COMPARISON BETWEN LABETALOL AND METHYLDOPA IN THE TREATEMNT OF PRE-ECLAMPSIA

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ABSTRACT

Objective: To compare the effects of labetalol and methyldopa on mean diastolic blood pressure in patients with pre-eclampsia.

Methodology: A randomized controlled trial was done in the Department of Gynecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi, from 20th August 2013 to 31st march 2014. A total of 300 women with singleton pregnancy (20-37 weeks) diagnosed with pre-eclampsia were randomly assigned to labetalol (n=150) and methyldopa (n=150). The outcome was determined as reduction in mean diastolic blood pressure 48 hours after intervention with labetalol and methyldopa.

Results: In labetalol group, the mean age of patients was 32.57 ±4.3 years, while in methyldopa group it was 33.09 ±4.2 years (p value =0.290). In labetalol group, mean diastolic blood pressure was reduced from 100.9 ±6.8 mmHg to 93.5 ±7.2 mmHg (p value =0.000). In methyldopa group, it was reduced from 99.7 ±9.9 mmHg to 93.4 ±7.8 mmHg (p value =0.000). There was no statistical difference in the mean diastolic blood pressure between the two groups after intervention (p value = 0.909).

Conclusion: Both labetalol and methyldopa reduced diastolic blood pressure significantly after 48 hours of intervention. The efficacy of both drugs was equal in reducing diastolic blood pressure and the difference was statistically not significant.

Key Words: Pre-eclampsia, Diastolic blood pressure, Labetalol, Methyldopa

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INTRODUCTION

Hypertension in pregnancy is a significant management problem. Approximately 12-22% of all pregnancies are complicated by hypertensive disorders, 70% of those are affected by gestational hypertension and 30% by essential hypertension. Prevalence of pre-eclampsia is 19% in Pakistan[1]. Pre-eclampsia is a multisystem disease, causing impaired intervillous blood flow leading to a state of oxidative stress that activates vascular endothelial cells, leading to wide spread effects of pre-eclampsia[2]. Pre-eclampsia can lead to maternal and fetal complications. Maternal complications include placental abruption, target organ damage (eclampsia, HELLP syndrome, renal failure and disseminated intravascular coagulation) and are associated with a very high maternal mortality (15%). Fetal complications include growth restriction and prematurity mainly related to worsening maternal condition[3].

Management of pre-eclampsia is to control blood pressure as well as monitor fetal and maternal condition. Immediate delivery is done if patient develops signs and symptoms of fulminant pre-eclampsia such as headache, epigastric pain or platelet count <100 X 103 or AST > 50 IU /liter[4].

Commonly used anti-hypertensive drugs are methyldopa, labetalol, nifedipine and hydralazine[5,6]. In the absence of hypertensive crises methyldopa and oral labetalol are preferred drugs. Both these drugs are easily available in our country. Both drugs have been found effective in reducing blood pressure without any adverse effect on perinatal outcome[7,8]. Labetalol, is a combined alpha (α1) and beta (β1/β2) adrenergic receptor blocker with arteriolar vasodilator effect, thus reducing peripheral resistance and decreases blood pressure. Common side effects are dizziness, drowsiness and headache. Methyldopa is an agonist of pre-synaptic central nervous system α2 adrenergic receptors resulting in inhibition of sympathetic nervous system thus reducing blood pressure and it does not affect fetal hemodynamics[7]. Side effects of methyldopa are decreased mental alertness, fatigue or depression.

Although both drugs are known to be effective in reducing blood pressure which drug is better than the

other is yet not known. Moreover, the efficacy of both drugs is studied well in the west but the result of these studies are controversial. The reviews published in Cochrane libraries could not conclude their findings on one drug and suggested more studies on anti-hypertensive treatment of the pre-eclampsia. Moreover thorough literature search showed that no study regarding the efficacy of these drugs is conducted in Pakistan. We therefore conducted this study to compare the efficacy of two drugs because further research was needed due to variable results in blood pressure (BP) control by these drugs in different studies. We wanted to explore drug with better control of blood pressure so that it may constitute the basis of some novel recommendations in our setup.

METHODOLOGY

This was a single blind randomized control trial conducted in Fauji foundation Hospital, Rawalpindi from 20th August 2013 to 31st March 2014. Approval of study was taken from hospital ethical and research committee. All women at gestational age 20-37 weeks with singleton pregnancy diagnosed with pre-eclampsia were included in the study. Among those women presenting with pre-eclampsia who fulfill the inclusion criteria were offered to participate in the study. A written informed consent was also obtained from women after explaining in details the purpose and benefits of the study. All the cases with essential hypertension, already taking anti-hypertensive medication, depression, congestive heart failure, heart block or bronchial asthma, multiple pregnancy, fulminant pre-eclampsia (platelet count <100x10 or AST >50 IU/liter, persistent symptoms like headache, epigastric pain, visual disturbance) and those with eclampsia (generalized tonic colonic convulsions usually in association with pre-eclampsia) were excluded from this study.

A total of 300 women (150 patients in each group) were included in the study. The sample was calculated by WHO sample size calculator with level of significance =5%, power of test =80%, pooled standard deviation =1.03, test value of the population mean =85.48[9] and anticipated population mean =89.69[9]. After detailed history and examination all women who were included in the trial were randomly allocated into two groups by lottery method. Women in group A were subjected to labetalol while women in group B were subjected to methyldopa. The standard dose was started as described in Bristish National Formulary (BNF) after measuring baseline blood pressure using standard mercury sphygmomanometer (dose was decided according to diastolic blood pressure detailed below in Table 1).

All the women were kept under observation and blood pressure was recorded after every four hours as per NICE guidelines for the management of pre-eclampsia. Measurement of blood pressure 48 hours post-treatment was used to calculate the mean diastolic blood pressure and was recorded on proforma. Strict exclusion criteria were followed to control confounders and bias in the study results. All the observations and blood pressure recordings were done by the researcher. The statistical software used for data analysis was SPSS version 16.0. For numerical variables like age, gravidity, baseline diastolic BP, follow up diastolic BP, mean ± SD were calculated. Student-t test was used to compare the mean diastolic BP in two groups while keeping p value of <0.05 as significant. Mean diastolic BP in both groups was stratified among age and parity to see the effect modifications. All results were presented as tables.

RESULTS

The mean age of the patients of the whole study population (n=300), was 32.83 ±4.3 years. The mean age of patients in labetalol group was 32.57 ±4.3 years while in methyldopa group it was 33.09 ±4.2 years. We compared the demographic variables of the patients between group A and B including age and gravidity. No statistically significant difference was found between the two groups regarding these variables (Table 2).

The mean baseline diastolic blood pressure in labetalol group was 100.93 ±6.7 mmHg and it reduced to 93.47 ±7.23 48 hours post-treatment showing statistically significant difference, (p =0.000). In methyldopa group, mean baseline diastolic blood pressure was 99.77 ±9.97 mmHg and statistically significant reduction was seen 48 hours post-treatment with follow up mean diastolic BP of 93.37 ±7.89 (p value =0.000). We compared the mean baseline and follow up diastolic blood pressure between both treatment groups. The difference was statistically insignificant (Table 3) .

We also stratified the follow up diastolic BP in both groups with regards to different age categories (Table 4) and gravidity categories (Table 5).

DISCUSSION

The mean age of patients was comparable in both groups A and B (32.6 and 33.1 years) respectively. Most of the patients (70%) were between 26 and 35 years in this study in both groups. A previous study by Guzick et al[10] reported that age was linearly related with pregnancy induced hypertension. However, in contrast Venkateswaramurty and colleagues[11] found out that younger age group (18–25 years) was involved in majority (59%). Similarly, Verma et al[12] reported that majority of their cases were between 19 to 24 years in both labetalol group (51.1%) and methyldopa group (64.4%).

In the current study, majority of subjects were found to be multiparous in both groups i.e. 136 (95.5%) in group A and 143 (95.2%) in group B. Similarly, most

Table 1: Dose of anti-hypertensives according to diastolic blood pressure

Diastolic BP	Methyldopa	Labetalol
90-109 mmHg	250 mg stat and then eight hourly	100 mg stat and then BD
>110 mmHg	500mg stat and then eight hourly	200 mg stat and then BD

Table 2: Comparison of mean age and gravidity between both groups (n =150 each)

Variables		Labetalol Group (n=150)	Methyldopa Group (n=150)	P value
Age (Mean ±SD)		32.6 ± 4.3	33.1 ± 4.1	0.31
Gravidity	Primi-gravida	14 (9.5%)	07 (4.8%)	0.82
	Multi-gravida	136 (95.5%)	143 (95.2%)	0.90

Table 3: Comparison of baseline diastolic BP and follow up diastolic BP between both groups (n =150 each)

Diastolic BP	Treatment Group	n	Mean	Std. Deviation	Std. Error Mean	P value
Baseline Diastolic BP	Labetalol Group	150	100.93	6.790	.554	0.237
	Methyldopa Group	150	99.77	9.972	.814	
Follow up Diastolic BP	Labetalol Group	150	93.47	7.234	.591	0.909
	Methyldopa Group	150	93.37	7.890	.644	

Table 4: Age groups stratification of mean follow up diastolic blood pressure between both treatment groups

Age stratification	Treatment Group	n	Mean	Std. Deviation	Std. Error Mean	P value
Follow up Diastolic BP Age Groups= Up to 25 years	Labetalol Group	6	90.00	5.477	2.236	0.203
	Methyldopa Group	4	95.00	5.774	2.887	
Follow up Diastolic BP Age Groups= 25.01 to 30 years	Labetalol Group	41	90.37	7.105	1.110	0.650
	Methyldopa Group	45	91.11	7.969	1.188	
Follow up Diastolic BP Age Groups= 30.01 to 35 years	Labetalol Group	63	93.81	6.822	.860	0.393
	Methyldopa Group	58	95.00	8.429	1.107	
Follow up Diastolic BP Age Groups= 35.01 & above	Labetalol Group	40	96.63	6.923	1.095	0.034
	Methyldopa Group	43	93.37	6.789	1.035	

Table 5: Gravidity wise stratification of mean follow up diastolic blood pressure between both treatment groups

Gravidity	Treatment Group	n	Mean	Std. Deviation	Std. Error Mean	P value
Follow up Diastolic BP Primigravida	Labetalol Group	14	91.43	9.693	2.591	0.398
	Methyldopa Group	7	87.86	6.986	2.641	
Follow up Diastolic BP Multigravida	Labetalol Group	136	93.68	6.945	.596	0.964
	Methyldopa Group	143	93.64	7.854	.657	

of the cases were multigravida in both groups A and B (74.7% and 75.5%) respectively. In contrast Verma and colleagues12 found out that primigravida and nulliparous women were in majority (60%) with hypertension during pregnancy[12]. These findings were also quoted in other studies by Redman et al[13] and Plouin et al[14]. There is a need to study in depth the difference regarding parity and age of presentation of pre-eclampsia as in our study the mean age of whole study group was slightly older age which was contrary to other studies where mean age of presentation was younger age group. Similarly, in our study, majority of women with pre-eclampsia were multigravidas which is in contrast to other studies where nulliparous ladies were having pre-eclampsia predominantly. This difference may be attributed to the fact that this hospital provides services to families of retired army personnel so majority of women are of higher age group and multiparaous.

Regarding the efficacy of study interventions (labetalol and methyldopa) in controlling diastolic blood pressure it was proven that both labetalol and methyldopa significantly reduced diastolic BP. We found out that labetalol decreased diastolic to 93.5 ±7.2 mmHg and methyldopa succeeded in bringing down diastolic BP to 93.4 ±7.8 mmHg after 48 hours of intervention. There was no difference in the mean decrease in diastolic blood pressure between the two groups after intervention (p value =0.91). Similar findings were quoted by Verma et al[12]. In their study, mean diastolic BP after treatment with labetalol was 78.44 ±8.24 mmHg and with methyldopa it was 77.55 ±5.28 mmHg eight days after treatment and the difference was statistically not significant between the two treatment groups[12]. Similarly in another study mean diastolic blood pressure after treatment was 81 ±5 mmHg in both groups showing no difference in two drugs8. Venkateswaramurty and colleagues[11] reported that methyldopa decreased diastolic BP from 102.3 ±13.3 mmHg at baseline to 85.9 ±7.6 mmHg after treatment.

The Cochrane review of 35 randomized controlled trials including 3573 women found that anti-hypertensive drugs are effective in lowering blood pressure; however there is no evidence to show which drug is the most effective[15]. Patel et al[16] reported that treatment with methyldopa was associated with reduction in diastolic blood pressure by 30 mmHg at 72 hours post-intervention and labetalol was associated with reduction of 36 mmHg in diastolic BP after similar time with statistically significant difference. In another study conducted by Barathi[17], mean diastolic blood pressure after treatment with labetalol was 85.48 ±0.869 and after methyldopa it was 89.69 ±1.186 and the reduction in labetalol group was significant. In a study by Subhedar et al[18] the reduction in mean arterial pressure was compared between labetalol and methyldopa and it was found that both drugs significantly reduced diastolic blood pressure from the baseline value. The reduction after treatment with labetalol was more than with methyldopa (p =.0008) which is contrary to our study.

In the study conducted by El Qarmalawi et al[19], significant fall in BP was seen in 81.4% in labetalol group as compared to 68.5% in the methyldopa group showing labetalol to be better than methyldopa. In another study, the diastolic BP in labetalol group was reduced to 123 ±9mmHg/79 ±7 mmHg from baseline BP of 150 ±9mmHg/100 ±8mmHg (p value <0.05) while in methyldopa group it was reduced from 148 ±8 mmHg/102 ±9mmHg to 125 ±10mmHg/82 ±6 mmHg on 7th day after treatment (p <0.05). However drop in blood pressure was better in labetalol group as compared to methyldopa group and this finding was statistically significant[20]. In contrast, our findings showed that both interventions have similar efficacy in reducing blood pressure. One randomized controlled trial on patients with moderate hypertension reported that labetalol reduced incidences of preterm delivery, neonatal jaundice and respiratory distress syndrome [21,22].

LIMITATIONS

Though sample size was appropriate but data regarding side effects of labetalol or methyldopa was not collected, so tolerability of treatment was not studied.

Similarly, we could not collect data regarding short term or long term effects of interventions on maternal and perinatal outcome. Many queries regarding hypertension in pregnancy and pre-eclampsia e.g. effect on protienuria and subsequent progression to severe pre-eclampsia remained unanswered. For better understanding of these queries we need large collaborative multi-centered studies.

CONCLUSION

Both labetalol and methyldopa reduced diastolic blood pressure significantly after 48 hours of intervention. The efficacy of both drugs was equal in reducing diastolic blood pressure and the difference was statistically not significant.

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CONTRIBUTORS

NA conceived the idea, planned the study and drafted the manuscript. ZH and FN helped acquisition of data, did statistical analysis and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.