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COMPARATIVE STUDY BETWEEN ORAL NIFEDIPINE AND INTRAVENOUS LABETALOL IN MANAGEMENT OF SEVERE PREGNANCY INDUCED HYPERTENSION

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ABSTRACT

Objective: To evaluate efficacies of oral nifedipine and intravenous labetalol in the management of severe pregnancy induced hypertension and analyse fetomaternal outcome. **Methods:** In this nonrandomised controlled study one hundred cases having severe pregnancy induced hypertension divided into two groups. Each group had 50 cases; nifedipine group and labetalol group. Patients in nifedipine group was given 10 mg initially, with repeated doses of 10 mg, every 15 minutes, for up to a maximum of 5 doses, or until the goal blood pressure less than or equal to 150/100 mm Hg was attained. Patients in intravenous labetalol group, was given 20 mg initially followed by escalating doses of 40 mg, 80mg, and then 80 mg, every 15 minutes, until the therapeutic goal blood pressure was achieved, or for a maximum of five doses. Corresponding placebos either 0.9% isotonic saline solution or inactive tablet was given simultaneously in each regimen. If therapeutic blood pressure was not achieved over 5 doses then cross over treatment was given. **Results:** The results of the study showed that the mean time required to achieve target blood pressure is 71.00±66.60 minutes in labetalol group and 25.20±14.03 minutes in the nifedipine group with the p value of < 0.01. The nifedipine group required in average 1.12±.32 doses to bring about the desired action and the labetalol group required 2.04±1.37 doses to bring about the same action which is statistically very highly significant ('P' value <0.01). Urine output at 60 minutes of commencing treatment is 55.20±16.72 ml in labetalol group compared to 99.10 ± 27.15 ml in nifedipine group with a 'P' value <.001. urine output at 60 minutes of commencing treatment is 55.20±16.72 ml in labetalol group compared to 99.10 ± 27.15 ml in nifedipine group with a 'P' value <.001. 10% failure rate is noted only in labetalol group requiring cross over treatment (P = 0.22). Fetomaternal outcome was more or less similar in both the group. Only one case of maternal mortality was seen in labetalol group as a result of eclampsia related complications. **Conclusion:** Both oral nifedipine and intravenous labetalol are effective in the management of severe pregnancy induced hypertension; however oral nifedipine controls hypertension more rapidly and with fewer doses and is associated with a significant increase in urinary output.

KEYWORDS: Oral Nifedipine and Intravenous Labetalol.

INTRODUCTION

The National Institute of Health and Clinical excellence UK 2010 guidelines define severe hypertension in pregnancy as blood pressure is 160/110 mmHg or more.[1]

Severe hypertension in pregnancy is associated with maternal stroke, cardiopulmonary decompensation, fetal decompensation due to decreased uterine perfusion, abruption and stillbirth. There is general consensus that maternal risk is decreased by antihypertensive treatment that acutely lowers very high blood pressure. The National Institute of Health and Clinical Excellence UK 2010 guidelines recommends keeping systolic blood pressure below 150 mm Hg and diastolic blood pressure between 80 and 100 mm Hg for women with severe hypertension in critical care.[1]

Given the recent emergence of newer or alternative first line agents in the management of severe hypertension in pregnancy, a study to compare the efficacy of nifedipine and labetalol is warranted..

MATERIALS AND METHODS

The comparative study between oral nifedipine and intravenous labetalol in management of severe pregnancy induced hypertension was carried out in the Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal. One hundred cases having severe pregnancy induced hypertension attended in the labour room was taken for the study and divided

into two groups. Each group had 50 cases; nifedipine group and labetalol group.

Inclusion criteria for the study

- Severe hypertension (160/110 mm Hg or more) with a viable fetus.
- Pregnant women at 34 weeks of gestation or more.

Exclusion criteria

- Allergy to either nifedipine or labetalol.
- Any antihypertensive treatment in the preceding 72 hours.
- Pregnancy less than 34 weeks.
- Intra uterine fetal death cases.
- Women with a history of heart disease, asthma.

Procedure

Once patients were enrolled, vital signs were recorded every 15 minutes, including blood pressure measurement. Volume of urine output was recorded after collecting in the urobag through Foleys catheter for 24 hours after the initial dosing. Monitoring of the fetal heart rate and any abnormalities was noted and also the maternal adverse effects like eclampsia, stroke, heart failure and decreased urine out was recorded. Additional neonatal outcome included 5 minutes APGAR score of <7 and NICU admission was recorded.

Patients in nifedipine group was given 10 mg initially, with repeated doses of 10 mg, every 15 minutes, for up to a maximum of 5 doses, or until the goal blood pressure less than or equal to 150/100 mm Hg was attained. Patients in intravenous labetalol group, was given 20 mg initially followed by escalating doses of 40 mg, 80mg, and then 80 mg, every 15 minutes, until the therapeutic goal blood pressure was achieved, or for a maximum of five doses. The dosing regimens for each study medication corresponded with the regimens from two previous clinical trials. Corresponding placebos either 0.9% isotonic saline solution or inactive tablet was given simultaneously in each regimen. If therapeutic blood pressure was not achieved over 5 doses then cross over treatment was given. If the therapeutic blood pressure goal still was not achieved, then open label treatment was started. The measurement of blood pressure was continued every 15 minutes for at least 60 minutes or longer until the target blood pressure was achieved. Once the target blood pressure was achieved, no further trial medication was given unless two consecutive blood pressure readings was recorded more than or equal to 160/110mm Hg, in which case the trial medication was started.

Data analysis

Statistical analysis was performed by using IBM: SPSS Statistics Version 20. Numerical/continuous variables, which follow normal distribution, are presented as Mean ± SD (standard deviation) while continuous variables, which do not follow normal distribution, are exhibited in terms of Median ± Interquartile range. Qualitative/categorical variables are again described as number of cases and percentages.

For normality test for continuous data, One-sample Kolmogorov-Smimov test was conducted. The two means for normally distributed data, one from each group, for every parameter is compared by Independence Sample t-test, commonly known as unpaired t-test. Whilst for non-normally distributed data, the comparison between the means is made by Mann-Whitney U test. χ^2-test or Fisher's Exact test for 2X2 contingency table is applied according to the suitability of the test for the categorical data.

All comparisons are two-sided and the P-values of < 0.05, < 0.01 and < 0.001 are taken as the cut off values for significance, highly significance and very highly significance respectively.

RESULTS AND OBSERVATIONS

Table1 shows baseline characteristics of the participants of the both groups in regards of age (years), gravida, parity, gestational age (days), systolic blood pressure at enrolment (mm Hg), diastolic blood pressure at enrolment (mm Hg). It is observed that the variations in baseline characteristics are not significant statistically as none of the corresponding P-value is less than .05, the significant level adopted for the purpose.

Table 1: Group-wise baseline characteristics of pregnant women.

Parameters	Mean±SD		t-value/U-value*	Df	P-value
	Labetalol (n=50)	Nifedipine (n=50)			
Age (year)	28(22.75-30)	27 (25 -32)	.483*		
Gravida	2.44±1.63	2.86±1.06	1.103	98	.088
Parity	1.14±1.38	.70±.97	1.837	98	.069
Gestational age (days)	270(252-280)	271 (264.75-276.50)	.489*		
Systolic blood pressure	180.32±17.66	176.76±16.58	1.039	98	.301
Diastolic blood pressure	114.00±13.09	114.72±12.75	.279	98	.781

Table-2: Group-wise antihypertensive doses to achieved BP 150/100 mm of Hg.

Parameters	Mean±SD		t-value	Df	P-value
	Labetalol (n=50)	Nifedipine (n=50)			
number of doses taken to achieve target blood pressure	2.04±1.37	1.12±.32	4.619	98	<.001
time in minutes taken to achieve target blood pressure	71.00±66.60	25.20±14.03	4.758	98	<.001

Table-3: Group-wise comparison of cross over treatment.

Parameters		Group			χ^2-value	d.f.	P-value
		Labetalol (n=50)	Nifedipine (n=50)	Total (n=100)			
Cross over treatment	No	45(90.0%)	50(100.0%)	95(95.0%)	5.263	1	.022
	Yes	5(10.0%)	-	5(5.0%)			

Table-4: Group-wise Urine output (ml) at 60 minutes

Parameters	Mean±SD		t-value/U-value*	df	P-value
	Labetalol (n=50)	Nifedipine (n=50)			
Urine output (ml) at 60 min	55.20±16.72	99.10±27.15	9.734	98	<.001

It is worthwhile to mention that urine output at 60 minutes are found very highly significant (P<.001) respectively.

Table-5: Group-wise comparison of side effects of drugs and maternal and fetal complications

Parameters	Group			χ^2-value/ Fisher's Exact Test*	d.f.	P-value
	Labetalol (n=50)	Nifedipine (n=50)	Total (n=100)			
HELLP syndrome	1(2.0%)	1(2.0%)	2(2.0%)	-	-	-
Acute renal failure	1(2.0%)	-	1(1.0%)	1.396*	1	.237
Impending eclampsia	3(6.0%)	4(8.0%)	7(7.0%)			
Hypotension	-	4(8.0%)	4(4.0%)	4.167	1	.041
Headache	-	-	-	-	-	-
Nausea, vomiting, sweating	-	-	-	-	-	-
Palpitation	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	-
Fetal tachycardia	-	-	-	-	-	-
Fetal distress	7(14.0%)	4(8.0%)	11(11.0%)	.919	1	.338
Abruptio placenta	1(2.0%)	1(2.0%)	2(2.0%)			
IUGR	5(10.0%)	4(8.0%)	9(9.0%)	.122*	1	.727
Postpartum haemorrhage	3(6.0%)	3(6.0%)	6(6.0%)	-	-	-
Other complications	1(2.0%)	-	1(1.0%)	1.396*	1	.237

Table-6: Group-wise mode of delivery.

Parameters	Group			χ^2-value/ Fisher's Exact Test*	d.f.	P-value
	Labetalol (n=50)	Nifedipine (n=50)	Total (n=100)			
NVD	34(68.0%)	23(46.0%)	57(57.0%)	4.937	1	.026
LSCS	11(22.0%)	17(34.0%)	28(28.0%)	1.786	1	.181
Forceps	1(2.0%)	1(2.0%)	2(2.0%)	-	-	-
Ventouse	3(6.0%)	8(16.0%)	11(11.0%)	2.554	1	.110
Other mode of delivery	1(2.0%)	1(2.0%)	2(2.0%)	-	-	-

Table-7: Group-wise baby's condition at birth

Parameters	Mean±SD		t-value/ U-value*	df	P-value
	Labetalol (n=50)	Nifedipine (n=50)			
Birth weight in grams	2600 (2150-3025)	2950 (2475 -3400)	.045*		
APGAR score at 5 min	8.20±2.22	8.04±2.53	.335	98	0.738

Table-8: Group-wise NICU admission.

Parameters		Group			χ^2-value	d.f.	P-value
		Labetalol (n=50)	Nifedipine (n=50)	Total (n=100)			
NICU admission	Admitted	7(14.0%)	2(4.0%)	9(9.0%)	3.053	1	.081
	Not admitted	43(86.0%)	48(96.0%)	91(91.0%)			

Table-9:Group-wise comparison of neonatal and maternal mortality.

Parameters		Group			χ^2-value/ Fisher's Exact Test*	d.f.	P-value
		Labetalol(n=50)	Nifedipine(n=50)	Total (n=100)			
Neonatal mortality	No	49(98.0%)	47(94.0%)	96(96.0%)	1.042	1	.307
	Yes	1(2.0%)	3(6.0%)	4(4.0%)			
Maternal mortality	No	50(100.0%)	50(100.0%)	100(100.0%)	-	-	-
	Yes	-	-	-			

DISCUSSION

In this study, pregnant women in the group of oral nifedipine achieved target blood pressure significantly more rapidly and with fewer doses as compared with those receiving intravenous labetalol. The findings are similar with results mentioned in studies conducted by Vermillion et al[2] and Shekhar et al.[4] However, Raheem et al[3] found both nifedipine and labetalol to be equally efficacious.

In the present study, variation in all baseline characteristics (age, gravida, parity, gestational age, systolic blood pressure and diastolic blood pressure) in both groups is insignificant. The mean systolic blood pressure in this study is 180.32±17.66 mm Hg in labetalol group and 176.76±16.58 mm Hg in the nifedipine group with a 'P' value of 0.301. While in the study of Raheem et al[3], the mean systolic blood pressure was 175(170-180) mm of Hg in nifedipine group and 170 (165-180) mm of Hg in labetalol group with 'P' value 0.25. Again in the study of Shekhar et al[4], the mean systolic blood pressure was 168±13.8 mm Hg in labetalol group and 165±6.7 mm of Hg in nifedipine group.

In this study, the mean diastolic blood pressure is 114.00±13.09 mm Hg in the labetalol group and 114.72±12.75 mm Hg in nifedipine group with a 'P' value of 0.781. Raheem et al[3] showed that the mean diastolic blood pressure was 110 (110-116) mm Hg in nifedipine group and 108 (100-112) mm of Hg in labetalol group with a 'P' value of 0.012. And in the study of Shekhar et al[4], the mean diastolic blood pressure was 110.00±7.5 mm Hg in the labetalol group and 108±5.9 mm Hg in nifedipine group.

In our study, the mean time required to achieve target blood pressure is 71.00±66.60 minutes in labetalol group and 25.20±14.03 minutes in the nifedipine group with the p value of < 0.01. Raheem et al[3] showed that the median time taken to achieve target blood pressure was 30 minutes (interquartile range 22.5 to 67.5 minutes) versus 45 mins (interquartile range 30-60 minutes) for nifedipine and labetalol respectively (p=0.59). In a study by Vermillion et al[2], mean times needed to achieve target blood pressure were 25 minutes and 43.6 minutes for the nifedipine group and the labetalol group respectively. Shekhar et al[4] study showed that the median time required to achieve target blood pressure 40 minutes in nifedipine group and 60 minutes in labetalol group.

In the present study the nifedipine group required in average 1.12±.32 doses to bring about the desired action and the labetalol group required 2.04±1.37 doses to bring about the same action which is statistically very highly significant ('P' value <0.01). Raheem et al[3] showed total antihypertensive doses to achieve target blood pressure were 2(1.5 – 4.5) in nifedipine group and 3(2 – 4) in labetalol group with a 'P' value 0.60. In the study by Shekhar et al[4], doses required for desired action were 3(2-4.25) and 2(1-3) in the labetalol and nifedipine groups respectively (P =.008). Study conducted by Dhali B et al[5] also concluded that oral nifedipine lowers blood pressure in less time and with fewer doses as compared to intravenous labetalol.

Raheem et al[3] reported 20% failure rate with both drugs and requiring crossover treatment. Shekhar et al[4] mentioned that nifedipine was more successful (one failure) in achieving the target blood pressure in comparison with the labetalol group (five failures).

Vermillion et al[2] reported 100% success rate in achieving the target blood pressure with both drugs. In this study, only in the labetalol group five failures (failure rate 10%) are noted requiring cross over treatment and in nifedipine group 100% success is seen (P =0.22).

In this study, urine output at 60 minutes of commencing treatment is 55.20±16.72 ml in labetalol group compared to 99.10 ± 27.15 ml in nifedipine group with a 'P' value <.001. Vermillion et al[2] study reported that urine output was significantly increased ('P' < .001) at 1 hour after nifedipine dosing (99±99ml) compared with labetalol (44.8±19.1 ml).

In this study, in nifedipine group, only in four cases hypotension was noted compared with no case was noted in labetalol group (P =.041). But in all 3 pregnant women with eclampsia in nifedipine group there was no hypotension. The variation of percentage of maternal and fetal complications such as HELLP syndrome, acute renal failure, impending eclampsia, fetal distress, abruptio placenta, intrauterine growth restriction, postpartum haemorrhage, etc. are insignificant. The concern of overshoot hypotension and profound neuromuscular blockade due to synergistic action of nifedipine and magnesium sulphate have been disproven by a number of trials evaluating nifedipine as an antihypertensive agent[6,7,8] or as a tocolytic agent.[9-13] In the retrospective review by Magee et al[14], it was found that contemporaneous use of magnesium sulphate and nifedipine does not increase the risk of neuromuscular blockade and maternal hypotension. There are no data in the literature to suggest prolongation of labour or uterine atonia after delivery due to tocolytic effects of nifedipine. In my study, a majority of participants required only one to two doses of nifedipine to achieve target blood pressure; therefore they were exposed to only smaller concentrations of the drug than when used for tocolysis.

In the present study, there is no significant difference in the mode of delivery between two groups. But in labetalol group there was more normal vaginal delivery compared to nifedipine group (P =.026). These results were more or less similar to the results of the study conducted by Raheem et al.[3]

In labetalol group the mean birth weight is 2600(2150-3025) grams and in nifedipine group it is 2950(2475-3400) grams in the present study (P =0.045). In the study of Raheem et al[3], in both groups average birth weight were 2.9 kg with interquartile range of 2.2-3.1 kg in nifedipine group and 2.7- 3.2 kg in the labetalol group.

There is insignificant variation in percentage of NICU admission in the both group (labetalol group = 14% versus nifedipine group = 4%; P =.081) in the present study. In the study conducted by Raheem et al[3], results were similar (3 cases in both groups) with 'P' value 1.0. Shekhar et al[4] study also showed insignificant 'P' value in terms of NICU admission in both groups (labetalol group = 6.7% versus nifedipine group = 13.3%).

There are four neonatal mortality in this study (nifedipine group = 3 cases and labetalol group = one case with 'P' value = 0.307). In labetalol group neonatal mortality can be explained by prematurity (34 weeks). In nifedipine group 3 neonatal mortality can be explained by prematurity, intrauterine growth retardation and abruption of placenta. There is no maternal mortality in both the groups.

CONCLUSION

From this study, it is concluded that both oral nifedipine and intravenous labetalol are effective in the management of severe pregnancy induced hypertension; however oral nifedipine controls hypertension more rapidly and with fewer doses and is associated with a significant increase in urinary output.

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