Original Article

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COMPARISON OF HYDRALAZINE AND LABETALOL IN THE MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

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ABSTRACT

Objective: To compare the efficacy of intravenous hydralazine and intravenous labetalol for acutely lowering blood pressure in pregnancy.

Study Design: Randomized control trial (RCT).

Place and Duration of Study: M.C.H center, Unit I PIMS, Islamabad, one year from June 2011-June 2012.

Material and Methods: In this randomized control trial 80 patients with gestational hypertension were enrolled systematically randomizing 40 each to inj Labetalol and inj Hydralazine groups. The study was conducted in the Department of Obstetrics & Gynaecology, Maternal and Child Health Centre, Unit I, Pakistan Institute of Medical Sciences, Islamabad and was completed in one year. The study included indoor patients with hypertensive disorders of pregnancy, monitored in high dependency area admitted through Emergency and OPD. The outcome measures include adequate control of hypertension.

Results: Labetalol was more effective than Hydralazine in lowering diastolic BP in the first hour from the baseline BP (*p*-value 0.009). 19 (47%) patients in Labetalol and 8 (20%) patients in hydralazine had a reduction in diastolic BP. However the reduction of diastolic BP in second and third hours was not significant (*p* values 0.446, 0.314) . In the fourth hour the diastolic BP fell to less than 100 mm of Hg in both the group.

Patients in Hydralazine group suffered more headache as compared to Labetalol (*p*-value = 0.043 and Chi-square value = 4.114). Similarly the incidence of tachycardia was more in hydralazine group (*p* value =0, Chi square value 23.226).

Conclusions: The efficacy (Diastolic BP ≤ 100 mm of Hg) of Labetalol in the first hour was was highly significant as compared to Hydralazine group whereas the efficacy in the second, 3rd and 4th hour were not significant. Labetalol is affordable, readily available and has minimal side effects than Hydralazine.

Keywords: Eclampsia, Hydralazine, Labetalol, Preeclampsia.

INTRODUCTION

Hypertension is the most common medical problem encountered during pregnancy, complicating 2-3% of pregnancies. Eclampsia is the occurrence of one or more convulsions superimposed on pre-eclampsia[1]. Preeclampsia is pregnancy-induced hypertension in association with proteinuria (> 0.3 g in 24 hours) ± oedema and virtually any organ system may be affected[2]. Severe pre-eclampsia is variously defined[1,2]. There is consensus that severe hypertension is confirmed with a diastolic blood pressure ≥ 110 mmHg on two occasions or systolic blood pressure ≥ 160 mmHg on two occasions and that, together with significant proteinuria (at least 1 g/litre), this constitutes severe pre-eclampsia. Preeclampsia is an idiopathic, unpredictable, multiorgan disorder unique to human pregnancy and the puerperium. It has been estimated by the World Health Organization (WHO) that worldwide approximately 60,000 women will die each year from pre-eclampsia.

Pre-eclampsia is a major cause of poor outcome in pregnancy: the category "hypertensive diseases of pregnancy" remains a leading cause of direct maternal deaths in the United Kingdom[3,4]; pre-eclamptic conditions represent one in three cases of severe obstetric morbidity[5]; hypertension and/or proteinuria is the leading single identifiable risk factor in pregnancy associated with stillbirth (one in five stillbirths in otherwise viable babies)[6]; and pre-

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eclampsia is strongly associated with fetal growth restriction, low birth weight, preterm delivery, respiratory distress syndrome, and admission to neonatal intensive care[7].

Finding a drug which is cheap and readily available to the population is the prime focus of this study. All drugs used to treat hypertension in pregnancy cross the placenta, and so many affect the fetus directly by means of their action within the fetal circulation, or indirectly by their effect on uteroplacental perfusion.

Hydralazine and Labetalol have been the preferred drugs for treating severe hypertension. Both drugs are easily available in Pakistan. We aim to find a drug which produces fewer side effects and is safe for the fetus. We will compare the efficacy of intravenous hydralazine and intravenous labetalol for acutely lowering blood pressure in pregnancy.

MATERIAL AND METHODS

This randomized control trial was conducted at M.C.H center, Unit I PIMS Pakistan Institute of Medical Sciences, Islamabad, one year from June 2011-June 2012. The study was approved from institutional ethical review board. Patients were enrolled for the study from the outpatients and ER after having informed written consent. All women with severe hypertension, after 28 wks. of gestation with a live fetus and hypertensive disorders with no concurrent antihypertensive therapy or absolute contraindication for labetalol or hydralazine were recruited in the study. Whereas women with major fetal anomalies not compatible with life, known asthmatics patients with a history of heart failure or preexisting renal disease were excluded from the study.

The patients were admitted in the high dependency unit. Informed and written consent was taken for participation in the study. Detailed history and clinical examination was performed on all patients using an appropriate-sized blood pressure cuff, for BP measurement. Blood pressure was measured after a rest period of 10 minutes or more. Blood pressure measurement were done with the patient in an upright or left lateral recumbent position with the arm at the level of the heart. Proteinuria was assessed by dip stick and 24 hour collection for quantitative analysis.

Eligible women were randomized by lottery method into two groups, Labetalol group and Hydralazine group. Blood samples were sent for complete blood count, Serum uric acid, ALT, PT/APTT, urine RE were sent to the Laboratory for analysis. Patient's vital signs were monitored every 15 minutes for the effect of these drugs and were recorded.

In Labetalol group, Injection labetalol was administered parentally by repeated intravenous injection. An initial dose of 20 mg followed by additional doses of 40 or 80 mg at 10 minute intervals, or a total of 220 mg was given. Decrease in blood pressure $\leq 100\text{mm Hg}$ diastolic was considered as successful treatment.

In Hydralazine Group, 5 mg of hydralazine was given intravenously ,and repeated every 20 min up to a maximum of five doses or labetalol (20-mg intravenous bolus dose followed by 40 mg if not effective within 20 min, followed by 80 mg every 20 min up to a maximum dose of 300mg). Management of hypertensive disorders of pregnancy included bed rest; to prevent seizures, all patients received magnesium sulphate as a 4 gram IV loading dose followed by 1 gm IV per hour before delivery, intrapartum and for 24 hours postpartum.

Two 12.5mg doses of Dexamethasone were given intramuscularly 12 hours apart for pregnancies between 28 and 34 weeks gestation.

A plasma volume expansion of 1000 ml of Ringers lactate at a rate of 75 ml/hr was administered in all patients over 12 hours. In the presence of oliguria one or two fluid boluses of 300-500 ml were given.

The data was analyzed on SPSS version 12. Frequency and percentages were calculated for catagoric data and mean and standard deviation were expressed for quantitative data. Independent Sample T test was used to compare the efficacy of both drugs at different time period and to compare prolongation of

pregnancy with both drugs. Chi square test was used to compare presenting complaints, parity and complication between two groups. *p* value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of eighty patients were enrolled and randomized in this study with severe hypertension. The majority of patients were from Rawalpindi and Islamabad 33 patients (41.25%) from each group respectively, followed by 8 patients (10%) from Azad Kashmir and 6 patients (7.5%) from rest of Pakistan. There was no significant difference between the booking status of both the study group. There were 23 booked patients (23.7%) in Labetalol group and 20 (25%) in hydralazine group. The number of non-booked patients in Labetalol group were 20 (25%) and 17 (21.25%) patients in Hydralazine group.

In our study it was seen that the maximum number of patients presented between 26 to 30 years of age with 16.25% (13 patients) with Hydralazine and 22.55% (18 patients) with Labetalol group. Between 21-25 years of age equal number of patients that is 13.75% (11 patients) presented. Fewer patients presented at the extremes of reproductive ages which was less than 20 years or more than 35 years.

When we compared the blood pressure readings of patients at baseline and then after one hour of administering the drugs intravenously it was seen that the systolic blood pressure reduction reading was not significant (*p*-value of 0.074) . However the diastolic blood pressure was reduced significantly(*p* value .022) implying I/V Labetalol did lower the blood pressure significantly after one hour.

The BP reading after two hours from the baseline showed a significant drop in systolic

Table-1: Side effects observed during the study.

		Group of drug			
		Hydralazine	Labetalol	Total	
Edema	Yes	35	36	71	Chi-square value = 0.125, df = 1 *p*-value = 0.723
	No	5	4	9	
Headache	Yes	8	2	10	Chi-square value = 4.114, df = 1 *p* -value = 0.043
	No	32	38	70	
Tachycardia	Yes	18	0	18	Chi-square value = 23.226, df = 1 *p* -value = 0
	No	22	40	62	

Table-2: Comparison of efficacy at different times (1 to 4 hours) between study groups.

Efficacy	Hydralazine (40)	Labetalol (40)	*p* - value
Efficacy at 1 hour			
Yes	8 (20%)	19 (47.5%)	0.009
No	32 (80%)	21 (52.5%)	
Efficacy at 2 hours			
Yes	28 (70%)	31 (77.5%)	0.446
No	12 (30%)	9 (22.5%)	
Efficacy at 3 hours			
Yes	40 (100%)	39 (97.5%)	0.314
No	0	1 (2.5%)	
Efficacy at 4 hours			
Yes	40 (100%)	40 (100%)	-
No	0	0	

Efficacy: was measured in terms of decrease in diastolic BP ≤ 100 mm of Hg.

blood pressure (*p*-value 0.011), showing that there was a marked reduction in blood pressure with Labetalol. The diastolic blood pressure was also significantly reduced (*p*- value of 0.000) which again was highly significant emphasizing that not only the systolic but also the diastolic blood pressure dropped from the baseline.

Comparison at 3 hours showed that the fall in systolic blood pressure had a *p*-value of 0.011 which was highly significant showing that there was a marked reduction in BP. The diastolic BP reading also had a *p*-value of 0.000 which again was highly significant

Again comparing the blood pressure readings from the baseline after 4 hours it was seen that the fall in the systolic BP was 0.002 which again was highly significant. The diastolic BP had a *p*-value of 0.001 which was highly significant. Thus after starting the medication there was a fall in both the systolic and diastolic BP. The reduction was more marked at the fourth hour. This signifies that the efficacy Labetalol in lowering BP and control of hypertension is higher table-2.

The *p*-value was 0.723 when we compared edema in both the study group which was not statistically significant (table-1). 35 patients developed edema in hydralazine and 36 patients in labetalol had edema. Only 5 patients in hydralazine and labetalol group did not developed edema.

We compared two side effects which were headache and palpitations between the two groups. Eight patients in Hydralazine group suffered from headache whereas only two patients had headache in Labetalol group (table-1) with a P-value of .043 which was statistically significant, fewer patients in Labetalol group had headache.

When we compared the side effect tachycardia in both the groups it was seen that 18 patients in Hydralazine group had tachycardia whereas none in Labetalol group had tachycardia. The *p* -value was 0.000 which was highly significant. Chi-square value was 23.226 (table-1).

When we compared the mode of delivery it was seen that in both the group majority of patients delivered through Em LSCS accounting to 68.8% of the total deliveries. 29 patients in Labetalol underwent emergency LSCS and 26 patients in Hydralazine group delivered via Em LSCS making a total of 55 patients. It was

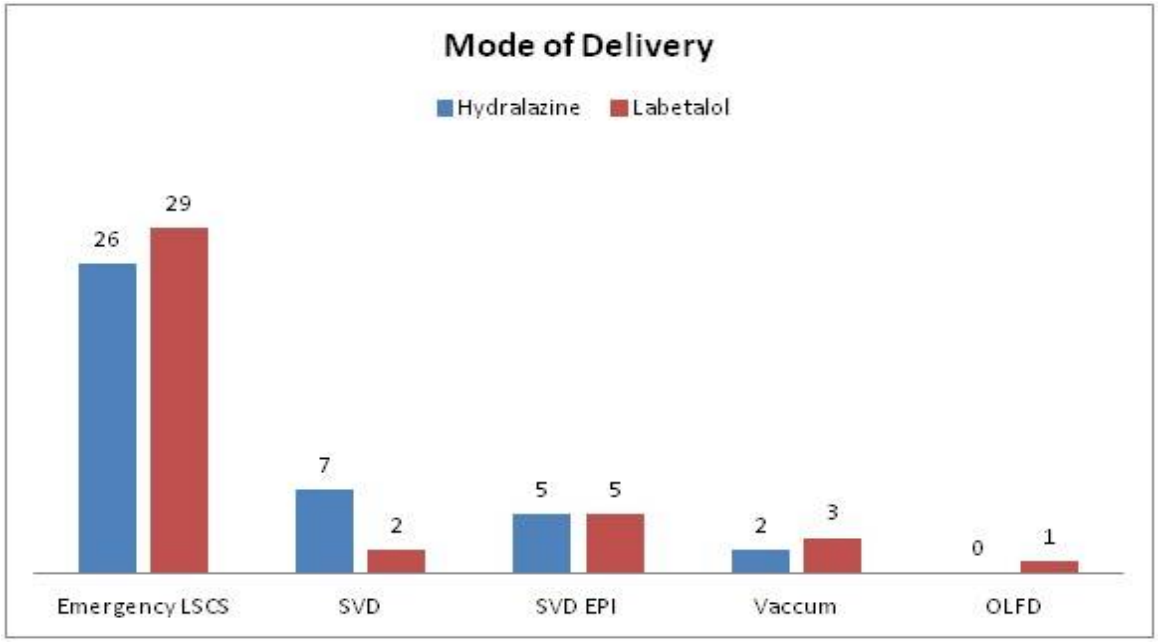

Figure-1: Mode of delivery in the two groups.

followed by SVD with episiotomy in which 10 patients five from each group delivered through SVD with episiotomy. SVD,s were slightly less which were 9 deliveries 7 in Group A and 2 in group B. and finally only 6 patients had instrumental vaginal delivery with 5 patients undergoing vacuum and OLFD was applied in only one patient.(Fig-1)

The neonatal weight was compared between the two drugs and the Std.Deviation for Hydralazine was 0.75003 and Labetalol was 0.73273 which was not statistically significant.

DISCUSSION

Hypertensive disorders occur in around 12-22% of pregnancies depending on the populations and definitions used[8].

Preeclampsia occurs in 3% to 8% of pregnancies, and is a major cause of maternal mortality and morbidity in developed countries[9]. Pre-eclampsia and eclampsia has also been called toxemia of pregnancy. The incidence of eclampsia in Pakistan ranges from 0.51% to 4%[10].

According to a study conducted by Khan and a similar study by Lewis in 2007 pre - eclampsia is the leading cause of fetal growth restriction, intrauterine fetal demise and planned preterm birth. Our study shows that Em LSCS were performed in 68.8% which is in accordance with Khans study[11]. One of the major causes of planned preterm delivery also supported by a study conducted by Sarsam DS, at Al-Batool teaching hospital in Mosul city, Iraq[12].

Severe pre-eclampsia is more common in the last trimester of pregnancy and this was also seen in our study were most patients presented in the last trimester.

The use of Hydralazine is often accompanied by maternal tachycardia which was observed in a trial conducted by Magee[13]. In our study 18 patients suffered from tachycardia which strongly supports the study by Magee. Labetalol group patients did not suffer from the side effect supporting our study that Labetalol is better than Hydralazine with fewer side effects.

Cifkova R[14] does not recommend Hydralazine as a first therapy of choice because of its association with multiple side effects such as tachycardia, palpitations and headache which were also observed in our study.

According to a study conducted by Razia Abbasi on the safety and efficacy of hydralazine in Hypertensive disorders of pregnancy it was found that hydralazine was safe and effective in controlling blood pressure in severe Hypertensive disorders but patients had side effects such as headache[15]. It was also observed in our study that side effects such as headache and tachycardia were more common in group hydralazine patients as compared to labetalol group patients.

In a study conducted by Paulino Vigil the neonatal outcome between Hydralazine and labetalol were very similar 8 which were also seen in our study. The outcome of male babies in Labetalol was 22 and female babies were 18. In Hydralazine group there were 21 male babies and 19 female babies.

A multiparous woman older than 35 years is more likely to be affected with pre eclampsia[8]. In our study Majority of the patients were multiparous in both the groups as compared to primigravida or grand multiparous women.

There was no significant difference between the maternal age, booking status, BMI, comparison of the total duration of the study, as well as the initial baseline blood pressure of both the groups.

The current study was designed and conducted as a randomized control trial comprising of two arms (group-A patients were given Inj Hydralazine and group-B were given Inj Labetalol). The study was designed to compare the efficacy of intravenous Hydralazine and intravenous Labetalol for acutely lowering blood pressure in pregnancy and an evaluation of the results was performed.

In our study it was seen that Labetalol efficacy in sharply reducing the diastolic blood pressure in the first hour was better than Hydralazine with fewer side effects[16].

Comparing the blood pressure readings from the baseline, at 1 hour, 2, 3, 4 hours it was seen that a statistically significant reduction was observed in both the groups with fewer side effects in Labetalol group. This finding was consistent with a similar study[13]. However the efficacy of Labetalol in lowering the diastolic blood pressure was superior in the first hour compared to hydralazine.

Vigil compared intravenous bolus doses of Labetalol versus Hydralazine, repeated doses after 20 minutes if required[8]. The study found no clear differences between groups in persistent hypertension, need for additional doses, or hypotension. In our study it was shown that Labetalol did lower blood pressure more effectively than Hydralazine with fewer side effects.

The current study was designed and conducted as a randomized control trial comprising of two arms (group-A patients were given Inj Hydralazine and group-B were given Inj Labetalol). The study was designed to compare the efficacy of intravenous hydralazine and intravenous labetalol for acutely lowering blood pressure in pregnancy and an evaluation of the results was performed. The efficacy of Labetalol was found to be superior to Hydralazine in sharply lowering the blood pressure in the first hour.

CONCLUSION

Our study shows that I/V Labetalol can safely and effectively be used in patients with severe hypertension in pregnancy and even after delivery. It has fewer side effects than I/V Hydralazine.

It is affordable, easily available so by using this drug we can reduce the morbidity and mortality related to severe hypertension with minimum side effects.

AUTHORS CONTRIBUTION

Humaira Osman Jaffery, manuscript writing, data analysis and data interpretation, Kausar Tasleem Bangash, design and conception.

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CONFLICT OF INTERESTS

This study has no conflict of interest to declare by any author.

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