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A comparative study of IV labetalol with oral nifedipine in severe preeclampsia

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Abstract
Aims and Objectives: To compare the efficacy and safety of intravenous Labetalol over Nifedipine in severe preeclampsia patients and to study the effect of Labetalol on maternal and fetal outcome in severe preeclampsia patients.
Methodology: This is a prospective comparative study in antenatal mother with sever preeclampsia done from June 2017 and May 2018. All the data were entered and analyzed using SPSS version 22.
Results: Among 50 study patient population 25 patients received oral nifedipine (group A) and 25 patients received i.v. Labetalol (group B). Result shows that from1 hr to 6 hrs the mean systolic BP in the labetalol group was found to be lower than nifedipine group and mean diastolic BP from 1 hr to 6 hrs in the labetalol group was found to be lower than nifedipine group. 32% of antenatal mothers in the nifedipine group delivered before 36 weeks whereas in labetalol group only 4% of antenatal mothers delivered before 36 weeks. 32% of newborn, born to the mothers in the nifedipine group required NICU admission whereas in the labetalol group it was only 4%.
Conclusion: Thus, concluded that both the drugs were found to be safe and effective in the reduction of blood pressure. But intravenous labetalol showed a rapid reduction of blood pressure at a shorter duration with a minimal dosage compared to oral nifedipine along with a lower incidence of preterm and lesser admission to NICU among the antenatal mothers treated with labetalol compared to oral nifedipine.

Keywords: Preeclampsia, Labetalol, Nifedipine, Antenatal mother

Introduction
Hypertensive disorders complicate 5-10% of all pregnancies. Preeclampsia is identified in 3.9% of all pregnancies [1]. I t forms one of the deadly triads, along with hemorrhage and infection. They contribute greatly to maternal mortality rate. In developed countries 16% of maternal deaths were due to hypertensive disorders [2]. In India around 18- 15% of maternal deaths were due to hypertensive disorders. Importantly half of these deaths were preventable [3].
Preeclampsia is a pregnancy specific syndrome related to vasospasm and endothelial damage. Where in the patient returns back to normal following delivery. Preeclampsia is hypertension with proteinuria after 20 weeks of gestation in women with previously normal blood pressure which returns to normal within 12 weeks post-partum [4]. Proteinuria is defined as 24 hour urinary protein excretion exceeding 300 mg, a urine protein: creatinine ratio of ≥ 0.3, or persistent 30 mg / dl (1+) in dipstick two times 6 hours apart. Diagnosis of gestational hypertension is made in women whose systolic blood pressure reaches 140 mm of hg and above or when diastolic blood pressure reaches 90 mm hg and above, for the first time after 20 weeks gestation, without proteinuria. The blood pressure returns to normal by 12 weeks postpartum [5].
Abnormal laboratory findings in tests of renal, hepatic and hematological function increase the certainty of preeclampsia. Preeclampsia often affects young and nulliparous women. The incidence is markedly influenced by race, ethnicity and has genetic predisposition. Other risk factors include obesity, multi fetal gestation, and thrombophilia's. Taking into consideration the various devastating complications of preeclampsia such as abruption, eclampsia, HELLP syndrome, cerebrovascular accidents and various neonatal complications, the need to curtail this disease from progressing is evident. Hypertensive disorders of pregnancy affect one of every ten pregnant women, and are one of the leading causes of maternal and perinatal mortality and morbidity [7, 8].
In these women, blood pressure (BP) can rise acutely to dangerous levels, posing a serious threat to the life and wellbeing of mother and fetus by inflicting end organ damage. Maternal and fetal

risks are decreased by swift but controlled lowering of BP to safer levels, with antihypertensive drugs [9-11]. Most of the authorities recommend labetalol, hydralazine and nifedipine as first line alternatives for the treatment of severe hypertension during pregnancy [12-14].

Hydralazine had been the drug of choice for a long time; however, the faith in hydralazine has dwindled over the past decade due to evidence of increased maternal and fetal complications associated with its use [15, 16]. Moreover, manufacturing shortages have made it unavailable in many parts of the world [17]. Labetalol and nifedipine have fast emerged as alternative drugs and can be judged from the change in usage pattern of these drugs in the past decade. A recent online poll among health care providers found intravenous labetalol as the first choice (57%) followed by hydralazine (33%) and nifedipine (9%) [18].

This is in sharp contrast to the study by Heazell *et al*. in 2004 in which 90% of the respondents were using hydralazine and only 7% and just over 2% were using labetalol and nifedipine, respectively.[19] Although nifedipine is cheap, widely available and easily administered, the usage pattern highlights a strong preference for labetalol and reflects a trust deficit for oral nifedipine among health care providers. Both intravenous labetalol and nifedipine have been compared directly with many other antihypertensive agents for hypertensive crisis during pregnancy; however, their direct comparison with each other is limited to a very few RCTs [20-24].

Materials and Method

This is a prospective comparative study carried out in the Obstetrics and Gynecology department of Vinayaka Missions Kirupananda Variyar Medical College Hospital Salem. Duration of the study is One-year June 2017 and May 2018. Study population for this study are Antenatal mother with severe preeclampsia. Patients selected based on the inclusion and exclusion criteria. Inclusion criteria are Antenatal mothers with blood pressure >/= 160/110 mmhg, Urine albumin >/=1+ by dipstick, Age between 18 and 30 years, Primi and multi gravida, Gestational age >32 weeks, Single/multi fetal gestation.

Exclusion criteria include patients with asthma, history of congestive cardiac failure, diabetes, heart block, severe liver disease and peripheral vascular disease**,** patients with history of eclampsia with Glasgow coma scale <6, patients with chronic hypertension or hypertension due to secondary causes. Total number of patients enrolls in this study are 50 patients. 25 patients receiving oral nifedipine (group A) and 25 patients receiving i.v. Labetalol (group B).

Study procedure:

The study was started after getting the clearance from the institutional ethical committee and the informed consent was obtained from all the patients involved in the study. Severe PIH was defined as a sustained systolic blood pressure of ≥160 mmHg & diastolic blood pressure of ≥110 mmHg on repeat measurement of 30 minutes apart in a lateral recumbent position with head of the bed elevation not exceeding 15 degree. Once patients were enrolled, vital signs were recorded every 30 minutes, including blood pressure measurement by a mercury column sphygmomanometer. The blood pressure cuff width was 15 cm & the length of the cuff was about 1.5 times mid arm circumference. 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 & any abnormalities were noted & also the maternal adverse effects like eclampsia, stroke, heart failure & decreased urine output were recorded. Additional neonatal outcome like 5 minutes Apgar score of <7 & NICU admission were recorded.

Patients randomized to intravenous labetalol, received 20 mg initially, followed by escalating doses of 40 mg, 80 mg, & then 80 mg every 20 minutes until the therapeutic goal blood pressure systolic ≤140 mmHg & diastolic ≤100mmHg was achieved, or for a maximum of five doses. Patients randomized to oral nifedipine received 10 mg initially, with repeated doses of 20 mg every 20minutes for up to a maximum of 5 doses, or until the goal blood pressure was achieved. The dosing regimens for each study medication correspond with the regimens from two previous clinical trials. The primary outcome was the time interval required to achieve the goal therapeutic systolic blood pressure of ≤140 mmHg & diastolic ≤100 mmHg. Secondary outcomes analyzed included urinary output, agent failure, &maternal adverse effects like eclampsia, decreased urine output, stroke, & heartfailure. Additionally, fetal heart rate abnormality, 5 minutes Apgar scores of <7& NICU admission were analyzed as secondary outcomes as infant's adverse effects.

Investigations included complete hemogram, platelet count, blood urea, serum creatinine, serum uric acid, liver function test, fundoscopy, NST, ultrasound & Doppler in somecases. Patients with gestational age less than 35weeks were given steroid prophylaxis to help fetal lung maturity. Those patients with impending eclampsia were given MgSO4. Decision to continue with conservative management of pregnancy or to deliver & mode of delivery was made depending on maternal & fetal indications. Then patient's were followed until delivery & the various modes of delivery were noted. The indications for induction of labor if done were noted. The birth weight, APGAR score were recorded. The side effects if any, during the treatment were noted, neonatal outcome was noted. All the data were entered and analyzed using SPSS version 22. Numerical data were analyzed by unpaired t test & the categorical variables were analyzed by Fischer exact test or chi-square test, whichever is applicable. The level of significance was $p<0.05$.

Results

The age wise distribution of the study subjects in both the groups were in the age group between 25 and 30 years and the mean age of group A was 26 and that of group B was 27 years. The distribution of the study subjects based on the socioeconomic status shows that majority of the study subjects in both the group belong to grade III to grade IV socio-economic status according to modified B G prasad classification of socio-economic status. The distribution of the study subjects based on the gravida score results in more than 50% of the study subjects in both the group belong to 2nd gravida. The distribution of the study subjects based on the gestational weeks shows that majority of antenatal mothers were in the gestational week of 34 to 35 in both the groups. Headache and blurring of vision were the most common presenting complaint which were present in almost all the study subjects in both the groups.

Based on their previous medical history, it is depicted that more than 60% of the study subjects in both the groups have a previous history of gestational hypertension and more than 20% had previous history of preeclampsia. The mean weight and height are almost similar in both the groups. Based on the grading of pedal edema, it is depicted that majority of the study subjects in both the groups were having grade II or III pedal edema. The mean heart rate and blood pressure among the study subjects at the time of admission were found to be very high

among both the groups. The mean HR was 107 among Nifedipine and it was 105 among Labetalol group and the mean BP was 186/114mmhg among nifedipine group and it was 188/112 mm hg among Labetalol group and the difference between the two groups was not statistically significant. Fetal movements and fetal heart sounds were present in all the study subjects of both the groups. The mean and SD of the various blood parameters measured among the study subjects. It is depicted from the table that the mean of all the blood parameters between the two groups were almost similar and no statistically significant difference was seen between the two groups. Table 1 shows the distribution of the study subjects based on the grading of hypertensive retinopathy. It is depicted from the table that more than 50% of the study subjects were having grade II or III hypertensive retinopathy in their fundus examination

Table 1: Distribution based on the grading of hypertensive retinopathy

Pedal edema	Group A (Nifedipine)	Group B (Labetalol)	P value
Grade I	4 (16%)	3(12%)	0.638
Grade II	11(44%)	10(40%)	
Grade III	9(36%)	9(36%)	
Grade IV	1(4%)	3(12%)	
Total	25(100%)	25(100%)	

The distribution of the study subjects based on the proteinuria status shows that more than 85% of the study subjects in both the group were having proteinuria in the grade of 3+. The time taken to achieve target blood pressure among the Labetalol group was between 1 and 2 hrs, whereas among nifedipine most of them achieved the target BP at 12 hrs. And the difference was found to be statistically significant. For achieving the target blood pressure in study subjects is that a greater number of additional dosages was required in the nifedipine group when compared to labetalol group in achieving the target BP and this difference was found to be statistical significant. Table 2 shows the mean systolic BP between the two groups at various intervals. It is inferred from the table that from 1 hr. to 6 hrs. The mean systolic BP in the labetalol group was found to be lower than the mean systolic BP in the nifedipine group and the difference was found to be statistically significant. Whereas from 12 hrs to 24 hrs, the systolic BP between the two groups did not show a statistically significant difference as both the groups reached the target BP by that time.

Table 2: Mean systolic BP between the two groups at various intervals

Time interval	Groups	Mean systolic BP	P value
At 30 minutes	Group A (Nifedipine)	160.8± 21.5	0.314
	Group B (i.v. Labetalol)	154.4± 20.8	
At 1 hr.	Group A(Nifedipine)	150.6 ± 18.9	<.001
	Group B (i.v. Labetalol)	140.6 ± 21.1	
At 2 hr.	Group A(Nifedipine)	146.4 ± 22.5	<.001
	Group B (i.v. Labetalol)	130.2 ± 17.8	
At 6 hr.	Group A(Nifedipine)	140.4 ± 16.5	<.001
	Group B (i.v. Labetalol)	128.8 ± 21.4	
At 12 hrs.	Group A (Nifedipine)	132.4 ± 19.2	0.412
	Group B (i.v. Labetalol)	128.8 ± 18.6	
At 24 hrs.	Group A (Nifedipine)	130 ± 16.9	0.568
	Group B (i.v. Labetalol)	128 ± 15.9	

Table 3 shows the mean diastolic BP between the two groups at various intervals. It is inferred from the table that from 1 hr. to 6 hrs, the mean diastolic BP in the labetalol group was found to be lower than the mean diastolic BP in the nifedipine group and the difference was found to be statistically significant. Whereas from 12 hrs to 24 hrs, the diastolic BP between the two groups did not show a statistical significant difference as both the groups reached the target BP by that time.

Table 3: Mean diastolic BP between the two groups at various intervals

Time interval	Groups	Mean systolic BP	P value
At 30 minutes	Group A (Nifedipine)	108.8 ± 16.9	0.714
	Group B (i.v. Labetalol)	99.4 ± 17.5	
At 1 hr.	Group A(Nifedipine)	100.6 ± 18.2	<.001
	Group B (i.v. Labetalol)	94.6 ± 10.3	
At 2 hr.	Group A (Nifedipine)	96.4 ± 9.8	<.001
	Group B (i.v. Labetalol)	92.2 ± 8.6	
At 6 hr.	Group A (Nifedipine)	94.4 ± 7.4	<.001
	Group B (i.v. Labetalol)	90.8 ± 7.1	
At 12 hrs.	Group A (Nifedipine)	92.4 ± 6.8	0.542
	Group B (i.v. Labetalol)	88.8 ± 6.2	
At 24 hrs.	Group A (Nifedipine)	90 ± 6.3	0.628
	Group B (i.v. Labetalol)	88 ± 5.9	

The mean HR between the two groups at various intervals shows that from 1 hr to 6 hrs, the mean HR in the labetalol group was found to be lower than the mean HR in the nifedipine group and the difference was found to be statistically significant. Whereas

from 12 hrs to 24hrs, the mean HR between the two groups did not show a statistical significant difference.

Table 4 shows the time and mode of delivery between the two groups. It is inferred from the table that 32% of antenatal mothers in the nifedipine group delivered before 36 weeks whereas in labetalol group only 4% of antenatal mothers delivered before 36 weeks and similarly 64% underwent LSCS for delivery in nifedipine group and it was only 16% in labetalol group and this difference was found to be statistically significant.

Table 4: Time and mode of delivery between the two groups

Variable	Group A (Nifedipine)	Group B (i.v. Labetalol)	P value
Induction of delivery <36 weeks	8 (32%)	1 (4%)	<.001
LSCS	16 (64%)	4 (16%)	<.001

Table 5 shows the fetal parameters between the two groups. It is inferred from the table that 32% of the newborn, born to the mothers in the nifedipine group required NICU admission whereas in the labetalol group it was only 4% and similarly the mean birth weight and the mean APGAR score of the new born in nifedipine group was found to be statistically significantly lesser than that of the labetalol group.

Table 5: Fetal parameters between the two groups

Variable	Group A (Nifedipine)	Group B (i.v. Labetalol)	P value
NICU admission required	8(32%)	1 (4%)	<.001
Mean birth weight	2.23 ± 0.31	2.89 ± 0.24	<.001
Mean APGAR score at 5 mins	6 ± 1.2	8 ± 1.4	<.001

Discussion

Hypertensive emergency in pregnancy is associated with a considerable morbidity and mortality in both maternal and neonatal populations. The primary aim is to reduce the dangerously elevated blood pressure and ameliorate the severity of the disease. In the present study, intravenous labetalol was compared with oral nifedipine in terms of efficacy and safety. The maternal and fetal outcome measures and side effect profiles of the drugs were also studied. The patients enrolled in both the groups were comparable in terms of age, parity, booking status, gestational age at admission and body mass index. The mean age of the patients enrolled in the study was 27.2 years and 26.1 years in labetalol and nifedipine groups respectively.

According to the study by Duckett *et al*., [25] primiparity is one of the risk factors for preeclampsia, but in the present study more than 50% were 2nd gravida and only 8% in nifedipine group and 12% in Labetalol group were primigravida.

In the present study 40.57% patients presented in the gestational age of 34 to 36weeks. Early onset disease at gestational age of less than 24 weeks was seen in 2.83% of the enrolled patients.

The progressive risk of preeclampsia in obese is elucidated in the study by Sibai and colleagues. The risk is said to be increased by 13.3% in women with body mass index more than 35 kg/m^2. 45- 48% of the patients enrolled in the labetalol and nifedipine groups fell under the category of overweight or obese.

All the patients enrolled in the study were homogenous in terms of proteinuria. 88% of patients in labetalol group and 92% of the patients in nifedipine group had 3+ proteinuria on urine dipstick estimation which approximates to 1 to 2 g/day of proteinuria.

A similar study conducted by Vermilion *et al*. shows that oral nifedipine is superior when compared to labetalol in blood pressure control [26]. The drug protocol used in the study differed from the present study. Vermilion used 20mg oral nifedipine after the initial 10 mg dose. In the present study, out of the 25 patients enrolled in labetalol group, 14 patients, constituting 56% of the study population achieved the target blood pressure of ≤ 140/90 mm Hg in 60 minutes of commencement of the treatment, requiring three incremental doses of intravenous labetalol. The total dose administered in labetalol group was140 mg. In the nifedipine group only 20% achieved the target BP in 60 mins and this difference was found to be statistically significant.

On statistical analysis of the trend in reduction of the systolic blood pressure with respect to time, the difference of reduction in blood pressure was found to be significant at 60 minutes cut off. But at the end of 6 hrs and 12 hrs. The reduction of systolic BP is achieved in nifedipine group in par with the labetalol group. Similar trend was not seen in the case of reduction in diastolic blood pressure. Both the drugs were comparable in their reduction in diastolic blood pressure in the present study. None of the enrolled patients developed hypotension during the study. The lowest blood pressure recorded during the study was 130/80 mm Hg.

In the current study 64% of the antenatal mothers in the nifedipine group and 16% in labetalol group delivered by LSCS. Similarly, 32% the newborn, born to the mothers in the nifedipine group required NICU admission whereas in the labetalol group it was only 4% and the mean birth weight in nifedipine group was 2.2 kgs compared to 2.89 kgs in labetalol group and the difference was found to be statistically significant. The causes of neonatal ICU admission were extreme prematurity and respiratory distress syndrome. The outcome was similar in both the groups. None of the newborn had neonatal hypoglycemia or hypotension after birth.

Majority of the patients enrolled in the study did not report any notable adverse effects. The most commonly reported adverse effect in labetalol group was dizziness and that in nifedipine group was head ache and nausea. None of the patients in the labetalol group had palpitations, though 20% of patients in the nifedipine group had complained of the same. 3.8% of the patients enrolled in the labetalol group had complained of tremor and pain at the injection site. On the whole, there was no statistically significant difference in maternal adverse effects between both the groups.

The present study has certain limitations. The blood pressure and drug titration after the initial control of hypertension was not taken into account in the study. None of the patients with severe preeclampsia were managed expectantly because of the institutional protocol.

Conclusion

From the present study, both the drugs were found to be safe and effective in the reduction of blood pressure. But i.v. labetalol showed a rapid reduction of blood pressure at a shorter duration with a minimal dosage compared to oral nifedipine along with a lower incidence of preterm and lesser admission to NICU among the antenatal mothers treated with i.v. labetalol compared to oral nifedipine. Intravenous labetalol provided a smooth and steady reduction in blood pressure. The use of nifedipine may be recommended in low resource settings since it has an oral regimen and dosage is simple when compared to incremental intravenous dosing of labetalol.

Compliance with Ethical Standards

Conflict of interest: There is no conflict of interest among the authors. There is no financial relationship with any organization.

Ethical Statement: All procedures followed were in accordance with the ethical standards of the responsible Institutional Committee on human experimentation.

Informed consent: Informed consent was obtained from all patients for being included in the study.

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