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A Prospective Comparative Study on Intravenous Labetalol and Oral Nifedipine for Control of Blood Pressure in Severe Pre-Eclampsia

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ABSTRACT

Severe preeclampsia is the second common cause for maternal morbidity and mortality and also leads to fetal complications. Although hypertensive disorders in pregnancy cannot be prevented, early diagnosis and treatment (secondary prevention) helps in favourable maternal and foetal outcome. The most commonly recommended hypertensive drugs used in the management of preeclampsia include hydralazine (i.v), labetalol (oral and i.v) and nifedipine (oral).The study was carried out on 60 pregnant women attending the antenatal OPD and emergency room at Moran Medical Centre, Dibrugarh, Assam. Patients were further divided into 2 groups (Group A- Labetalol injection was given 20 mg and Group B- nifedipine 10mg was given orally at 20 mins interval) The target blood pressure was 150/90 mm Hg and at this point study regimen was stopped. After the successful control of BP further antihypertensive was given orally as chosen by provider. The time interval and dosage of the drugs required to achieve the target BP was noted. Mean SBP was 180.7±14.99 mm Hg in group A and 182.0±15.53 mm of Hg in group B (p = 0.7401). Mean DBP was 119.1±8.46 mm of Hg in group A and 117.7±8.89 mm of Hg in group B (p = 0.5407). Most of the patients were controlled by two doses of each drug, 56.67% in the labetalol group and 60% in the Nifedipine. Labetalol had less maternal side effects when compared to nifedipine. Labetalol seems to be safer, with quick control of blood pressure with fewer side effects.

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Key Words
Labetalol, nifedipine, hypertensive, severe pre-eclampsia, pregnancy

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INTRODUCTION

Severe Pregnancy induced hypertension (PIH) is a disorder in pregnancy which is characterized by a systolic blood pressure of ≥160 mm of Hg and a diastolic blood pressure of ≥110 mmHg[1]. Various complications occur due to hypertensive disorder. When mean arterial pressure exceeds 140 mm of Hg (equivalent to 180/120) there is a significant risk of maternal cerebral vascular damage. Pregnant woman with preeclampsia has an increased risk of developing serious complications such as kidney failure, liver failure, abnormalities of clotting system, stroke, premature delivery, still birth or death of the baby in the first few weeks of life. Once the blood pressure reaches 170 mmHg systolic or 110 mmHg diastolic, the woman is at increased risk of harmful effects. Therefore, it is recommended that BP ≥160 /110 mm of Hg with or without proteinuria (≥300mg/24 hours urine) must be treated as hypertensive urgency[2].

Severe preeclampsia is the second common cause for maternal morbidity and mortality and also leads to fetal complications. Although hypertensive disorders in pregnancy cannot be prevented, that means primary prevention is not possible, early diagnosis and treatment (secondary prevention) helps in favorable maternal and fetal outcome. It has been shown that early treatment decreases not only the frequency of hypertensive crisis, but also the rate of neonatal complications. The definitive management of hypertensive disorders in pregnancy is mainly termination of pregnancy, which cannot be done in many cases due to prematurity. It is thus prudent to continue the pregnancy till the stage wherein the fetal survival is good. During this period the maternal and fetal conditions are monitored along with control of hypertension by anti-hypertensive drugs. Various anti-hypertensive agents have been used in the management of preeclampsia. The most commonly recommended drugs include hydralazine (i.v.), labetalol (oral i.v) and nifedipine (oral).

Of the anti-hypertensive drugs nifedipine was most commonly used for treatment of hypertension during pregnancy based on its effectiveness and safety for both mother and fetus, but it takes longer time to act. Labetalol (a +ß blocker) gives better control of blood pressure[2,3]. The advantage of labetalol is its availability as both injectable and oral preparations and time of onset of action is earlier when compared to nifedipine. To date, there have not been many randomized clinical trials comparing these two agents in pregnancy. Moreover results are also varying. This confuses the clinician. So the clinicians are forced to follow the regimen they are familiar with. Hence, the above study was conducted to find better anti-hypertensive agent for acute control of high blood pressure in severe pre-eclampsia. Any additional drug or crossover of drug required if BP not controlled.

MATERIALS AND METHODS

Study place: The study was conducted in the antenatal ward of maternity block of Moran Medical Centre, Dibrugarh, Assam from 2022 Jan to 2022 Dec).

Study Design: Prospective, randomized, comparative study.

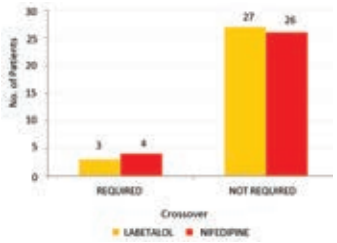

Fig. 1: Crossover therapy in both the groups

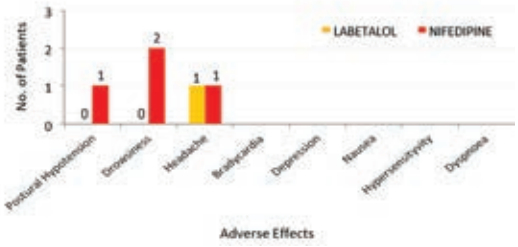

Fig. 2: Comparison of adverse effects of the drug

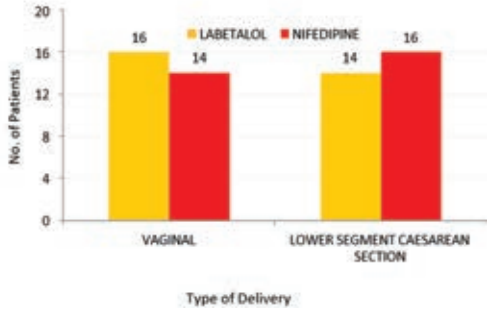

Fig. 3: Comparison of type of delivery between two groups

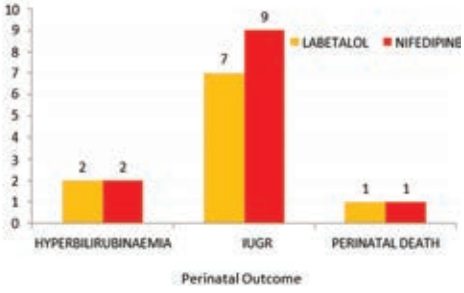

Fig. 4: Comparison of perinatal outcome between the two groups

Inclusion Criteria: Pregnant women with Systolic Blood Pressure ≥160, Diastolic Blood Pressure ≥

Table 1: comparision of age distribution of the two groups

	labetalol		nifedipine		
Age(years.)	**no.**	**Percentage**	**no.**	**Percentage**	
19 - 24	13	43.33	12	40	p= 0. 8271
25 - 29	14	46.67	13	43.33	
30 - 35	3	10	5	16.67	
total	30	100	30	100	

Table 2: comparison of the systolic bp of the groups

	labetalol		nifedipine		
Sbp(mm of hg)	**No.**	**Percentage**	**No.**	**Percentage**	
160-180	16	53.33	14	46.67	P= 0 .7401
181-200	8	26.67	11	36.67	
> 200	6	20	5	16.66	
TOTAL	30	100	30	100	

Table 3: comparison of the diastolic bp of the two groups

	labetalol		nifedipine		
DBP(Mm of hg)	**No.**	**Percentage**	**No.**	**Percentage**	
110 - 130	25	83.33	23	76.67	P= 0. 5407
> 130	5	16.67	7	23.33	
TOTAL	30	100	30	100	

Table 4: comparison of no. Of doses of drugs required to control bp between the two groups

	labetalol		nifedipine		
No. of doses	**No.**	**Percentage**	**No.**	**Percentage**	
1	5	16.67	6	20	P=0 . 8673
2	17	56.67	18	60	
3	3	10	1	3.33	
4	2	6.67	1	3.33	
5	3	10	4	13.33	

Table 5: comparison of time required to control bp of the two groups

Time (in mins)	labetalol		nifedipine		
	No.	**Percentage**	**no.**	**Percentage**	
20	5	16.67	6	20	p= 0 . 8673
40	17	56.67	18	60	
60	3	10	1	3.33	
80	2	6.67	1	3.33	
100	3	10	4	13.33	
Total	30	100	30	100	

Table 6: Amount of drug required for controlling bp between the two groups

	Labetalol		Nifedipine			
Amt. of Drug(mg)	**No.**	**Percentage**	**No.**	**Percentage**		
20	5	16.67	10	6	Z = 5.536	P = 0.00001
60	17	56.67	20	18	t = 4 . 624	
140	3	10	30	1		
220	2	6.67	40	1		
300	3	10	50	4		
Total	30	100	Total	30		

110, Proteinuria ≥300mg/24 hours urine, Gestational Age >34 weeks up to 41 weeks, ready to give written consent.

Exclusion Criteria: Patients complicated with eclampsia, post-partum women, pregnant women with known hypertension-essential or secondary, pregnant women with known heart disease, DM or other medical disorder.

Sample Size: 60 (30 in each group.

Data Analysis: Data was analyzed with the Student's t-test and non-normally distributed with Mann- Whitney U test. Categorical variance was analyzed with Fisher's exact test. All tests are two sided and $p<0.05$ taken as the level of significance.

Ethical Considerations: The study was performed after getting approval from the institutional ethical committee of Moran Medical Centre.

The selected pregnant women were randomly allocated by computer generated number into two Groups (Group A and B).

Group A: In this group labetalol injection was given 20 mg i.v. route with escalating doses of 40, 80, 80 and 80 mg every 20 mins interval i.e. up to maximum of 300 mg total dose.

Group B: In this group nifedipine 10mg was given orally at 20 mins interval up to maximum of 5 doses i.e. 50mg.

The target blood pressure was 150/90 mm Hg and at this point study regimen was stopped. After the successful control of BP further anti-hypertensive was given orally as chosen by provider. The time interval and dosage of the drugs required to achieve the target BP was noted. Any additional drug or crossover of drug required if BP not controlled was also noted.

RESULTS AND DISCUSSIONS

All the patients were aged between 19-35 years. In the labetalol group, 46.67% of the patients were between 25-29 years and in the nifedipine group, 43.33% of all the patients were between 25-29 years. The youngest was 19 years in both the group. In the labetalol group, 46.67% of the patients were between 25-29 years and in the nifedipine group, 43.33% of all the patients were between 25-29 years. The youngest was 19 years in both the group. The eldest was 31 years in labetalol group and 34 years in nifedipine group. The mean age in labetalol and nifedipine group was 25.1 and 25.9 years respectively. Most of the patients had a systolic BP of 160-180mm of Hg 53.33 and 46.67% in the labetalol and nifedipine group respectively. Mean SBP was 180.7±14.99 mm of Hg in the labetalol group and 182.0±15.53 mm of hg in the nifedipine group. Most of the patients had a diastolic BP of 110-130 mm of Hg 83.33 and 76.67% in the labetalol and nifedipine group respectively. Mean DBP was 119.1±8.46 mm of Hg in the labetalol group and 117.7±8.89 mm of hg in the nifedipine group. Most of the patients were controlled by two doses of each drug 56.67% in the labetalol group and 60% in the nifedipine group. 10% and 13.33% in the labetalol and nifedipine group respectively were not controlled by 5 doses of either drug and required crossover drug therapy. Most of the patients were controlled within 40 minutes of each drug 56.67 % in the labetalol group and 60% in the nifedipine group. The mean time required were 47.3±23.18 mins in the labetalol group and 46±24.72 mins in the nifedipine group. The comparison showed no difference in the two groups with a p value of 0.8673. Most of the patients were controlled with two doses of each drug i.e. 56.67% patients in the labetalol group required 60 mg of the drug and 60% patients in the nifedipine group required 20 mg of the drug. The mean amount of drug required were 96±85.57 mg in the labetalol group and 23.3±12.12 mg in the nifedipine group. The data was compared using the student's-t test and the Mann Whitney U test for which the value of t, Z, U were 4.624, 5.5368 and 75 respectively. The p value was 0.00001 which signifies a significant difference in the dosages of the two drugs. Most of the patients were controlled by two doses of each drug 56.67% in the labetalol group and 60% in the nifedipine group. Ten and thirteen point thirty three percentage in the labetalol and nifedipine group respectively were not controlled by 5 doses of either drugs and required crossover drug therapy. 3.3% patients had headache in each Group. In the Nifedipine Group 3.3% of the patients had postural hypotension, 6.7% of them had drowsiness.

There was no significant difference in the mode of delivery in both the groups with a p-value of 0.7965. But spontaneous vaginal delivery was more in the labetalol group i.e., 30% when compared to the nifedipine group i. e., 13.3%. Caesarean section rate was 46.67% and 53.33% in the labetalol and nifedipine group respectively. IUGR neonates were 23.33% and 30% in the labetalol and nifedipine group respectively. Hyperbilirubinaemia were 6.67% in both the labetalol group and nifedipine groups. There was 1 perinatal death in each group. The comparison was statistically insignificant with a p-value of 0.8939.

On comparison both Systolic Blood Pressure and Diastolic Blood Pressure showed statistically non-significant difference (p value of 0.7401) between the two groups in the present study, before the initiation of treatment. Majority of patients of both groups had a Systolic Blood Pressure of 160-180 mm of Hg (53.33 and 46.67% in the labetalol and nifedipine group respectively). Mean Systolic Blood Pressures were 180.7±14.99 mm of Hg in the labetalol group and 182.0±15.53 mm Hg in nifedipine group. In a study conducted by Raheem *et al*.[2] which was double blind randomized trial with the similar objectives of comparing oral nifedipine with intravenous labetalol in their rapidity to control hypertensive emergencies of pregnancy, 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 a p value of 0.25. Majority of the patients, in the present study, had a Diastolic Blood Pressure of 110-130 mm Hg (83.33% and 76.67% in the labetalol and nifedipine respectively). Mean Diastolic Blood Pressure was 119.1±8.46 mm of Hg in the labetalol group and 117.7±8.89 mm Hg in the nifedipine group. Study conducted by Raheem *et al*. had a mean Diastolic Blood Pressure of 110 (110-116) mm of Hg in nifedipine group and 108 (100-112) mm of Hg in labetalol group with a p value of 0.012

In above study, mean time required to achieve target blood pressure were 47.3±23.18 minutes in the labetalol group and 46±24.72 minutes in the nifedipine group, which was statistically non-significant (p value of 0.8673). The study conducted by Vermillion *et al*.[4] revealed that the time to achieve the blood pressure goal was significantly shorter with nifedipine (mean±SD), (25±13.6 mins) than with labetalol (43.6 ±25.4mins) with a p = 0.002. This difference of result can be explained by the difference in their

methodology where they used nifedipine in an escalating dose. Vermillion *et al*.4 used escalating oral nifedipine doses (10 mg initially, then 20 mg for a further four doses, as required) Blood pressures of majority of the patients in above study were controlled by two doses of each drug, 56.67% in the labetalol group and 60% in the nifedipine group. In a study conducted by Shekhar *et al*. (2013)5 the median dose required was two (interquartile range 1-3) compared with three (interquartile range 2-4.25) for nifedipine and labetalol, respectively (p=0.008). The above study showed that the blood pressures of 10% patients in labetalol group and 13.33% of patients in nifedipine group were not controlled by 5 doses of either drugs and required crossover drug therapy as compared to the study of Raheem *et al*[2]., which required crossover therapy in 20 % of patients (i.e. 5 out of 25 patients) in each group. The study conducted by Vermillion *et al*. (1999)[4] found none of the patients required crossover therapy.

The above study showed that there was no significant difference in the mode of delivery between two groups with a p value of 0.7965. But spontaneous vaginal delivery was more in the labetalol group i.e. 30% when compared to the nifedipine group i.e. 13.3 %. A significantly higher incidence of induction of labor was found in the nifedipine group i.e. 33.33%. Caesarean section rate was 46.67% and 53.33% in the labetalol and nifedipine group respectively. These result were more or less similar to the result of the study of Raheem *et al*[2]. where vaginal delivery was more in labetalol group 48% (12 out of 25) as compared to 36% (9 out of 25) in the nifedipine group. Caesarean section rate was 52% (13 out of 25) in the labetalol group while 64% (16 out of 25) in the nifedipine group. The p-value was 0.57. These differences can be explained by the tocolytic effect of nifedipine. Most of the babies were vigorous having 5 minute APGAR greater than 7 i.e. 90 % in the labetalol group and 93.33% in the nifedipine group. The comparison was statistically similar with a p value of 0.6766. Shi Q *et al*. (2015)[6] also in their meta-analysis found no statistically significant difference for the neonate 5 -min Apgar score<7 (RR = 2.07 (95% CI = 0.4-10.65, P = 0.38)) between the two groups. The study conducted by Scardo JA (1999)[7] revealed that nifedipine group had a cardiac index of 3.08±0.51 l/min per square meter. There was a 43 % increase in the cardiac index after nifedipine administration (p = 0.0008) while there was no significant effect in the labetalol group (p = 0.697). The systemic vascular resistance index was significantly decreased after nifedipine administration (p = 0.002) but not after labetalol administration (p = 0.479). The mean arterial pressure was significantly affected in both groups (nifedipine, p = 0.001; labetalol, p=0.004). An insignificant increase in heart rate with nifedipine (p = 0.147) and a significant decrease with labetalol (p = 0.034) were noted.

CONCLUSION

From the above study, it can be concluded that Labetalol had less maternal side effects when compared to nifedipine. Labetalol and nifedipine had similar foetal effects. The chances of spontaneous onset of labor were greater in the labetalol group when compared to the nifedipine group. There was no difference between two groups with regard to number of doses, time required to control the blood pressure or operative obstetric intervention. At proper doses of ensuring blood pressure control, both the drugs were found to be safe and effective.

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