ORIGINAL ARTICLE

To Compare the Side Effects of Intravenous Labetalol Vs Intravenous Hydralazine in Management of Pregnancy Induced Hypertension

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ABSTRACT

Background: Pregnancy-induced hypertension (PIH) contributes significantly to adverse feto-maternal outcome in a developing nation like ours. Significant hypertension must be treated to reduce the possible risks. The threshold at which treatment needs to be initiated remains a big question, depending on priority for fetus or mother.
Aim: To compare the side effects of labetalol versus hydralazine given intravenously for control of pregnancy induced hypertension.
Methodology: It was a Randomized Controlled trial in which total of 330 cases of age range 20-35 with >20 weeks of gestation with sustained severe hypertension participated through non- probability, Purposive sampling. Informed consent taken and demographic information was recorded. Patients in group A were given an intravenous bolus infusion of labetalol 20mg. Group B patients were given an intravenous hydralazine 5-10mg in bolus. Patients were followed for 60 minutes to observe the side effects of drug like by researcher. The results were noted on a specially designed performa.
Results: The mean age of females was 27.42±3.49 years. The mean gestational age of females at time of presentation was 28.97±4.48weeks. The mean SBP of females was 109.44±16.92 mmHg while mean DBP was 77.29±14.74 mmHg. Total 135(40.9%) women developed maternal hypotension, out of which 27(16.36%) belongs to labetalol group while 108(65.45%) belong to hydralazine group and 55(16.67%). Women developed abnormal FHR, out of which 1(0.61%) belongs to labetalol group while 54(32.72%) belong to hydralazine group. The difference between both groups was highly significant.
Conclusion: Thus it was concluded that use of hydralazine was associated with more side effects in females with PIH as compared to labetalol. Now we have better drug to manage PIH with low rate of complications.
Keywords: Labetalol, Hydralazine, Pregnancy Induced Hypertension, hypotension, headache, palpitation,

INTRODUCTION

Hypertensive disorders of pregnancy are seen 10-15% of all pregnancies, giving rise to fetal, maternal and neonatal morbidity[1,2]. Gestational hypertension (GH) is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg in a pregnant lady who was previously normotensive at ≥20 weeks of gestation and has no proteinuria at least two times at least six hours apart[3,4,5].

PE usually occurs after 20 weeks of pregnancy and has wide spread manifestations. PE is elevation of BP during pregnancy along with more than 300 mg of proteinuria in 24 hours Eclampsia is the presence of a grand mal seizure along with PE, although it may be the first harbinger of the disease[6].

Gestational Hypertension is seen in 5 to 9% of cases and preeclampsia (PE) in 5 to 7 % among nulliparous women without any co morbidity[7,8,9,10].

During normal pregnancy the blood pressure fluctuates. During the initial weeks the Blood pressure falls, due to overall relaxation of muscles of the blood vessels. From around the middle of pregnancy it rises slowly again PE has been associated with risk factors like pre pregnancy hypertension, obesity, age, family history, ethnicity, and presence of co morbidities, twin pregnancy and hydrops fetalis. It is seen more in primigravidas[13].

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until, at term, BP is close to the level it was before pregnancy[11,12].

Although the prognosis for most of these pregnancies is good, women with pre-eclampsia develop serious problems, such as hepatorenal failure, coagulation disorders, prematurity, stillbirth or neonatal loss... Once BP crosses a certain level, there exists a risk of direct damage to the blood vessel wall, irrespective of the causative factor. This risk stands similar for non-pregnant women with highly raised BP[14].

Once BP reaches 170/ 110mm of Hg, the woman is at increased risk of these harmful effects. It is advisable that she receives antihypertensive drugs in a hospital. The aim of treatment is to quickly bring about a smooth reduction in BP to levels that are safe for mother and baby, but avoiding any sudden fall that may be potentially harmful. Once BP is controlled, in many cases a decision will be made to deliver the baby soon especially if the term has been achieved. If the baby is very premature, the BP settles down after initial treatment, and there are no other risk factors, the pregnancy may be continued[15].

Severe HTN in pregnancy defined as >160/110mmHg, requires treatment, because of the threat of adverse events, and treatment avoids them.(2,16) Those with hypertensive complications require treatment with parenteral agents to lower mean arterial pressure by 25% over minutes to hours and then to 160/100mmHg over subsequently[2].

The aim of therapy should be a DBP of less than 100-105 mm Hg and an SBP less than 160mm Hg. Women with chronic hypertension should have a lower threshold for starting antihypertensive medication and aim for lower blood pressure[17,18].

For years, hydralazine has been the antihypertensive of choice for women with severe hypertension in pregnancy. However, its side effects are common and resemble symptoms of deteriorating preeclampsia. Intravenous labetalol is also used to treat acute Anti-hypertensive agents should be started at lower doses, because these patients may be intravascular volume depleted and may be at increased risk for hypotension[19].

Rationale of this study was to compare intravenous labetalol with intravenous hydralazine for management of pregnancy induced hypertension. Often gynecologists prefer I/v hydralazine but it has more side effects as compared to labetalol. As labetalol has fewer side effects and its action starts quickly so it must be the first line drug to manage patients with PIH . It is not usually practiced in developing countries like Pakistan as there is controversy in results. We want to conduct this study to confirm the pattern of side effects of labetalol and hydralazine, so that in future we would have a better drug for management of PIH.

The objective of the study was to compare the side effects of intravenous labetalol with intravenous hydralazine in management of pregnancy induced hypertension.

PATIENTS & METHODS

It was a Randomized Controlled trial conducted at Gynecology, Unit IV, Lady Aitchison Hospital , Lahore for a period of 6 months. Non-probability, Purposive sampling was used. Patients of age range 20-35 with >20 weeks of gestation with sustained severe hypertension and maternal. Heart rate 60-100 beats per minute were included. First trimester pregnant women with Twin pregnancy, history of cardiac problem, asthma, allergy to hydralazine or labetalol, hypertension and use of any antihypertensive before pregnancy, treatment in the preceding. 72 hours for PIH or eclampsia/pre-eclampsia were excluded. Informed consent was obtained and patient demographic information (name, age, contact, gestational age) was recorded. Patients were divided into two equal groups (A:B) by using lottery method. Patients in group A were given an intravenous bolus infusion of labetalol 20mg. The dose was increased every 10 minutes by 40 and 80mg up to maximum dose of 300mg. BP was noted after every 10 minutes as its action is fast. Thereafter repeated doses were given for 1 hour/ till blood pressure control. Group B patients were given an intravenous hydralazine 5-10mg in bolus depending on severity of hypertension and may be repeated after every 20 minutes up to maximum dose of 30mg (maximum 5 doses). BP was noted after every 15-20 minutes as its effect is slow. Thereafter repeated doses were given for 1 hour/ till blood pressure control and then were discontinued. Patients were followed for 60 minutes to observe the side effects of drug like maternal hypotension, other side effect like headache and palpitation/tachycardia and abnormal fetal heart rate (as per operational definition) by researcher herself. All this information was noted on proforma. Data was analyzed through SPSS 10. Quantitative variables like age and gestational age were calculated as mean$\pm$SD. Qualitative variables like maternal hypotension, other side effects and abnormal fetal heart rate were presented as frequency and percentage. Chi-square was used to compare the maternal hypotension, other side effects and abnormal fetal heart rate in both groups. P-value $\leq$0.05 was considered as significant.

RESULTS

Three hundred and sixty patients participated in the study with the mean age of 27.42±3.49 years. The minimum and maximum age of the females was noted as 20years and 35years respectively. The mean gestational age of females at time of presentation was 28.97±4.48weeks. The minimum and maximum gestational age was noted as 21 weeks and 35 weeks respectively. The mean SBP of females was 109.44±16.92 mmHg while mean DBP was 77.29±14.74 mmHg. In IV Labetalol group, the mean SBP of females was 116.76±12.75 mmHg while mean DBP was 86.00±10.14mmHg. In IV Hydralazine group, the mean SBP of females was 102.12±17.45 mmHg while mean DBP was 68.58±13.42mmHg.

In this study, there were total 135(40.9%) women who developed maternal hypotension, out of which 27(16.36%) belongs to labetalol group while 108(65.45%) belong to hydralazine group (Table 1). The difference between both groups was highly significant and hydralazine group found to be associated with more maternal hypotension as compared to labetalol (p-value=0.000). There were total 55(16.67%) women who developed abnormal FHR, out of which 1 (0.61%) belongs to labetalol group while 54(32.72%) belong to hydralazine group (Table 2). The difference between both groups was highly significant and hydralazine group found to be associated with more abnormal FHR as compared to labetalol (p-value=0.000).

In this study, there were total 11(3.33%) women who developed some other side effects as well, out of which 2(1.21%) belongs to labetalol group while 9 (5.45%) belong to hydralazine group. Hydralazine group found to be associated with more side effects as compared to labetalol (p-value=0.032). In this study, there were total 18(5.45%) women who complaint of headache, out of which 2(1.21%) belongs to labetalol group while 16(9.69%) belong to hydralazine group(Table 3). The difference between both groups was highly significant and hydralazine group found to be associated with more headache as compared to labetalol (p-value=0.001).

In this study, there were total 14(5.45%) women who developed tachycardia, out of which 2 (1.21%) belongs to labetalol group while 12(7.27%) belong to hydralazine group. The statistical differences was highly significant and hydralazine group found to be associated with more tachycardia as compared to labetalol (p-value=0.006). In this study, there were total 16(5.45%) women who developed palpitation, out of which 3(1.81%) belongs to labetalol group while 13(7.87%) belong to hydralazine group (Table 4). The difference between both groups was significant and hydralazine group found to be associated

with more palpitation as compared to labetalol (p-value=0.010).

Table 1: Comparison of Maternal hypotension in accordance with study groups

Maternal Hypotension	Study Group		Total
	Labetalol Group	Hydralazine Group	
Yes	27(16.36%)	108(65.45%)	135(40.90%)
No	138(83.63%)	57(34.54%)	195(59.09%)
Total	165(100%)	165(100%)	360(100%)

Chi-square = 82.246 p-value = 0.000 (Significant)

Table 2: Comparison of abnormal fetal heart rate in accordance with study groups

Abnormal FHR	Study Group		Total
	Labetalol Group	Hydralazine Group	
Yes	1(0.61%)	54(32.72%)	55(16.67%)
No	164(99.39%)	111(67.27%)	27583.33%)
Total	165(100%)	165(100%)	360(100%)

Chi-square = 61.287, p-value = 0.000 (Significant)

Table 3: Comparison of headache in accordance with study groups

Headache	Study Group		Total
	Labetalol Group	Hydralazine Group	
Yes	2(1.21%)	16(9.69%)	18(5.45%)
No	163(98.78%)	149(90.30%)	312(95.54%)
Total	165(100%)	165(100%)	360(100%)

Chi-square = 11.517 p-value = 0.001 (Significant)

Table 4: Comparison of palpitation in accordance with study groups

Palpitation	Study Group		Total
	Labetalol Group	Hydralazine Group	
Yes	3(1.81%)	13(7.87%)	16(4.84)
No	162(99.38%)	152(92.12%)	314(95.15%)
Total	165(100%)	165(100%)	360(100%)

Chi-square = 6.658 p-value = 0.010 (Significant)

DISCUSSION

Pregnancy induced hypertension is a very common pregnancy related disorder afflicting about240,000 women each year[2,20,21].

Hypertensive disorders result in problematic maternal and fetal long term consequences... A large number of medications are available which can be used by oral or intravenous routes. They differ in their side effects, dosage and safety profiles. A number of trials have been conducted which compare the efficacy of these agents to placebo but their results are not conclusive. The same can be said about as far as their effects on the fetus are considered[21].

Thus we included 360 females who had PIH with the mean age of 27.42±3.49 years. The mean gestational age of females at time of presentation was 28.97±4.48weeks. Literature has also reported almost same mean age of females and gestational age at time of presentation with PIH[19,22].

In our trial, females were randomized in two groups and treatment was given. After 60 minutes, again BP was measured to note the BP and other side effects of both treatments. It was noticed that the overall decrease in mean SBP/DBP of females was 109.44/77.29±16.92/14.74 mmHg. In IV Labetalol group, the mean SBP/DBP of females was 116.76/86±12.75/10.14 mmHg and in IV Hydralazine group, the mean SBP/DBP of females was 102.12/68.58±17.45/13.42 mmHg. The difference between both groups was highly significant and it seemed that BP was lower with hydralazine as compared to labetalol.

But when hypotension it was found that there were total 135(40.9%) women who developed maternal hypotension, out of which 27(16.36%) belongs to labetalol group while 108(65.45%) belong to hydralazine group. The difference between both groups was highly significant and hydralazine group found to be associated with more maternal hypotension as compared to labetalol (p-value=0.000). Thus it is proved through our trial that hydralazine is associated with more hypotension as compared to labetalol. Recent Literature has also reported that hydralazine can cause more maternal hypotension as compared to labetalol[23] A meta-analysis showed that hydralazine is associated with more maternal hypotension as compared to labetalol (66.67% vs. 16.67%).(27s) But another study did not show any significant difference which generated controversy[19]. But now through our study it was proved that hydralazine is associated more maternal hypotension as compared tolabetalol.

In our trial, in 55(16.67%) women abnormal FHR was observed, out of which 1(0.61%) belongs to labetalol group while 54(32.72%) belong to hydralazine group. The difference between both groups was highly significant but a study reported that abnormal FHR was very similar per group (Hydralazine: 7.8% vs. Labetalol: 5.8%). (19) Hydralazine was associated with more adverse effects on fetal heart rate than other antihypertensive (11%) (0-56%) v 0% (0-50%)). This also support that hydralazine should not be used for reduction in BP in PIH[27].

Other side effect were also observed in 11(3.33%) women, out of which 2 (1.21%) belongs to labetalol group while 9 (5.45%) belong to hydralazine group. Headache was most common complaint in 18(5.45%) women, out of which 2(1.21%) belongs to labetalol group while 16(9.69%) belong to hydralazine group, 14(5.45%) women developed tachycardia, out of which 2(1.21%) belongs to labetalol group while 12(7.27%) belong to hydralazinegroupand16(5.45%) women developed palpitation, out of which3(1.81%) belongs to labetalol group while 13(7.87%) belong to hydralazine group. Hydralazine was associated with more palpitations than other antihypertensive (18% vs. 0%). (27). Overall, rates of maternal complications were higher in the hydralazine group; however, this difference was not significant.

The unfavorable outcome seen in fetuses and mothers with hypertensive disorders is not only due to the medication used to control blood pressure but it could also be due to the disease itself. . (19, 24, 25, 26, 27,) Other side effects like headache, palpitation (10% vs. 2.5%) and adverse effects on fetal heart rate (33.33% vs. 0). Effect of labetalol starts within 5 minutes but there were no significant differences for maternal hypotension (Hydralazine: 2% vs. Labetalol: 0) and headache (Hydralazine: 7% vs. Labetalol: 11%), palpitations (Hydralazine: 10% vs. Labetalol: 2%) and maternal tachycardia (Hydralazine: 6% vs. Labetalol: 1%) occurred significantly more often in patients treated with hydralazine.

The fetal heart rate was very similar per group (Hydralazine: 7.8% vs. Labetalol: 5.8%)[19]. Some showed that there were similar adverse maternal problems between both groups[28].

CONCLUSION

In our trial, the difference between both groups was highly significant and it seemed that maternal hypotension, abnormal FHR and other side effects like headache, palpitation and tachycardia were significantly lower with labetalol as compared to hydralazine. As labetalol has fewer side effects and its action starts quickly so it must be the first line drug to manage patients with PIH as controversy is cleared. Thus it was concluded that in future use of hydralazine will be discouraged in females with PIH and use of labetalol will be promoted.

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