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Comparative study of intravenous labetalol vs oral nifedipine in controlling blood pressure in pregnant women with hypertensive disorder

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Abstract
Introduction: Oral nifedipine & parenteral labetalol are most commonly recommended for treating hypertension disorders in pregnancy. The aim of the study was to compare the effectiveness & safety of both the drugs.
Methods: Every pregnant woman with severe gestational hypertension >160/110 mmHg who came to our university hospital at Chidambaram were taken for the study. They received acute treatment by either nifedipine (10 mg tablet, orally, up to five doses) or intravenous labetalol injection (in an escalating dose regimen of 20, 40, 80, 80 and 80 mg) and a placebo tablet or 0.9% saline every 15 minutes until the target blood pressure of <150/100 mmHg was reached.
Results: All the patients recruited in the study achieved blood pressure control. Most patients in both groups achieved the target blood pressure within 45 minutes or less (36.8 ± 15.3 minutes and 38.1 ± 12.2 minutes respectively in the labetalol and nifedipine) and received 3 or lesser number of doses (averaged 2.4 and 2.5 times in the labetalol and nifedipine). No crossover & not statistically significant adverse maternal or fetal outcomes were noted in both groups.
Conclusions: Oral nifedipine and intravenous labetalol are similarly effective & safe in the acute control of severe hypertension in pregnancy.

Keywords: Hypertension, labetalol, nifedipine, pre-eclampsia, pregnancy

1. Introduction
Hypertension disorders affect about 10% of all pregnancies worldwide [1]. Chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia are the diverse group of hypertension disorders seen in pregnancy [2]. These disorders, if not identified and treated, it affects both woman as well as fetus [3]. The incidence of preeclampsia has risen dramatically over the past few decades. According to the World Health Organization, hypertension during pregnancy is a leading cause of maternal mortality at 16% in industrialized countries and up to 25% in developing countries.
Maternal outcomes such as eclampsia, HELLP syndrome, acute renal failure, cerebrovascular accidents are unique to Pre-eclampsia. Fetal growth restriction, oligohydramnios, and fetal distress are some of the outcomes related to fetus.
The management is aimed at pregnancy termination, as this cannot be done in all cases, as most cases are preterm or very preterm. In such scenarios, pregnancy is extended by administering anti-hypertensive agents till there is a good fetal endurance, thereby increasing the gestational age of fetus and minimizing the fetal exposure to medication that may have adverse events. Many authors recommend labetalol, hydralazine and nifedipine as first line alternatives for the treatment of severe hypertension during pregnancy [4-6].
Nifedipine has the advantage of being cost effective, rapid onset of action, long duration of action and can be administered orally, however it is known to cause sudden maternal hypotension and fetal distress caused by placental hypo perfusion, palpitation and transient neuromuscular weakness when used concomitant with magnesium sulphate. Whereas, Intravenous Labetalol is considered to control severe hypertension in pregnancy. Its advantages include little placental transfer, less palpitation and less maternal tachycardia, however neonatal hypotension and neonatal bradycardia has been observed in some trials and is not as cost effective as Nifedipine.

Hence, there is a greater than ever need to produce strong evidence about comparative effectiveness and safety of intravenous labetalol and oral nifedipine that can be used to guide clinical practice.

2. Materials & methods

We performed an observational prospective study in hypertensive disorders of pregnancy. The study was conducted in a tertiary care centre & teaching hospital located in Chidambaram, Tamil Nadu. In our centre, women with severe hypertension who required acute blood pressure control were admitted to the hospital for further observation & treatment. Study took place between June 2018 and May 2019. Pregnant women of age between 18 – 35 years at >20 weeks of gestation with sustained severe hypertension were enrolled for the study. Sustained severe hypertension is defined as systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg measured on at least two occasions at least 4 hours apart. The recent blood pressure interpretation prior to enrolment of study must fulfil the criteria of severe hypertension. Women with abnormal heart rhythm, congestive heart failure, asthma, allergy to either drugs were excluded from the study. Women who agreed to participate provided written informed consent in a local vernacular language. The study was done after getting approval from the medical ethics committee of the University.

Each patient was given either parenteral intravenous labetalol or oral nifedipine. The intravenous 'labetalol or placebo' solution was prepared, which contained either labetalol at 5 mg/ml or 0.9% saline, and the fluid was drawn into a 60-ml syringe labelled as 1, and it was given as an intravenous administration together with the five tablets from package 1. Twenty-four patients were selected to receive the package containing intravenous labetalol injection in escalating doses of 20 mg, 40 mg, 80 mg, 80 mg, 80 mg and a placebo tablet for every fifteen minutes until the target blood pressure of ≤ 150 / ≤ 100 mm Hg was achieved.

The oral nifedipine and placebo tablets were identical in appearance. Each tablet contained either 10 mg of nifedipine or placebo. Twenty-six patients were selected to receive the package 2 containing nifedipine 10 mg tablet orally and intravenous placebo saline injections of 4 ml, 8ml, 16 ml, 16 ml, 16 ml up to five doses, every fifteen minutes till the target blood pressure of ≤ 150 / ≤ 100 mm Hg was achieved.

Participants were put in bed in a semi recumbent position. Physicians administered one tablet for the patient to swallow from package 1 and to administer 4 ml intravenously from syringe 1 as the initial treatment. After 15 minutes, if blood pressure was >150 mmHg systolic, or >100 mmHg diastolic, a second tablet was given and 8 ml from syringe 1 was administered intravenously. After another 15 minutes, if the target blood pressure of <150 mmHg systolic and <100 mmHg diastolic was not achieved, a third tablet was given and another 16 ml from syringe 1 was administered intravenously. This was repeated for another two rounds of treatment, as required, to achieve the target blood pressure range. If after five cycles of regimen the target blood pressure was not achieved, crossover to regimen 2 was carried out. Regimen 2 was carried out in a similar manner to that described for regimen 1. If the treatment goal was not achieved after completion of five cycles of regimen 2, then open-label treatment was allotted according to the physician's preference.

Blood pressure was obtained with a mercury sphygmomanometer, taking the fifth Korotkoff sound for the diastolic blood pressure. Blood pressure measurement was continued every 15 minutes for at least 60 minutes or longer until target blood pressure was attained. Once blood pressure was < or equal to 150/100 mmHg, no further medication was given unless there were two consecutive blood pressure readings > or equal to 160/110 mmHg, in which case the medication was restarted. We chose a systolic blood pressure reading of > or equal to 160 mmHg as an inclusion criterion, and a target blood pressure reading of < or equal to 150/ 100 mmHg.

During treatment with study drugs, continuous fetal monitoring was done electronically. The maternal heart rate was taken every fifteen minutes at the time of blood pressure measurement. In the event of non-reassuring fetal or maternal status, the study was abandoned, and appropriate measures were initiated to control blood pressure and/or delivery expedition was instituted according to the physician's judgment. If any clinically significant maternal hypotension was noted, intravenous fluid bolus or parenteral ephedrine was given accordingly. After completion of the study, patients were asked to answer a questionnaire with a yes or no on the adverse drug reactions experienced such as nausea, vomiting, dizziness, palpitations, headache, chest pain and shortness of breath experienced during the study. After attaining target blood pressure further antihypertensive treatment was started as decided by the physician. It was usually started 2 hours after the last medication. Delivery of the baby was the definitive treatment for any severe pregnancy related hypertension disorders for patients at or near term. Stabilised patients were managed expectantly. They were discharged to the normal ward for further observation. The primary outcome of the study is the time taken to achieve the target systolic blood pressure of >150 mmHg and diastolic blood pressure of >100 mmHg and total number of antihypertensive doses to achieve target blood pressure. Secondary outcomes were to study the maternal and fetal outcomes.

2.1 Sample size calculation

Using Vermillion *et al*. [7] results as guidance data, using an alpha value of 0.05 and a beta value of 0.1 (to give 90% power), 21 participants are required in each group in respect to the need of time to achieve the target blood pressure. Factoring in the possibility that the distribution of these outcome measures may not be normal, that the Mann–Whitney U-test may be required in place of the Student's t-test (i.e. an additional 10% increase in number) and also a 10% drop-out rate, we decided to study a total of 50 women for a suitably powered study.

2.2 Statistical analysis

Analysis was done based on the aim to treat. Categorical 2 x 2 data sets were analysed with the Fisher's exact test. Normally distributed continuous data were analysed with the Student's t-test. Non-normally distributed or ordinal data were analysed with the Mann–Whitney U-test, if any. Repeated measures analyses of the variance were applied to repeated blood pressure and heart rate readings. All tests were two sided and $P<0.05$ was taken as the level of significance.

3. Results

Study was clearly evident that both the groups had taken almost similar time to get control of high BP, i.e., 36.8 ± 15.3 minutes and 38.1 ± 12.2 minutes respectively in the labetalol and nifedipine groups.($p>0.05$) Even the number of top-ups required averaged 2.4 and 2.5 times in respective groups. ($p>0.05$) The statistical used here was Independent t-test.

Table 1: All these attributes as analysed by independent t-test were not found to be significantly different ($p>0.05$) and hence confounding factors were reduced

Variables	Labetalol group (n=24)		Nifedipine group (n=26)		p-value
	Mean	SD	Mean	SD	
Time taken to achieve BP control (minutes)	36.8	15.3	38.1	12.2	0.75
No of top-ups required (counts)	2.4	1.0	2.5	0.7	0.86
Age (in years)	25.3	4.6	25.8	3.5	0.68
GA (in weeks)	33.8	3.4	35.3	2.8	0.11
BMI (kg/m^2)	30.4	2.0	30.7	1.8	0.69
SBP (in mm Hg)	168.1	7.1	169.2	3.9	0.51
DBP (in mm Hg)	112.8	10.6	109.8	7.5	0.25
Pulse Rate (per minute)	83.8	8.7	84.8	9.3	0.67

(GA- Gestational Age; SBP- Systolic Blood Pressure; DBP- Diastolic Blood Pressure; BMI- Body Mass Index) (Independent t-test used; p-value <0.05 is significant)

The mean age of the participants in labetalol group were 25.3 ± 4.6 years and nifedipine group were 25.8 ± 3.5 years. Similarly, the mean BMI, Systolic BP, Diastolic BP, Heart rate as well as Gestational age at delivery were comparable and shown in table.

All these attributes as analysed by independent t-test were not found to be significantly different ($p>0.05$) and hence confounding factors were reduced. (Table 1)

Table 2: Gravida

Gravida	Labetalol	Nifedipine	χ2	p-value
G1 (Primi)	21 (53.8%)	18 (46.2%)	2.4	.01
G2	0	7 (26.9%)		
G3	1 (4.2%)	1 (3.8%)		
G4	1 (4.2%)	0		
G5	1 (4.2%)	0		

(Pearson chi-square test used; p-value <0.05 is significant)

The table 2 shows the gravida comparison among the participants. Most of the patients (78%) came under primi gravida in both the groups and was found statistically significant.

Table 3: Booked Status

Booked	Labetalol	Nifedipine	χ2	p-value
Yes (n=17)	9 (37.5%)	8 (30.8%)	.25	0.76
No (n=33)	15 (62.5%)	18 (69.2%)		

(Fisher's exact test used; p-value <0.05 is significant)

The proportion of non-booked mothers were higher in both groups. The same is depicted in table 3. This is a serious note as it might have remained a risk factor in causing this condition.

There was no statistically significant difference as evident from Fisher's exact test. ($p>0.05$)

Table 4: Proteinuria

Variables	Labetalol	Nifedipine	χ2	p-value
Proteinuria			2.8	0.27
1+ (n=19)	12 (50%)	7 (26.9%)		
2+ (n=15)	6 (25%)	9 (34.6%)		
3+ (n=16)	6 (25%)	10 (38.5%)		

(Fisher's exact test used; p-value <0.05 is significant)

The mothers with proteinuria ranging 1+, 2+ and 3+ were included comparably in both the groups and shown in table 4. There was no statistically significant difference as evident from Fisher's exact test. ($p>0.05$)

Secondary outcomes of this study were displayed in table 5. Pearson's chi-square and Independent t-test were applied here. The maternal attributes like need for induction with Cervi prime gel, time interval between induction and delivery in addition to the mode of delivery were similar between the groups. ($p>0.05$)

The fetal attributes like NICU admissions, adverse fetal outcomes although varied between the groups, was not observed to any statistical significance. ($p>0.05$)

The interval between induction and delivery averaged 13.8 ± 7.5 and 13.5± 7.7 minutes respectively in labetalol and nifedipine group. The average birth weight was 2.2 ± 0.4 and 2.4 ± 0.5 kg in the above groups respectively. There was no statistically significant difference among the groups. ($p>0.05$).

Table 5: Comparison of secondary outcome

Variables	Labetalol	Nifedipine	χ2	p-value
Induction with Cervi prime gel [a]				
Given (n=49)	24 (100%)	25 (96.2%)	.94	.33
Not Given (n=1)	0	1 (3.8%)		
Mode of delivery [a]				
NSVD (n=25)	13 (54.2%)	12 (46.2%)	.32	.57
LSCS (n=25)	11 45.8%)	14 (53.8%)		
NICU admissions [a]				
Yes (n=19)	10 (58.3%)	9 (34.6%)	.26	.61
No (n=31)	14 (41.7%)	17 (65.4%)		
Fetal outcomes [a]				
Alive (n=49)	23 (95.8%)	26 (100%)	1.1	.48
Dead (n=1)	1 (4.2%)	0		
Adverse effects [a]				
Present (n=9)	4 (16.7%)	5 (19.2%)	.06	.81
Absent (n=41)	20 (83.3%)	21 (80.8%)		

	Mean	SD	Mean	SD	t-value	p-value
Interval between induction & delivery (minutes)	13.8	7.5	13.5	7.7	.13	.89
Birth Weight (in kg)	2.2	0.4	2.4	0.5	1.4	.14

(NSVD- Normal Spontaneous Vaginal Delivery, LSCS- Lower Segment Caesarean Section)
(A indicates Pearson Chi-square test used; b indicates Independent t-test used; p-value <0.05 is significant)

Table 6: Birth Weight

Birth Weight (In Kgs)	Labetalol	Nifedipine	χ2	p-value
VLBW (<1.5)	3 (12.5%)	1 (3.8%)	2.2	.31
LBW (<2.5)	14 (58.3%)	13 (50%)		
Normal	7 (29.2%)	12 (46.2%)		

(VLBW- Very Low Birth Weight, LBW- Low Birth Weight)
(Fisher's exact test used; p-value <0.05 is significant)

In this study the proportion of children who were born as low birth weight were seen slightly high in the labetalol group than the nifedipine group (Table 6). However, this difference was not statistically significant. (p>0.05).

Table 7: Birth Weight & NICU admissions

		Labetalol	Nifedipine	p-value
Birth Weight <2.5 kg	**NICU admissions**			
	Yes (n=15)	10 (58.8%)	6 (42.9%)	.37
	No (n=16)	7 (41.2%)	8 (57.1%)	
Birth Weight ≥2.5 kg	**NICU admissions**			
	Yes (n=16)	7 (100%)	9 (75%)	.14
	No (n=3)	0	3 (25%)	

(NICU- Neonatal Intensive Care Unit)
(Pearson Chi-square test used; p-value <0.05 is significant)

The relationship between low birth weight and NICU admissions of the two groups were analysed and the distribution was similar which further prongs that there are no significant adverse effects due to the drugs on the fetal outcomes**.** (Table 7). In table 8 the relationship between maternal overweight and mode of delivery was assessed and compared between the groups. There was no difference observed between the groups. (p>0.05).

Table 8: BMI & Mode of Delivery

		Labetalol	Nifedipine	p-value
BMI <30	**Mode of delivery**			
	NSVD (n=15)	5 (45.5%)	6 (75%)	.35
	LSCS (n=16)	6 (54.5%)	2 (25%)	
BMI ≥ 30	**Mode of delivery**			
	NSVD (n=14)	8 (61.5%)	6 (33.3%)	.11
	LSCS (n=17)	5 (38.5%)	12 (67.7%)	

(Pearson Chi-square test used; p-value <0.05 is significant)

Overall both the drug groups required 2.4 ± 1 and 2.5 ± 0.7 doses respectively to achieve the target blood pressure of 140/90. In addition, the maternal and fetal outcomes of the both these drugs were identical as evident from the insignificant difference uncovered from the statistical test results.

4. Discussion

Labetalol and nifedipine have arose as drug of choice for hypertension disorders in pregnancy. A recent online survey found intravenous labetalol as the first choice (57%) followed by hydralazine (33%) and nifedipine (9%) [8]. In 2004, Heazell *et al*. found 90% were using hydralazine and only 7% and just over 2% were using labetalol and nifedipine, respectively [9]. Even though nifedipine is low-priced, widely available and can be administered with ease, the usage pattern shows a strong preference for labetalol and a confidence deficit for oral nifedipine among physicians. Both intravenous labetalol and nifedipine are associated directly with many other antihypertensive agents for hypertensive crises during pregnancy; yet, their direct comparison with each other is inadequate to a very few RCTs [7, 10-15].

Principal outcomes (number of doses and time taken to lower BP) studied by Shi *et al*. are of little clinical relevance, as relative differences in these parameters alone cannot guide clinical practice. Functional outcomes that are important to both women and fetus, such as persistent hypertension, stroke, placental abruption, fetal heart rate (FHR) abnormalities and perinatal mortality, have not been studied [15]. Shekar *et al*., found that oral nifedipine was associated with significantly reduced risk of persistent hypertension, lesser maternal side effects and neonatal death rate [12]. Zulfeen *et al*., found nifedipine to control blood pressure more rapidly [16]. Sridharan *et al*. did a network meta-analysis and trial sequential analysis of the RCTs on drugs for treating severe hypertension in pregnancy. This study concluded a similar efficacy between nifedipine, hydralazine and labetalol in the treatment but reported the quality of evidence was low [17]. While Lakshmi *et al*. concluded labetalol may be more effective in achieving the target control with lesser number of doses [13]. Vermillion *et al*., found that target blood pressure was achieved better with the oral nifedipine and more rapidly effective and required fewer

drug doses compared with an intravenous labetalol [7].

Cochrane study on drugs for the treatment of pregnancy related hypertension disorders determined that until better evidence is available, the antihypertensive drug of choice should depend on clinician's experience and knowledge of the drug such as efficacy and safety outcomes [6].

Our study showed that oral nifedipine and intravenous labetalol had similar rapidness of drug activity, and a similar number of doses to achieve blood pressure control. However, Vermillion used a higher oral nifedipine dose (10 mg initially, then 20 mg for a further four doses, as required; we used a 10 mg nifedipine dose throughout) and an intravenous labetalol regimen of 20, 40, 80, 80 and 80 mg (similar to our study). Vermillion's patients had higher initial systolic (>170 vs >160 mmHg) and diastolic blood pressure readings (>105 vs >100 mmHg), compared with our blood pressure inclusion criteria at enrolment. His target systolic blood pressure readings were higher, but the target diastolic blood pressure readings were like ours (<160 and <100 vs <150 and <100 mmHg). At enrolment, all our patients were undelivered, whereas Vermillion included postpartum subjects [7].

For seizure prophylaxis, magnesium sulphate infusion is used in women with severe pre-eclampsia, as supported by Magpie trial [18]. Therefore, it is important to study the possible interaction between antihypertensive agents and magnesium sulphate. During hypertensive pregnancies, severe hypotension, neuromuscular blockade and symptomatic hypocalcaemia were seen when nifedipine was used alongside with magnesium sulphate infusion [19-22]. In Magpie trial of 10, 141 women with preeclampsia, 3029 women were treated with nifedipine after entering the trial. This much larger data proposes that the overlying of exposure to nifedipine and magnesium sulphate is well tolerated [18].

Our data show that both oral nifedipine and intravenous labetalol are effective in controlling severe hypertension in pregnancy. Both were effective, with the target blood pressure achieved in most of cases within four doses or within 60 minutes of commencing treatment. No major adverse effects were noted in either of the drugs. No cross over treatment of drugs were found in our study as compared. Our data supports recent protocol that oral nifedipine and intravenous labetalol are ideal first line drugs for pregnancy related hypertension disorders [3]. We established a target blood pressure of <150/100 mmHg for our patients, with stoppage of doses once the target is achieved, and with maintenance therapy typically starting 2 hours later.

Our study population is varied as we included patients with pre-eclampsia and non proteinuric pregnancy-induced hypertension, but all had sustained severe hypertension of pregnancy that needed immediate blood pressure control.

A systematic review and meta-analysis study showed that oral nifedipine was related with significantly reduced (58% risk reduction) risk of persistent hypertension. However, no difference was noted in the maternal morbidity between the two groups. One maternal death was reported in five trials included for analysis. Meta-analysis showed significantly fewer maternal side effects with nifedipine. The results varied minimally between studies when risk difference was used as the summary statistic. With respect to caesarean section analysis, no significant difference in the caesarean section rates with use of either drug [23]. FHR abnormalities & intrauterine fetal death showed no statistical difference between two groups. The risk of neonatal death was significantly reduced with nifedipine compared with labetalol. Regarding NICU admission, analysis showed a favourable trend towards nifedipine. However, both neonatal death and NICU admissions did not reach statistical significance [23].

5. Conclusion

Both nifedipine and labetalol are equally effective, safe and well tolerated in controlling blood pressure in pregnancy related hypertension disorders. Control of blood pressure, preventing as well as reducing maternal and fetal complications and expedited delivery if indicated are the mainstay of management.

Intravenous labetalol provided a smooth and steady reduction in blood pressure. Whereas, nifedipine can be ideal since a simple oral dose is needed in achieving target values and its use may be recommended in low resource settings as dosage is simple and flat when compared to incremental intravenous dosing of labetalol.

To conclude, both intravenous labetalol and oral nifedipine are equally successful and can be used as first line drugs for the use in acute blood pressure control of hypertensive emergency of pregnancy.

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