International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

A Comparative Study of Oral Nifedipine and Oral Labetalol in the Treatment of Pregnancy-Induced Hypertension

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Abstract: ***Background: Hypertensive disorders of pregnancy impact on maternal and neonatal mortality and morbidity. Various anti-hypertensive drugs have been used such as methyldopa, nifedipine, labetalol and hydralazine for treatment of pre-eclampsia. Aim: To compare the efficacy and safety of oral Labetalol with oral Nifedipine in the management of pre-eclampsia. Methodology: This is a longitudinal study in which 100 pregnant women diagnosed with pregnancy induced hypertension in severe pre-eclampsia in labour room were enrolled. Patients were given Nifedipine 10mg stat orally and BP was checked every 5min and repeat dosing was considered after 15-20min. Similar method was followed for oral Labetalol but with a dose of 100mg and BP was checked every 5min till target BP was achieved. Patients of both the groups were observed in the hospital till delivery. Results: In the present study there is a significant decline rate in diastolic BP in both the groups (p<0.05). But, the group that received oral Labetalol showed more decline rate (13.5%) as compared to the group receiving oral Nifedipine (13.2%). Conclusion: Hypertensive disorder of pregnancy is one of the life-threatening complication encountered in obstetrics and globally is major cause of maternal morbidity and mortality. Management of acute severe hypertension in pregnancy is challenging. Present study compares the efficacy and safety profile of oral Nifedipine and oral Labetalol in reaching the therapeutic goal. From the results of the study, we can conclude that oral Labetalol is more efficacious.***

Keywords: Labetalol, Nifedipine, Hypertension, Pregnancy, Pre-eclampsia

1. Introduction

Hypertensive disorders of pregnancy are one of the standard medical disorders having effects on both the expectant mother and the fetus.[1-3] The resultant impact on maternal and neonatal mortality and morbidity is very high in India and other developing countries.[4-5] The incidence of pregnancy-induced hypertension in India is about 10% of all antenatal admission.6 Pre-eclampsia is a disease of multiple organ system that is related to pregnancy and can cause maternal complications like eclampsia, HELLP syndrome, acute renal failure, cerebrovascular accidents, etc. It has effects on the fetus also like intra-uterine growth restriction, oligohydramnios and fetal distress.7[-10] In treating hypertension in pregnancy priority should be given to making the correct diagnosis to distinguish pre-existing [chronic] hypertension from pre-eclampsia or gestational hypertension. Then is to distinguish blood pressure levels as either mild [140/90 mmHg to 159/109mmHg] or severe [>160/110mmHg] rather than as stages. Definitive management here is the termination of pregnancy which cannot be done due to pre-maturity. It is therefore important to prolong the pregnancy till fetal survival is good. To achieve this, various anti-hypertensive drugs have been used such as methyldopa, nifedipine, labetalol and hydralazine. Many trials have been conducted so far to compare the efficacy of these drugs but each has its own risks and benefitsand no drug is superior to the other.

The efficacy of the drug controlling the high blood pressure is important in preventing complications both for the mother and the fetus.2At the same time the adverse effects of these agents on mother and fetuses is also important. The effect of maternal anti-hypertensive use during pregnancy on fetal growth and well-being remains uncertain. Meta-analysis of RCTs has highlighted the possible association between anti-hypertensive therapy and both IUGR and SGA baby. Multiple drug therapy had the strongest association with these events.4Gestational use of anti-hypertensive especially beta blockers, alpha-beta blockers or centrally acting adrenergic agents may increase the incidence of SGA births.[5]

Nifedipine is a calcium channel blocker and has been commonly used in India to treat pre-eclampsia. As per its name, it inhibits the influx of calcium ions to vascular smooth muscles resulting in arteriolar vasodilation. It is administered orally and is cost-effective. However it has side-effects like sudden unpredictable fall of blood pressure and cardiac side-effects. On the contrary labetalol, a beta blocker, has arteriolar vasodilating action that lowers blood pressure by lowering peripheral vascular resistance. It gives better control of BP with very little side-effects. It is now being considered the first-line drug in the management of pre-eclampsia.

2. Aims & Objectives

To compare the efficacy and safety of oral nifedipine with oral labetalol in the management of pre-eclampsia in relation to control of BP, time and number of doses required to lower the BP, adverse effects of drugs and maternal and perinatal outcome.

3. Methodology

The present study was a longitudinal study conducted in the Department of Pharmacology in collaboration with the

Department of Obstetrics and Gynaecology, VIMSAR, Burla from June 2022 – November 2022. The study was initiated after due approval from institutional ethics committee 044-2022/I-S-O/18/Dt 17.05.2022.

Inclusion criteria: All pregnant women diagnosed with severe pre-eclampsia presenting to labour room were enrolled in the study with diastolic BP either persistently 100mmHg or >100 mmHg.

Exclusion criteria:

1) Essential hypertension/ Pre-existing hypertension
2) Cardiac disease
3) Bronchial asthma
4) Hematological disorders
5) Allergy to labetalol/nifedipine
6) Diabetic
7) Liver disease

After taking informed consent, enrolled patients were recruited to receive either oral labetalol or oral nifedipine as per physician's prescription. A total sample size of 100 was taken. Patient details were entered into a preformed proforma.

Patients recruited to the oral nifedipine group were given 10mg stat dose and BP was checked every 5 minutes till the target BP was achieved. A second dose was given if there is no fall in BP after 15-20 minutes. Nifedipine was never given sub-lingually. The time required to reach the target BP and the number of doses required were noted.

Patients recruited to the oral labetalol group were started with 100mg stat dose and BP was checked every 5minutes till target BP was achieved. Additional 100mg dose was given if required. The time required to reach the target BP and the number of doses required were noted.

Patients belonging to both the groups were observed in the hospital till delivery occurred. If the gestational age was >34weeks with worsening clinical condition, termination of pregnancy was done. If gestational age was 28-34 weeks two doses of Betamethasone 12mg was given 24 hours apart for fetal lung maturity. At term, pregnancy was terminated by either vaginal delivery or LSCS.

4. Observation & Results

Table 1: Distribution of cases according to age group

Age	Nifedipine		Labetalol		P value
	No	%	No	%	
Upto 20years	10	20	11	22.6	0.465
21-25 years	25	50.6	24	48	
26-30 years	11	21.4	10	20	
>30 years	4	8	5	9.4	
Total	50	100	50	100	
Mean± SD	23.68±4.32		23.91±3.74		

Table 1 shows the maximum number of patients in the labetalol and nifedipine group belonged to age group 21-25 years. The difference was found to be statistically non-significant [p>0.05].

Table 2: Distribution according to gravid status

Parity	Nifedipine	Labetalol
G_1	25 [50%]	33 [66%]
G_2	14 [28%]	12 [24%]
G_3	10 [20%]	2 [4%]
>G_3	1 [2%]	3 [6%]

Value of χ^2 = 7.591, P=0.0553, not-significant

As shown in the table 2 both the groups had maximum percentages of primigravida cases, 3rd gravida and more were negligible. After applying Chi-square test there is no significant difference between the gravid status of both the groups.

Table 3: Distribution of cases according to gestational age

Gestational age [weeks]	No of patients	
	Nifedipine	Labetalol
28-32	7	14
33-36	27	25
>37	16	11
Mean	34.23	33.51

Value of χ^2 =3.3362, P=0.188607, not significant

In the above table 3 both the groups had maximum number cases in between 33-36 weeks of gestational age. While the nifedipine group had slightly more number of cases in the>37 weeks of gestational age group, the labetalol group had comparatively more cases in 28-32 weeks gestational age group. But the difference was statistically not significant i. e. comparable.

Table 4: Comparison of mean Diastolic BP pre and post medication

Measures	Nifedipine group			Labetalol group		
	Pre	Post	Decline rate	Pre	Post	Decline rate
Mean±SD	104.6±11.25	90.8±10.31	13.2%	104±10.26	90±11.06	13.5%
Max	120	100		130	100	
Min	90	80		100	80	

In the above table 4 by applying student's paired t-test there is a significant decline rate in diastolic BP in both groups [p<0.05]. But group labetalol showed more decline rate as compared to the nifedipine group.

Table 5: Distribution of cases according to maternal complications

Complications	Nifedipine group	Labetalol group
Imminent eclampsia	5	3
HELLP	4	3
Abruptio placenta	2	1
CVA	0	0
Renal failure	2	1

As shown here in table 5, 13 out of 50 cases in the nifedipine group had complications, whereas only 8 cases reported complication in the labetalol group.

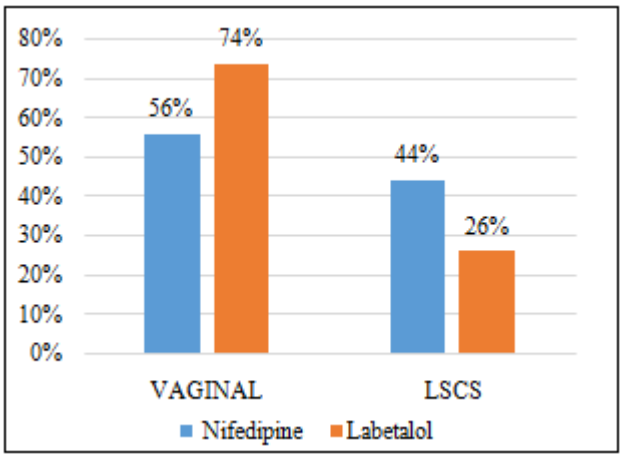

Figure 1: Distribution of cases according to the mode of delivery (N=100)

Figure 1 shows the comparison of the mode of delivery for the groups. In the nifedipine group higher number of women underwent LSCS while in the labetalol group majority of women had undergone normal vaginal delivery. The difference was found to be statistically significant [p<0.05].

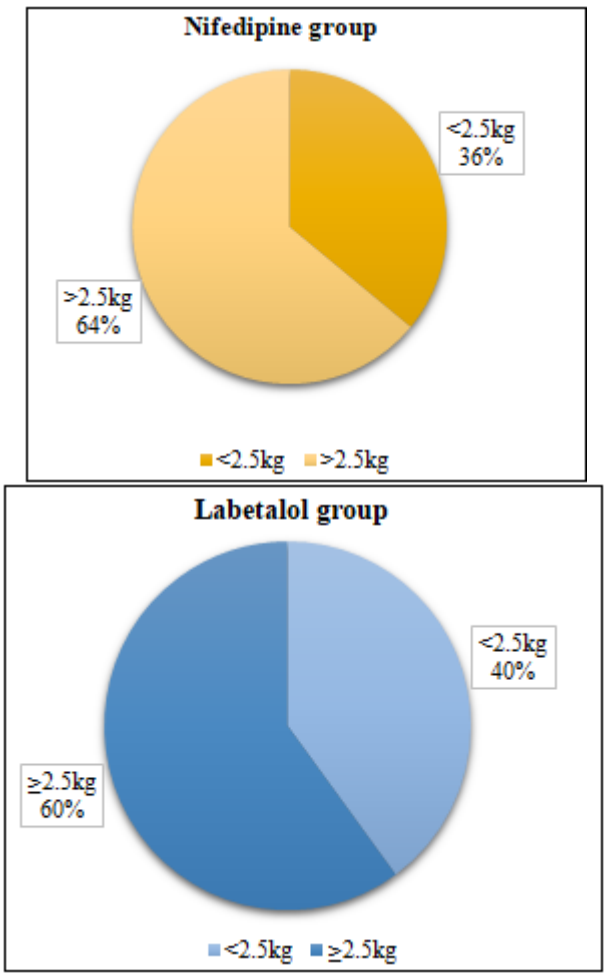

Fig 2. Distribution of cases according to birth weight

[P>0.05]

Comparison of birth weight was not statistically significant.

Table 6: Distribution of cases according to neonatal outcome

Neonatal outcome	Nifedipine group	Labetalol group
RDS	3	1
Jaundice	2	2
Hypoglycemia	1	0
SGA	1	1
Still birth	4	2

There was no significant difference between both the groups in terms of perinatal morbidity [p>0.05]. However, need for NICU admissions were seen more in the nifedipine group.

5. Discussion

The maximum number of patients in both the groups belonged to the age group 21-25 years and were primigravida. Similar results were obtained in studies of Shekhar et al. [2013][11]and Hangarga US et al. [2016][12]. Most of the patients were between 33-36 weeks of gestational age. Hangarga US et al. [2016][12] study had maximum patients belonging to gestational age 35-40 weeks.

In our study we compared the fall in diastolic BP in both the study groups which showed a significant difference. The fall in mean diastolic BP was 13.8 mmHg inthe nifedipine group and 14.0 mmHg in the labetalol group and was statistically significant.

Michael et al. [1982][13]and Stott et al. [2016][14] conducted studies on women with severe hypertension complicating pregnancy with oral labetalol and found that effective control of BP was achieved in maximum patients.

Scardoet al. [1996][15]evaluated the effects of oral nifedipine in pre-eclamptic patients and concluded that oral nifedipine was an effective anti-hypertensive agent.

Jorge Duro-Gomez et al. [2017][16] did an observational retrospective cohort study, included all pregnant women diagnosed with pre-eclampsia and were treated with oral nifedipine or oral labetalol. His findings were consistent with the current study.

The rate of LSCS for uncontrolled pregnancy induced hypertension was less in labetalol group compared to nifedipine group. The results in the current study are comparable to the study done by Raheem et al., Hangarga US et al, Thakur et al. stating that LSCS rate was higher in the nifedipine group.

Giannubiloet al. [2012][17]conducted a retrospective study in hypertensive patients treated during pregnancy with nifedipine or labetalol by monitoring maternal and fetal outcomes and found that there was higher incidence of IUGR babies in the labetalol group [p<0.05].

Present study showed insignificant difference in perinatal death. Nifedipine group had 4 cases of still birth whereas labetalol group had 2 such cases. All the babies who succumbed to death were extremely low birth weight with

baby weight <1.5kg. These findings were comparable to the study of Hangarga US et al. [2016][12].

The various maternal complications faced in this study are-

1) Incidence of severe hypertension [imminent eclampsia] was 6% in labetalol group compared to 10% in nifedipine group.
2) HELLP syndrome was seen in 8% cases of nifedipine group compared to 6% of labetalol group.
3) 4% cases had placental abruption in nifedipine group as compared to 2% cases in labetalol group.
4) 4% cases of renal failure was seen amongst nifedipine group.
5) Nil case of CVA/ maternal death was reported.

The study of Dhali B et al. [2012][18] comparing labetalol and nifedipinehad a little bit higher incidence of eclampsia in the labetalol group compared to our study.

Limitations: This a single centre based observational study having a small sample size with a short follow-up period.

6. Conclusion

The present study was a prospective observational study where the effects of oral nifedipine and oral labetalol were compared in patients with pregnancy induced hypertension. Even though nifedipine achieved the target BP more rapidly and with fewer initial doses than labetalol, it was found that overall labetalol was more effective. Regarding the side-effects, labetalol had very few side-effects compared to nifedipine. Due to more side effects, decreased patient compliance and patient satisfaction was seen with nifedipine. Thus, the present study concludes that labetalol seems to be a better alternative and is considered as a first line drug for the management of pre-eclampsia. In conditions where labetalol is contra-indicated, nifedipine is used for lowering the BP.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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