients in a range of 13-17 weeks and 18-22 weeks was 41 (70.7%) and 17 (29.3%) respectively (p=1.000). (Table 1) Mean birth weight was lower significantly in patients in the labetalol group in comparison to the nifedipine group (2.3±0.3 Kg vs. 2.6±0.3 Kg with a p-value of less than 0.01) (Table 2) The frequency of IUGR was higher significantly in patients of labetalol group in comparison to nifedipine (22.4% vs. 6.9% with a p-value of 0.018). (Table 3) Stratification of frequency of IUGR concerning age, BMI and therapy duration is given in Table 4.

Table-1: Baseline Characteristics of Study Groups

Characteristics	Nifedipine n=58	Labetalol n=58	p-value
Age (years)	25.8±4.0	25.3±4.8	0.517
• 18-26 years	31 (53.4%)	34 (58.6%)	0.575
• 27-35 years	27 (46.6%)	24 (41.4%)	
Duration of Treatment (weeks)	16.2±2.2	16.3±2.7	0.823
• 13-17 weeks	41 (70.7%)	41 (70.7%)	1.000
• 18-22 weeks	17 (29.3%)	17 (29.3%)	
BMI (Kg/m^2)	28.2±3.9	27.9±3.7	0.629
• 20-25 Kg/m^2	18 (31.0%)	18 (31.0%)	0.905
• 25-30 Kg/m^2	20 (34.5%)	22 (38.0%)	
• 30-35 Kg/m^2	20 (34.5%)	18 (31.0%)	

Table-2: Comparison of Mean Birth Weight (Kg) between the Study Groups

	Nifedipine n=58	Labetalol n=58	p-value
Birth Weight in Kg (mean±sd)	2.6±0.3	2.3±0.3	<0.001*

Table-3: Comparison of Frequency of IUGR between the Study Groups

Intrauterine Growth Retardation	Nifedipine n=58	Labetalol n=58	p-value
Yes	4 (6.9%)	13 (22.4%)	0.018*
No	54 (93.1%)	45 (77.6%)	
Total	58 (100.0%)	58 (100.0%)	

Table-4: Stratification of Frequency of IUGR between the Study Groups

Characteristics	Intrauterine Growth Retardation (IUGR)		p-value
	Nifedipine n=58	Labetalol n=58	
Age (years)			
• 18-26 years	2/31 (6.5%)	8/34 (23.5%)	0.057
• 27-35 years	2/27 (7.4%)	5/24 (20.8%)	0.164
Duration of Treatment (weeks)			
• 13-17 weeks	3/41 (7.3%)	9/41 (22.0%)	0.061
• 18-22 weeks	1/17 (5.9%)	4/17 (23.5%)	0.146
BMI (Kg/m^2)			
• 20-25 Kg/m^2	1/18 (5.6%)	3/18 (16.7%)	0.289
• 25-30 Kg/m^2	1/20 (5.0%)	5/22 (22.7%)	0.101
• 30-35 Kg/m^2	2/20 (10.0%)	5/18 (27.8%)	0.158

DISCUSSION

Even with all the progress in medical research, pregnancy-related hypertension remains a significant obstetrical concern. To treat hypertensive problems during pregnancy, several different medications have been employed. Beta-blockers, calcium channel blockers, a combination of alpha and beta blockers, and centrally acting alpha-agonist methyldopa are the medications that are most often utilized in Pakistan.

In the current study, the overall mean (SD) age, BMI, and treatment duration were 25.6±4.4 years, 28.0±3.8 $Kg/m^{2,}$ and 16.2±2.5 weeks respectively. Similar results were reported by Hossain et al. in 2011 who observed a mean (SD) age of 24±5.05 years amongst women presenting with PIH.[18] Another study done by Nazli et al. reported a mean age (SD) of 25.24±0.54 years among women at Khyber Teaching Hospital Peshawar.[19] Muhammad et al. in 2010 observed a comparable mean (SD) age of 24.8±4.1 years amongst pregnant women with IUGR and PIH presenting at Leady Reading Hospital, Peshawar.[20]

Our findings are comparable with the of Nazli et al. who reported a mean BMI of 29.27±1.12 Kg/m^2 in such women.[19]

In the present study, Mean birth weight was lower significantly in patients in the labetalol group in comparison to the nifedipine group (2.3±0.3 Kg vs. 2.6±0.3 Kg with a p-value of less than 0.01). Padmaja et al. (2017) reported a similar significant difference in the mean neonatal birth weight between women receiving nifedipine and labetalol (2.5±0.51 Kg vs. 2.4±0.6 Kg; p-value=0.07).[21] Similar observation was made by A Alam et al. in 2017 (2.9 Kg vs. 2.6 Kg; p-value=0.045).[22]

In the present study, the frequency of IUGR was higher significantly in patients of the labetalol group in comparison to nifedipine (22.4% vs. 6.9% with a p-value of 0.018). A previous study observed a similar prevalence of 5.7% for IUGR with nifedipine.[23] A similar frequency of IUGR with the use of labetalol has been reported by Munshi et al. (22.9%) and Cruickshank et al. (20.0%).[24,25]

A study carried out by Giannubilo et al. reported a comparable difference in the prevalence of IUGR between labetalol and nifedipine (38.8% vs. 15.5%; p-value<0.05.[15]

The current study is the first study on the local population that supports the previous studies on the supremacy of nifedipine over labetalol; nifedipine is associated with decreased frequency of IUGR in women with gestational hypertension. As mentioned earlier, the current practice is to use labetalol in pregnant women with gestational hypertension. However, in light of this evidence, nifedipine is better and should be preferred in future practices. One major drawback of the current research is that we did not compare the two groups on important measures of hypertension control and treatment-related problems, which should be

considered before any modification in practice is made. Future research should consider such a study.

CONCLUSION

Nifedipine was found superior to labetalol in the treatment of patients with hypertensive disorder of pregnancy as its use was associated with significantly higher mean neonatal birth weight and significantly lower frequency of IUGR which recommends its routine use in future practice.

AUTHOR'S CONTRIBUTION

UN: Main idea and article writing
RZ: Data collection
R: Data analysis
AA: Data analysis
SA: Literature review and discussion
HZ: Review of article

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