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Original Article

Labetalol Versus Methyldopa: Comparison of Frequency of Small for Gestational Age in the Treatment of Pregnancy Induced Hypertension

Shabana Kalsoom, Noreen Majeed, Mamoona Riaz, Shamsa Tariq
Department of Gynaecology and Obstetrics, Wah Medical College, Wah Cantt.

Abstract

Background: To compare the frequency of small for gestational age(SGA) babies between women treated with labetalol or methyldopa for pregnancy induced hypertension.

Methods: In this randomized controlled trial patients were divided into Labetalol and Methyldopa groups. Both drugs were administered as oral preparation. Patients were followed during their pregnancy till their delivery time and then baby weight was checked at the time of delivery and plotted against gestational age to detect small for gestational age babies.

Results: The frequency of SGA neonates was significantly higher in Group-A (labetalol) in comparison to Group-B. (Methyldopa) i.e. Group-A: 37.8% vs. Group-B 13.3%(p-value=0.008). In all age groups i.e. <25years, 25-35years and >35 years, frequency of SGA was higher in Group-A (Labetalol group) women but statistical significance was not seen in any age group. There was no statistically significant effect of parity on frequency of SGA. Women who were started treatment early i-e at 20-25weeks and 26-30weeks of gestation had more SGA babies in Labetalol group(p=0.033,P=0.032) . Although more number of SGA babies in Labetalol group were delivered at <34 weeks gestation but difference was not statistically significant (p=0.264)

Conclusion: Methyldopa is more effective in pregnant women in terms of low incidence of small for gestational age babies as compared to labetalol.

Key Words: Small for gestational age babies, Labetalol, Methyldopa, Pregnancy induced hypertension.

Introduction

Women having Pregnancy-induced hypertension have poor feto-maternal outcome as compared to normotensive women. Most commonly used drugs for treatment of pregnancy induced hypertension are methyldopa, combined alpha and beta blockers, beta blockers and calcium channel blockers. Studies have shown conflicting evidence about the foetal and maternal outcomes of these drugs during pregnancy. About 6-8% pregnancies are effected by pregnancy induced hypertension globally.[1,2] Complications in the form of pre-eclampsia and eclampsia result in one death every three minute worldwide.[3] Progression to adverse fetomaternal outcome can be prevented by using antihypertensive medicines. [4]The purpose of giving antihypertensive drugs is to minimize the risk of severe hypertension ,stroke, cardiovascular strain, and kidney damage.[5]A number of drugs are being used for treatment of pregnancy induced hypertension. Internationally methyldopa, labetalol and nifedipine are recommended as drugs of first choice.[6,7,8]

Since years, methyldopa is widely used in treatment of pregnancy induced hypertension. Methyldopa decreases blood pressure by acting centrally on alpha 2 receptors and by decreasing sympathetic nerve activity. [9,10] It takes 12-24 hoursfor adequate therapeutic response and large dose is required but it is helpful for long term control of blood pressure.[11]

In comparison to other antihypertensive drugs, labetalol is more effective in lowering the blood pressure.[12] Labetalol is a combined alpha- and beta-blocker and contributes to a reduction in peripheral vascular resistance due to its additional arteriolar vasodilator effect, with little or no decline in cardiac output. Therefore, it has advantages over other beta blockers. The benefit of labetalol is that it can be injected and administered orally and acts rapidly than methyldopa. Now this is an established fact that beta blockers cross the placenta, enter in foetal circulation and may cause foetal bradycardia.[13]

Evidence regarding perinatal outcomes of labetalol and methyldopa is controversial.[9, 14, 15]The purpose of our study was to compute the frequency of SGA babies in patients having pregnancy induced hypertension, treated with labetalol or methyldopa.

The actual birth weight below 10th percentile for gestational age (GA) is labelled as Small for gestational age (SGA). It increases the risk of intra-ventricular bleeding, neonatal convulsions, septicemia, necrotizing enterocolitis, cerebral palsy, duration of hospital stay and treatment cost.[16,17]In SGA babies, stillbirths and neonatal and infant mortality rate is higher as compared to appropriate for gestational age.[18-22] We compared the age, parity and gestational age at start of treatment and at delivery,between the two treatment groups,to determine which factors effected the frequency of SGA. This study will help to set a protocol for the management of pregnancy induced hypertension by decreasing burden of small for gestational age neonates.

Patients and Methods

The study was carried out in Obstetrics and Gynaecology department of POF hospital Wah Cantt. It was a randomized controlled trial. Sample size was calculated by WHO sample size calculator. Total 90 patients,45 in each group were included in study. Verbal informed consent was taken before inclusion in study. Patients who were given Labetalol were categorized as group A and those given methyldopa as group B. Patients having blood pressure ≥140/90mmHg on two occasions at least 4h apart were part of study. Ages of patients were between 15-40 years and had singleton pregnancy. Women having chronic hypertension, diabetes, cardiac or renal disease, malnutrition or any other medical disease were not part of this study. Sampling was done by non-probability consecutive sampling. Patients were randomized, by using computer generated sequence of random numbers, to either of two treatment arms-Labetalol or methyldopa. Both the drugs were administered as oral preparation. The starting dose of Labetalol was 100mg BD up to a maximum of 1.2gm/24hours.The staring dose of Methyldopa was 250mg TDS up to a maximum of 2gm/24hours. The data was collected on a pre-designed proforma which included demographic details, gestational age at start of treatment and delivery, birth weight of baby .The patients were followed up during their pregnancy till delivery. The birth weight of baby was plotted against gestational age at delivery on growth chart, to determine whether the baby is appropriate or small for gestational age. Qualitative variables like parity, small for gestational age babies were measured as frequencies and percentages. Chi-square test was used for comparison of small for gestational age babies between two groups. P value <0.05 was considered statistically significant.

Results

Total 90 patients were included in the study, 45 patients in each group. The patients in Group A were treatedwith Labetalol and group B with Methyldopa. The mean age of women in group A was 27.35±6.50 years and in group B was 28.26±6.47 years. The mean gestational age at start of treatment was 30.26±4.26 and 30.20±4.229 in group A and B respectively. The mean gestational age at delivery was 35.44±2.96 weeks in labetalol group and 36.04±2.60 weeks in methyldopa group. The mean birth weight of babies in group A was 2013.33±778.367gm and in group B was 2311.11±779.92gm. A higher frequency of SGA babies was observed in women treated with labetalol (37.8%) than those treated with methyldopa(13.3%).The difference was significant statistically (p=0.008).Maximum number of patients were from the age group <25years (n=36, 40%) and 39.4% SGA cases were observed in this age group. On comparing the frequency of SGA with use of two drugs in different age groups, statistically difference was insignificant (Table 1).Among the two groups 38.8% (n=34) patients were primigravidas. When we compared the frequency of SGA was more in primigravidas who took labetalol (42.1%) but the difference was not statistically significant. (Table 2).Most cases of SGA were observed when the treatment was started at early gestation in both groups (Table 3). Babies in labetalol group were more affected in gestational age groups 20-25wk and 26-30wk (p=0.033, P=0.032). No case of SGA was observed when treatment was started after 35weeks of gestation (Table 3).Overall 23 (25.6%) patients delivered at <34wk gestation, 15 (33.3%) in labetalol group and 8 (17.7%) in methyldopa group. The frequency of SGA was more in labetalol group at <34 week and ≥34wweek gestation, as shown in table-4 but not statistically significant (p=0.267, p=0.064) (Table 4).

Table-1: Small for gestational age in treatment groups stratified for age of women

Age	Small for gestational age	Labetalol Group	Methyldopa Group	p-value
<25Y	Yes	10(47.6%)	3(20%)	0.082
	No	11(52.4%)	12(80%)	
25-35y	Yes	4(30.8%)	2(10%)	0.134
	No	9(69.2%)	18(90%)	
>35Y	Yes	3(27.3%)	1(10%)	0.304
	No	8(72.7%)	9(90%)	

Table-2:Small for gestational age in treatment groups stratified for parity of women

Parity	Small for gestational age	Labetalol Group	Methyldopa Group	p-value
Primigravida	Yes	8(42%)	2(13.3%)	0.06
	No	11(57.9%)	13(86.7%)	
Multigravida	Yes	9(34.6%)	4(13.3%)	0.058
	No	17(65.4%)	26(86.7%)	
	No	5(71.4%)	7(100%)	

Table 3: Treatment groups stratified for gestational age at start of treatment

Gestational Age	Small for gestational age	Labetalol Group	Methyldopa Group	p-value
20-25	Yes	7(77.8%)	3(30%)	0.033
	No	2(22.2%)	7(70%)	
26-30	Yes	8(53.3%)	2(15.4%)	0.032
	No	7(46.7%)	11(84.6%)	
31-35	Yes	2(16.7%)	1(7.1%)	0.477
	No	10(83.3%)	13(92.9%)	
>35	Yes	0(0%)	0(0%)	-
	No	9(100%)	8(100%)	

Table 4: Small for gestational age in treatment groups stratified for gestational age at delivery

Gestational age at delivery	Small for gestational age	Group of drugs		P-value
		Labetalol Group	Methyldopa Group	
<34wk	Yes	11 (73.3%)	4 (50%)	0.267
	No	4(26.7%)	4 (50%)	
≥34wk	Yes	6 (20%)	2 (5.4%)	0.064
	No	24 (80%)	35(94.6%)	

Discussion

Pregnancy induced hypertension is a major obstetrical problem even after so much advancement in field of medical science. Many drugs have been used to manage hypertensive disorders of pregnancy. Most commonly used drugs in Pakistan are beta-blockers, combined alpha and beta blockers, calcium channel blockers and centrally acting alpha agonist methyldopa. In the present study frequency of SGA babies was significantly higher in labetalol group (37.8%) as compared to methyldopa group(13.3%)(P=0.008).In a retrospective cohort study by Petersen KM frequency of SGA babies was 17.7% and 11.84% in labetalol and methyldopa group [21]. Xie RN in his study showed the rates of SGA babies for both<10th percentile (aOR=1.24) and <3rd percentile (aOR=0.99) were significantly higher among neonates of mothers who used beta-blockers in comparison to those who used methyldopa.[14] CHIPS trial secondary analysis calculated SGA in 11.8% and 27% methyldopa treated cases of pre-existing and gestational hypertension as compared to 20.9% and 21.7% labetalol treated cases of pre-existing and gestational hypertension(post-randomization group) and proved methyldopa was a better choice for patients with pre-existing hypertension.[23] Thakur V compared three drugs and calculated high frequency of low birth weight(<2.5kg) in methyldopa group (36%) as compared to labetalol(32%) and nifedipine (28%) but he did not find out whether these babies were small for gestational age or not.[24] Molvi SN in his study showed that treatment with antihypertensive drugs decreased the frequency of SGA babies at delivery (p-value= 0.033). i.e. Labetalol: 18% vs. Methyldopa: 28.6% & Control: 40%.[9] Molvi SN findings did not support our results as in his study more number of SGA babies belonged to methyldopa and control group as compared to labetalol group.

A local study from Pakistan suggested that labetalol has better antihypertensive effects than methyldopa treatment, fewer maternal and fetal side effects, and established that it is drug of choice for pregnancy-induced hypertension.But they did not studySGA in both treatment groups.[15]

Majority of women (n=36 40%) were<25y, a finding similar to study of Babbar K (60% <25y).[25] The frequency of SGA babies was higher in women <25 years of age but when compared in both groups the difference was not statistically significant (P=0.082). The SGA babies frequency was higher in both primigravidas and multigravidas in labetalol group, reflecting Parity did not affect significantly. Starting treatment at an early gestation increased frequency of SGA in both groups, but affected labetalol group more significantly (P=0.033, P=0.032 at 20-25wk &26-30wk respectively). In our study 33.3% and 18.9% cases in labetalol and methyldopa group delivered at <34wk gestation, although non-significant statistically (p=0.267). This finding supported by CHIPS trial where 24% and 18.9% cases of gestational hypertension post-randomization in labetalol group and methyldopa group delivered at <34wk gestation (aOR0.97), indicating an increased risk of delivery<34wk in labetalol group.[23]

Antihypertensive drugs have a vital role in controlling blood pressure in pregnant women. In determining the treatment plan, practitioners must pay attention to the severity of maternal hypertension, the duration of pregnancy, the efficacy and side effects of the individual drugs.Results of this study indicate that Methyldopa as compared to Labetalol is more effective in pregnant women in reducing the frequency of small for gestational age babies. The most important responsibility of obstetricians is to carefully select drug

therapies and to consider the effectiveness as well as safety of the drug for mother and fetus.

Conclusion

Methyldopa is more effective in pregnant women in terms of low incidence of small for gestational age babies as compared to labetalol.

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