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A Longitudinal Study of Nifedipine Versus Labetalol in Hypertension in Pregnancy at A Teritiary Hospital

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Abbreviations

ACOG - American College of Obstetrics and Gynaecology

sFlt-1 - Soluble Fms-Like Tyrosine kinase-1

VEGF - Vascular Endothelial Growth Factor

PlGF - Placental Growth Factor

ET-1 - Endothelin-1

ROS - Reactive Oxygen Species

NO - Nitric Oxide

RBF - Renal Blood Flow

GFR - Glomerular Filtration Rate

DIC - Disseminated Intravascular Coagulation

FGR - Fetal Growth Restriction

NICE - National Institute for Health and Care Excellence

MTHFR - Methylenetetrahydrofolate reductase

CNS - Central Nervous System

FDA - Food and Drug Administration

IUGR - Intrauterine Growth Restriction

A-V - Arterio-Venous

SA - Sinoatrial

AV - Atrioventricular

COPD - Chronic Obstructive Pulmonary Disease

NICU - Neonatal Intensive Care Unit

PRES - Posterior reversible encephalopathy syndrome

ICU - Intensive Care Unit

Introduction

Pregnancy is complicated by hypertensive disorders to up to 5-10% **[**1**]**. Preeclampsia is seen in 3.9% of pregnant women **[**1**]**. It forms a lethal triad along with infection and haemorrhage, contributing to rise in rate of morbidity and mortality. Most commonly used medications for hypertension in pregnancy are oral labetalol and oral nifedipine **[**2**]**. Insufficient data on the efficacy of routinely used antihypertensive drugs may result in subpar treatment of hypertension in pregnancy **[**3**]**.

Etiopathogenesis includes Primigravida women exposed to significant number of chorionic villi, pre-existing conditions like vascular disease and a genetic predisposition.

In pre-eclampsia there is deficient endothelial nitric oxide synthase activity, which causes cell permeability to increase and thereby causing damage to endothelium. In some cases there may be endangering thrombocytopenia caused by platelet activation and coagulopathy.

Antihypertensive therapy should ideally be initiated only when blood pressure is more than or equal to 140/90mmHg. The optimal blood pressure antenatally should be 135/85 mm Hg. Cardiovascular disorders later in life maybe a result of having a history of hypertension in pregnancy.

According to the National Institute for health and care excellence guidelines (2010) Labetalol is the first line treatment, followed by Nifedipine **[**4**]**

Aim and Objectives

Aim:

To assess the efficacy of Labetalol and Nifedipine in hypertension in pregnancy

Objectives

1) To study the efficacy of Labetalol and Nifedipine in the controlling blood pressure in hypertension in pregnancy
2) To study the effects of Labetalol and Nifedipine on proteinuria
3) To study the maternal and foetal outcomes of pregnant women treated with anti-hypertensive drugs Labetalol and Nifedipine

Methodology

a) Study settings: Govt. Lady Goshen Hospital and KMC Hospital, Attavar.

b) Study design: Comparative prospective longitudinal study

c) Study participants: Antenatal women diagnosed with hypertension more than 20 weeks of gestation requiring Nifedipine and Labetalol drug therapy

d) Inclusion criteria:

All antenatal women diagnosed with hypertension more than 20 weeks period of gestation requiring the above-mentioned drugs. Patients will be followed up till date of discharge.

e) Exclusion criteria:

1) Patients on other hypertensive drugs other than the above-mentioned drugs
2) Patients who are a known case of Bronchial asthma/COPD
3) Cardiac failure
4) Chronic hypertension

f): Study duration: One and half year after ethical committee clearance

g) Sample size:

$$n = \frac{(Z\alpha\sqrt{2pQ} + Z\beta\sqrt{p1q1+p2q2}\ )^2}{(p1-p2)^2}$$

$$Z\alpha = 1.96\ AT\ 95\%$$

$$Z\beta = 0.84\ at\ 90\%\ power$$

$$P = \frac{p1+p2}{2} \qquad q = 100\text{-}p$$

p1=Proportion of 1st sample *q1= 100-p1*

p2- proportion of 2nd sample *q2= 100-p2*

With 95% CL and 88% power with respect to Thakur et al; the sample size comes to be 200

h) Sampling method:

Universal sampling

i) Outcome variables:

A proforma, excel sheet, patient information sheet, informed and written consent was taken. Patients diagnosed with hypertension more than 20 weeks of gestation was followed up till delivery. The patients were categorised into Group A & Group B. Group A being individuals prescribed Tablet Nifedipine 30–120 mg/day orally of a slow- release preparation. Group B consisting of individuals were started on Tab. Labetalol 200–2,400 mg/day orally in 2-3 divided doses. Patients were sub grouped into: Number of individuals needing additional antihypertensives, number individuals needing intravenous antihypertensive, number of individuals needing Capsule Nifedipine. Blood pressures were monitored at intervals based on severity of blood pressure.

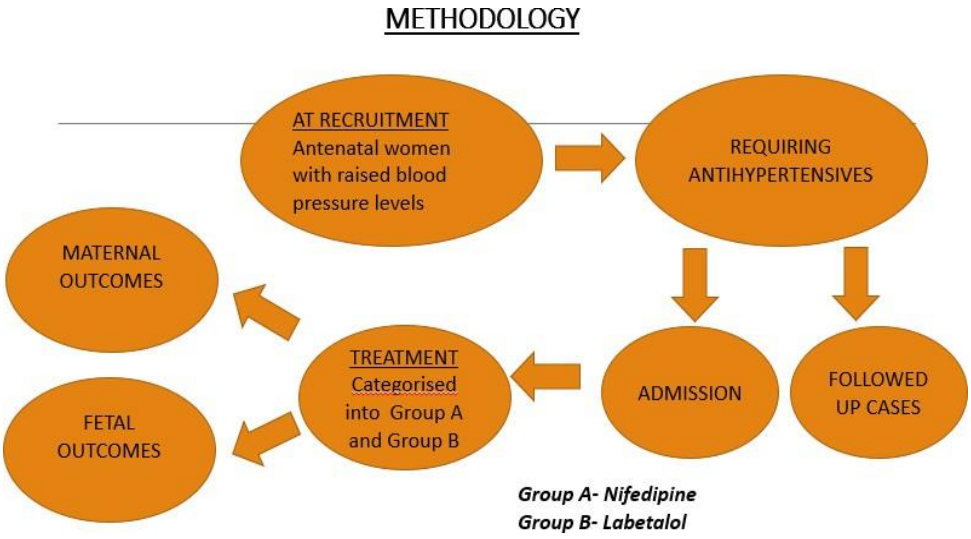
Blood pressures post treatment, Number of days of antihypertensives, dose of antihypertensives and the use of monotherapy or combined therapy were observed.

Maternal outcomes:

- Spontaneous labour/ Induced labour,
- Mode of delivery: Vaginal delivery or Caesarean section
- Eclampsia
- HELLP syndrome
- ICU admission – PPH

Fetal outcomes:

- Term/Preterm baby
- Birth weight
- NICU admission



i) Data analysis:

We used SPSS version 17.0 to do the analysis. If $P<0.05$ will be considered to be significant.

Chi square test will be done. A master excel sheet will be plotted and the data will be analyzed using various statistical methods:

1. For observational data: results will be indicated in percentages.
2. For categorical data: chi square test/ odds ratio will be used to prove significance.
3. For interval data: mean/ student T test/Z test will be used to prove significance.

j) Data collection tool:

Collecting data after taking consent from study participants using Performa.

Results

The total number of individuals studied was 200. 100 individuals from group Nifedipine and 100 individuals from group labetalol were studied. Factors studied include, age distribution, body mass index, parity, complications, mode of delivery, neonatal intensive care admission.

Age (years)	Nifedipine	Labetalol	Total (N=200)
<20	6 (6%)	5 (5%)	11
21-25	53 (53%)	57 (57%)	110
26-30	23 (23%)	20 (20%)	43
>30	18 (18%)	18 (18%)	36
Total	100	100	200

P=0.659

Table 1- Age distribution

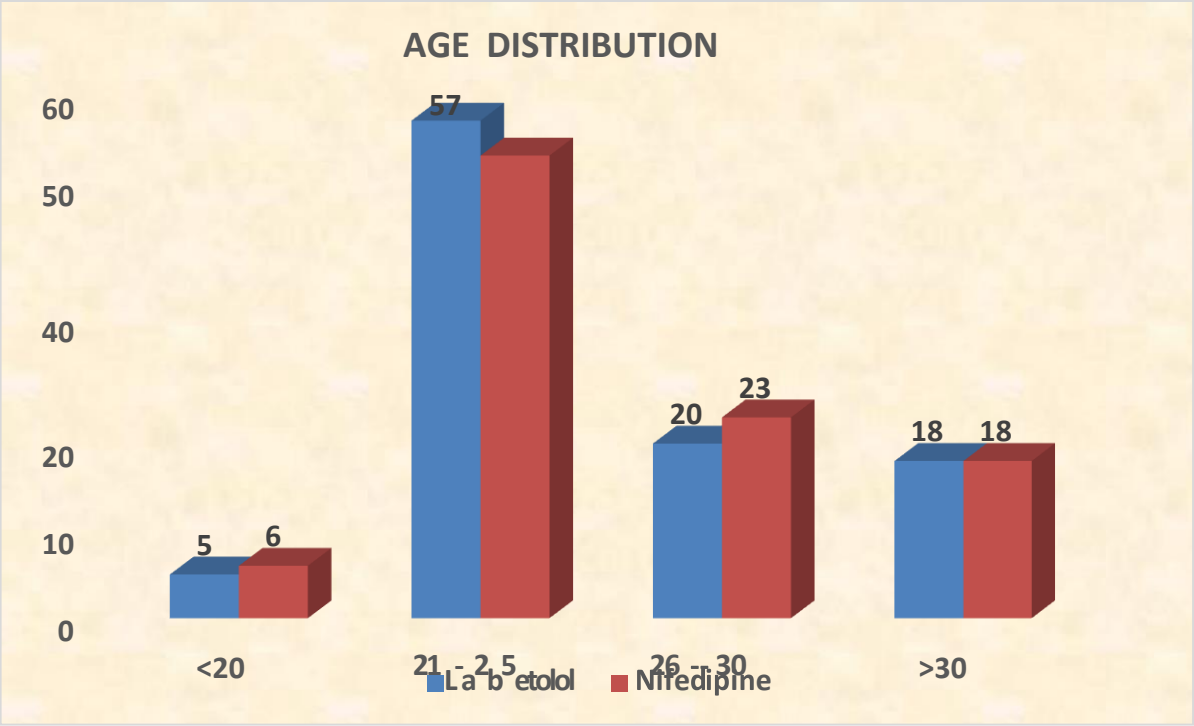


Figure 1

More than half of the sample size were young women aged 21-25 (Table no1). No significance noted.

Table 2

Drug group	Nifedipine	Labetalol	Total (N=200)
Primigravida	52 (52%)	51 (51%)	**103**
Multigravida	49 (49%)	48 (48%)	**97**
Total	100	100	**200**

P=0.777

Table 2- Parity

Just over half of the patients were Primigravida in both drug groups. Nifedipine group attributed to 52 % and Labetalol, 51%. The rest of the sample was multigravida.

Drug group	N=200	Mean BMI
Nifedipine	100	26.83
Labetalol	100	26.47

P= 0.384

Table 3- Body Mass Index

Front both drug groups, BMI was found be in the overweight range, no significance was noted.

Gestational at diagnosis(weeks)	Labetalol	Nifedipine	Total (N= 200)
25 – 29	5 (5%)	5 (5%)	10
30 – 36	37 (37%)	35 (35%)	72
37- 40	55 (55%)	58 (58%)	113
>40	3 (3%)	2 (%)	5

P= 0.977

Table 4- Gestational age at diagnosis

Gestational at delivery (weeks)	Labetalol	Nifedipine	Total (N=200)
25 – 29	2 (2%)	0	2
30 – 36	13 (13%)	8 (8%)	21
37 – 40	76 (76%)	82 (82%)	158
>40	9 (9%)	10 (10%)	19

Table 5- Gestational age at delivery

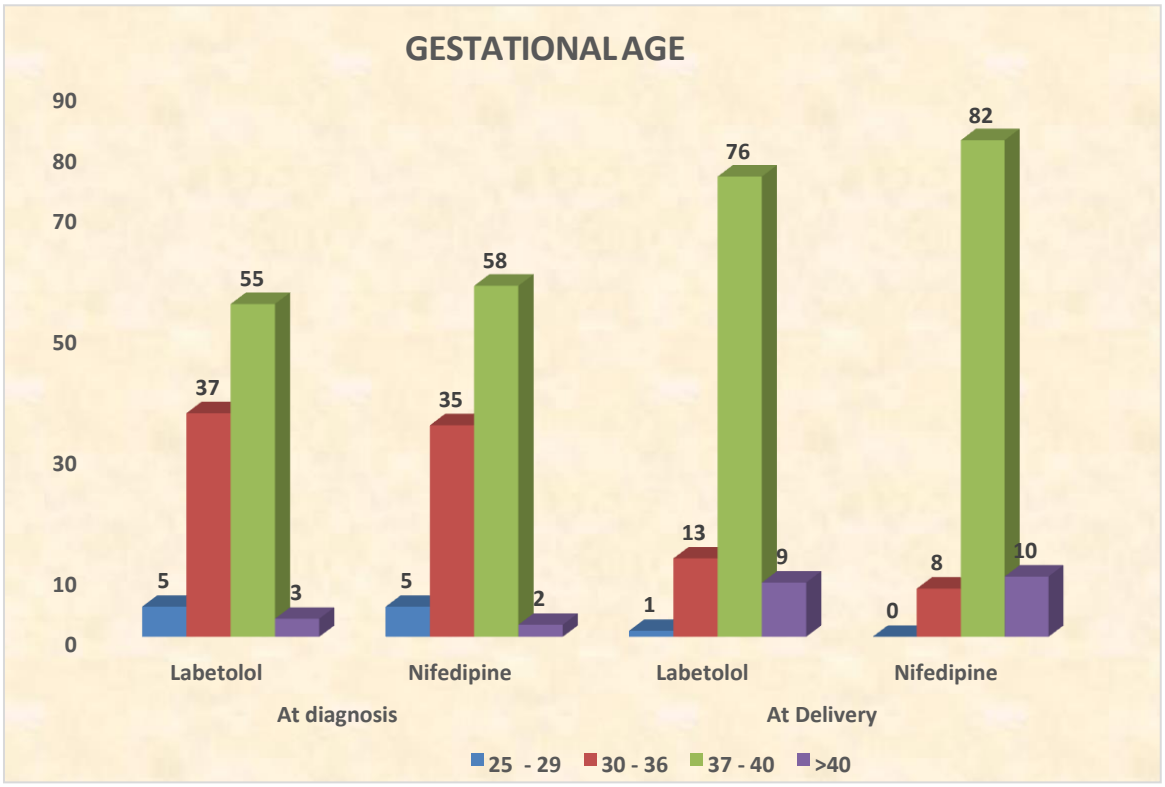


Figure 2

Just over half of the diagnosis was at term gestation seen in both drug groups (Table 3). Majority of the diagnosis at delivery was at term; 76 % were taking oral labetalol and 82%, were taking Nifedipine.

MAP	Group	Mean	P value
MAP 0 HOURS	Labetalol	135.20	
	Nifedipine	135.09	
MAP 6 HOURS	Labetalol	126.46	
	Nifedipine	125.75	P=0.067
MAP 12 HOURS	Labetalol	121.11	
	Nifedipine	122.56	P=0.012
MAP 24 HOURS	Labetalol	104.86	
	Nifedipine	107.70	P<0.001
MAP 48 HOURS	Labetalol	103.95	
	Nifedipine	105.41	P=0.002
MAP 72 HOURS	Labetalol	94.44	
	Nifedipine	94.48	P =0.917

Table 6

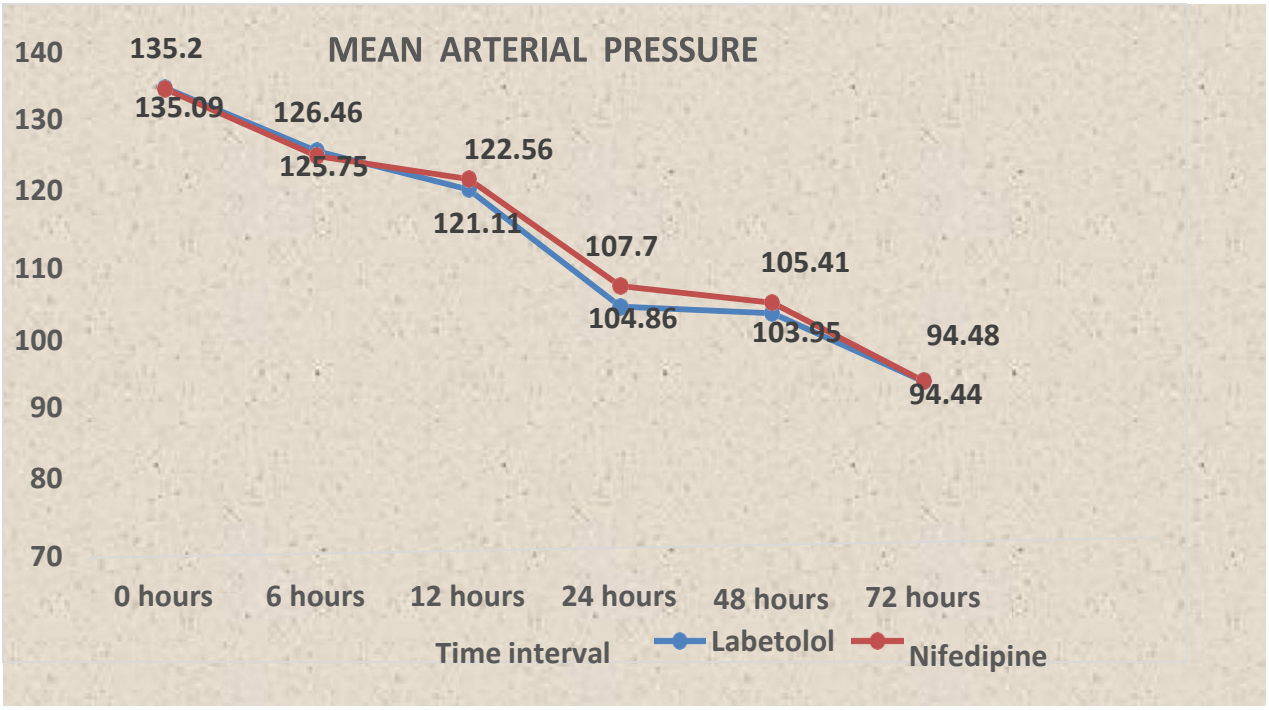


Figure 3

Mean arterial pressure in the first 6 hours after initiation of medication was 126.46 in group labetalol and 135.09 in group nifedipine. Labetalol was found to be statistically significant at 12, 24 and 48 hours after onset of medication depicted in the line diagram (Figure 4).

Urine Albumin	Nifedipine	Labetalol	
Absent	43 (43%)	37 (37%)	80 (40%)
+	31(31%)	34 (34%)	64 (32%)
++	18 (18%)	21 (21%)	39 (19.5%)
+++	8 (8%)	11(11%)	19 (9.5%)

P=0.826

Table 7- Proteinuria

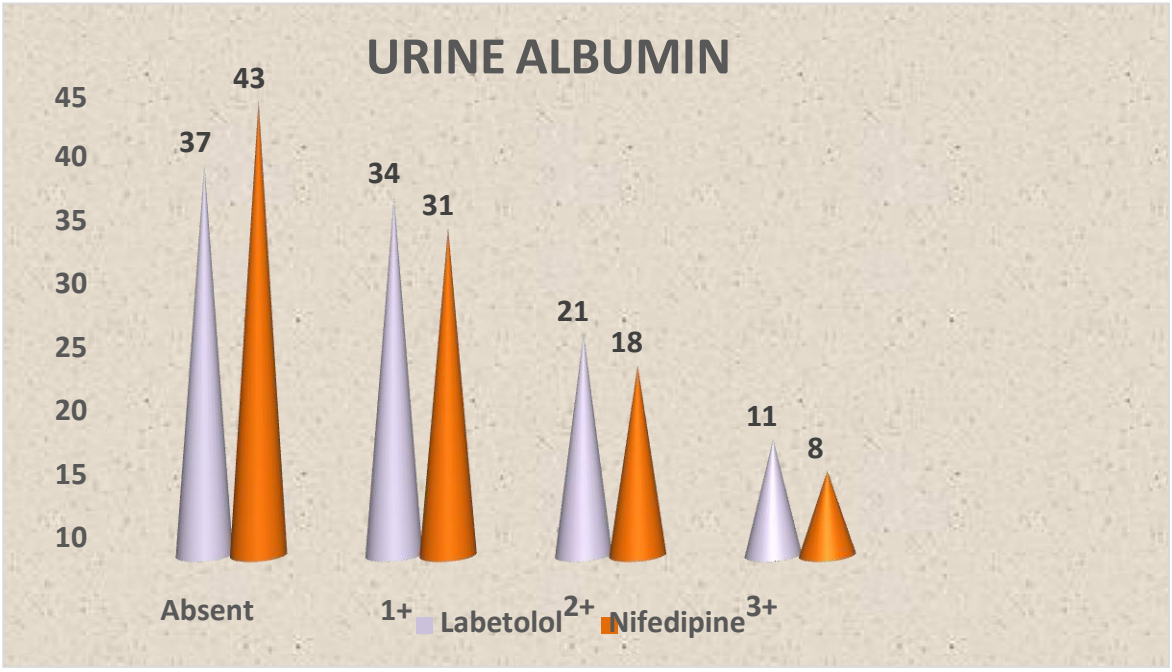


Figure 4 - Proteinuria

Proteinuria was noted in 57% of cases in Nifedipine group and 66% in Labetalol group. More number was noted in the Labetalol group than Nifedipine which not statistically significant (Table 6, Figure 5)

Complications	Nifedipine	Labetalol	Both drugs	Total (n)
Eclampsia	1	1	2	4
Abruptio placenta	1	-	2	4
HELLP syndrome	1	2	-	3
PRES syndrome	-	2	-	2
ICU admission	-	-	1	1

Table 8- Complications

Additional antihypertensive drugs

12 patients part of group Labetalol required additional Nifedipine. 8 patients from group Nifedipine group required Labetalol. 9 patients from group labetalol were given Intravenous labetalol for severe hypertension. 5 patients were given capsule Nifedipine. 6 patients from group Nifedipine were given Intravenous labetalol and 4 patients were given Capsule Nifedipine for the control of severe hypertension.

Hypertension related complications

4 patients had Eclampsia- 2 from group Labetalol, 1 from the Nifedipine group and 1 from the combined group. 3 patients had abruptio placenta, 2 of which were on both antihypertensive drugs. 1 patient was from the Nifedipine group. 3 patients developed HELLP syndrome. 2 patients on Labetalol and 1 patient on Nifedipine. 2 patients developed PRES syndrome both on Labetalol, one patient required ICU care for ionotropic support was on both antihypertensive therapies.

	Nifedipine	Labetalol	Total (n=200)
Elective LSCS	15 (15%)	11 (11%)	26
Induced	58 (58%)	61 (61%)	119
Spontaneous	27 (27%)	28 (28%)	55

Table 9- Mode of delivery

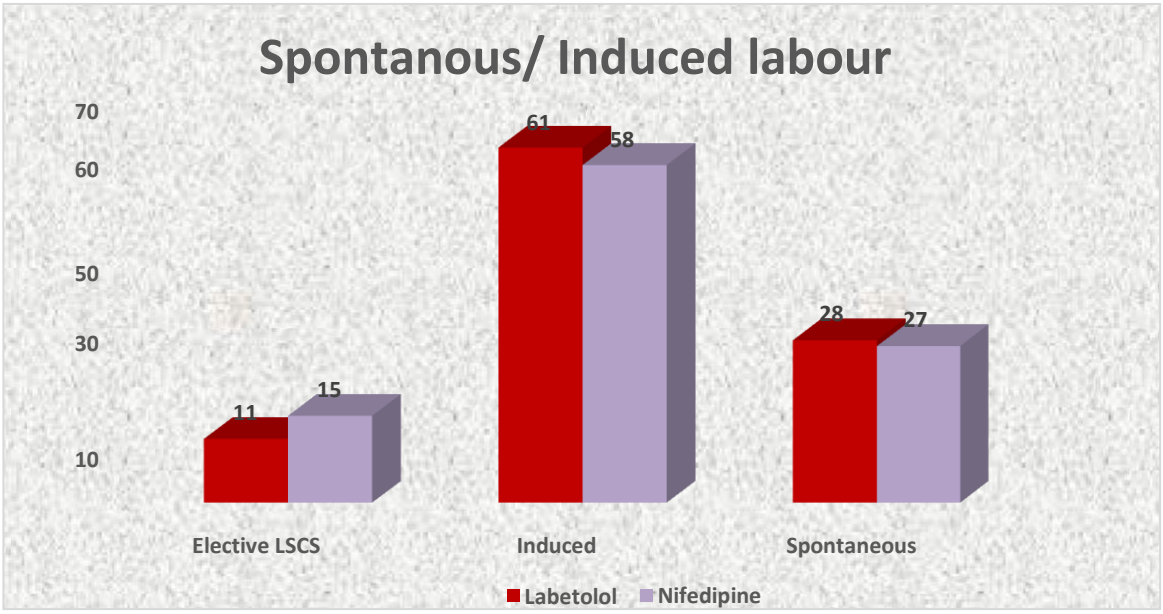


Figure 5- Mode of delivery

Elective LSCS was found to be 15% in Nifedipine group and 11 % in group labetalol. 58% of individuals were induced from the Nifedipine group and 61% form group labetalol. More number of individuals were found to be induced as compared to spontaneous labour.. (Table 7, Figure 6)

Mode of delivery	**Nifedipine**	**Labetalol**	**Total**
Elective LSCS	15 (15)%	11 (11%)	26
Emergency LSCS	15 (15%)	19 (19%)	34
Forceps assisted vaginal	2 (2%)	4 (4%)	6
Vaginal	68 (68%)	66 (66%)	134

p=0.619

Table 10- Mode of delivery

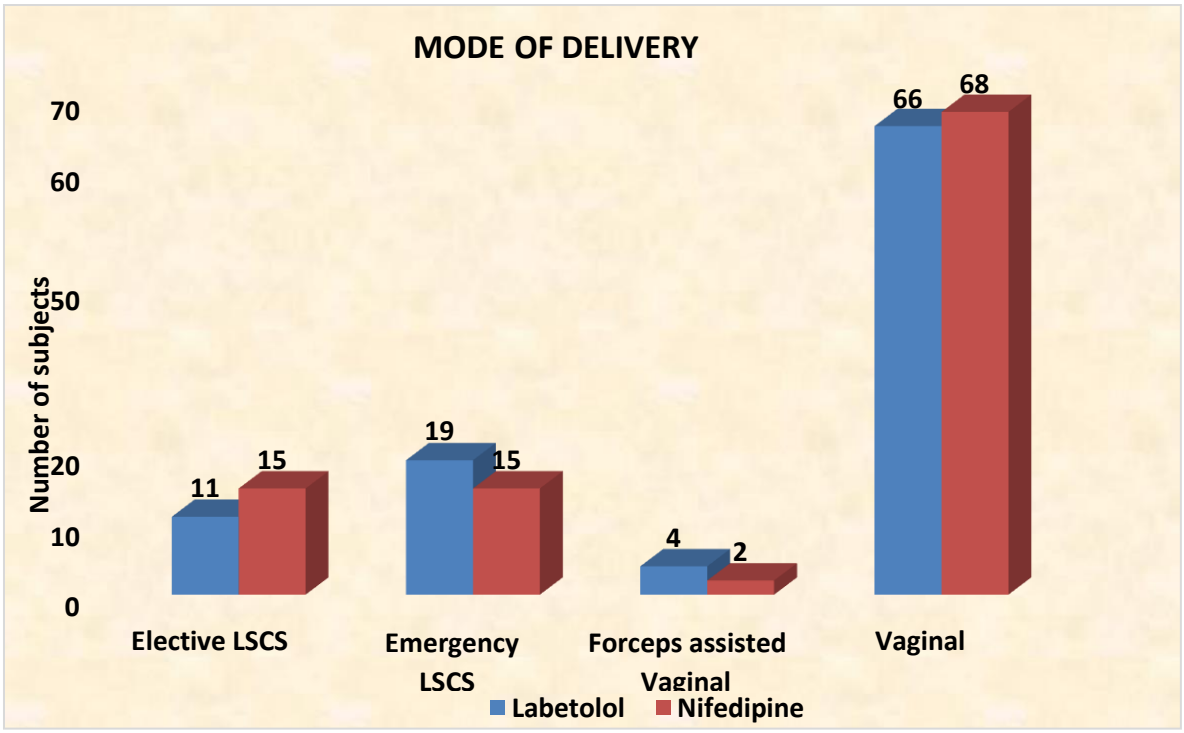


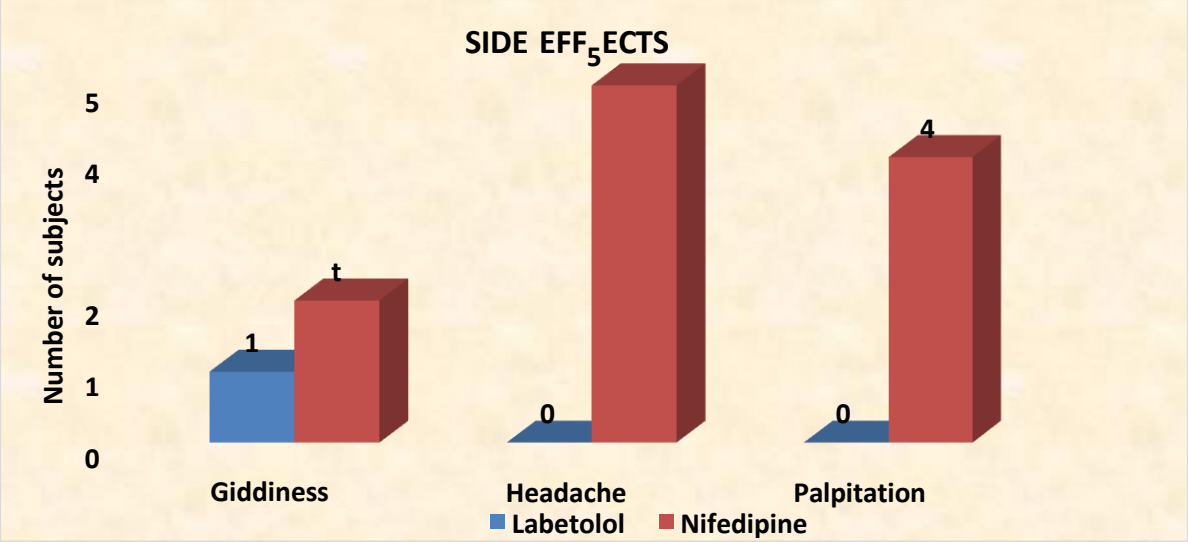
Figure 6

Total number of LSCS in was 30% in both drug groups (Table 9, Figure 7). Total number of vaginal delivery attributed to 68% in Nifedipine group and 66% in the Labetalol group (excluding forceps vaginal delivery).

Side effects	Labetalol	Nifedipine
Giddiness	1	2
Headache	-	5
Palpitations	-	4

P value= 0.02

Table 11- Side effects



Most common side effects were headache and palpitations noticed predominantly in group Nifedipine which was statistically significant. (P value= 0.02)

Required/Not required	Labetalol	Nifedipine	Total (N= 200)
No required	88 (88%)	92 (92%)	180
Required	12 (12%)	8 (8%)	20

P=0.346

Table 12- Additional Antihypertensive drugs

Additional antihypertensive drugs

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4 patients had Eclampsia- 2 from group Labetalol, 1 from the Nifedipine group and 1 from the combined group. 3 patients had abruptio placenta, 2 of which were on both antihypertensive drugs. 1 patient was from the Nifedipine group. 3 patients developed HELLP syndrome. 2 patients on Labetalol and 1 patient on Nifedipine. 2 patients developed PRES syndrome both on oral Labetalol, one patient required ICU care for ionotropic support was on both antihypertensive therapies.

	Labetalol	Nifedipine
Birth weight (kg)	2.78	2.69

P=0.195

Table 13- Birth weight

Mean birth weight was found to 2.6-2.7kg in both drug group. There was no statistical significance

	Labetalol	Nifedipine	Total no(n=200)
NICU Admission	11 (11%)	15 (15%)	26 (13%)

P value =0.4

Table 14- NICU admission

9 neonates from the Labetalol group had Fetal growth restriction, out of which 2 neonates had fetal bradycardia. 6 babies in the Nifedipine group had FGR. 3 babies developed cardiac anomalies. Out of 26 neonates in NICU, 15 were admitted due to extreme prematurity.

Discussion

The management in hypertensive disorders complicating pregnancy is recommended to reduce maternal and fetal complications. Labetalol and Nifedipine are known to be used for management of hypertension in pregnancy. Nifedipine is cheaper and readily available in tertiary care hospitals. We therefore wanted to collate the potency of the two drugs, Nifedipine retard and Labetalol in the management of hypertensive disorders in pregnancy. The mean maternal age in the present study was 24 -25 years which was similar to T Easterling et al, Thakur et al and Nilesh et al **[**20,7,32**]**

Body mass index was not statistically significant, though most of the sample size was overweight. T Easterling et al included multiple pregnancy in their study as opposed to the present study. Primigravida was predominant in both drug groups (almost half) which was comparable to Thakur et al where it is attributed to 24-48% in both drugs groups. Additional hypertensive drugs were required up to 12% in Labetalol group and 8% in the Nifedipine group, which was more than Easterling et al and Thakur et al.

A Meta-analysis constructed by Liu Q et al included the assessment of the potency, adverse effects and perinatal outcomes of nifedipine versus other antihypertensive drugs(5). Compared with other antihypertensives, nifedipine contributed greater efficacy in controlling blood pressure contrary to the present study

Stefano R. Giannubilo et al concluded that there was a higher occurrence of fetal growth restriction amid women treated with labetalol as opposed to the nifedipine group (38.8 vs.

15.5 %) **[**6**]**. In the present study, 9 neonates from the Labetalol group had Fetal growth restriction, out of which 2 neonates had fetal bradycardia (NICU admission).

More number of caesarean sections (64%) were observed in Easterling et al study which was contrary to the present study (30%). There was no statistical significance in maternal complications such as Abruptio placenta, Eclampsia and ICU admission. Dhali B et al, found higher incidence of eclampsia in the labetalol group **[**33**]**

Thakur et al **[**7**]** found that Labetalol, Nifedipine and Methyldopa were effective in Pregnancy induced hypertension; where Labetalol was more effective in reducing albuminuria.

Sivaranjani et al have seen that nifedipine has many pros like cheaper than other drugs, immediate action along with longer duration of action and can be taken orally. **[**8**]** Despite many advantages, it is known to cause maternal hypotension, foetal distress due to the placental hypoperfusion, palpitations and progressive neuromuscular weakness when used along with magnesium sulphate. Our study was conducted in a tertiary hospital; hence it can be concluded Nifedipine can be used as it is more versatile and cost effective.

Study	T Easterling et al (2019)	Thakur et al (2016)	Nilesh et al (2019)	Kanika et al (2019)	Present study
Maternal age (Years)	L- 25 N- 25	L- 23 N- 23	L-23 N-23	-	L- 24 N- 25
BMI	L- 27.1 N- 27.4		-	-	L- 26.8 N- 26.4
Parity	Included multiple pregnancy	Primigravida L- 28% N-24%	Primigravida L-46% N-56%	Primigravida L-60% N-56%	Primigravida L-52% N-51%
Gestational age at delivery (wk)	L – 36.9 N- 36.9	L- >68% (term) N- 72% (term)	L-70% (term) N-73% (term)	L-86% (term) N-83% (term)	L-92% (term) N-85% (term)

Table 14- Comparison with other studies

Conclusion

Labetalol was shown to be more efficacious in the first 48 hours after initiation of treatment. Nifedipine was proven to be equally efficacious after 72 hours of medication. Side effects such as headache and palpitations were found in group Nifedipine which not detrimental to patient health. Hence it can be concluded that Nifedipine can be used in low resource settings as it is readily available and cost effective. There was was no disparity in proteinuria as well as other maternal and neonatal outcomes in both drug groups. More number of ICU admission was noted in the combined drug group.

Bibliography

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Pregnancy Hypertension. Text Book of Williams Obstetrics. 23rd Edition. 2010 New York, McGraw Hill. 706-757 pp.

2. Ainuddin J, Javed F, Kazi S. Oral labetalol versus oral nifedipine for the management of postpartum hypertension a randomized control trial. Pak J Med Sci. 2019;35(5):1428-1433. doi:10.12669/pjms.35.5.812

3. Clark SM, Dunn HE, Hankins GD. A review of oral labetalol and nifedipine in mild to moderate hypertension in pregnancy. Semin Perinatol. 2015 Nov;39(7):548-55. doi: 10.1053/j.semperi.2015.08.011. Epub 2015 Sep 4. PMID: 26344738.

4. National Institute for Health and Care Excellence (2010) Hypertension in pregnancy: diagnosis and management. NICE Guideline (CG107)

5. Liu QQ, Yu YH, Gong SP, Huang LP. **[**Clinical efficacy and perinatal outcome of nifedipine for severe preeclampsia: meta-analysis**]**. Zhonghua Fu Chan Ke Za Zhi.2012 Aug;47(8):592-7.

6. Stefano R. Giannubilo. Archives in Obstetrics and Gynaecology (2012) 286:637– 642

7. Thakur V et al. International Journal of Reproduction and Contraception, Obstetrics and Gynecology. 2016 January 5(1):17-22

8. Sivaranjani.B.S, Aruna.V. Comparison of Efficacy of Intravenous Labetalol versus Oral Nifedipinein Control of Acute Hypertension in Severe Pre-Eclampsia/ Eclampsia. IOSR-JDMS. 2016;15(12(X):71-74.

9. Hangarga, U., D., R., & Harshitha, K. (2016). Comparative study of labetalol and nifedipine in management of hypertensive disorders in pregnancy. International Journal of Reproduction, Contraception, Obstetrics and Gynaecology, 6(1), 194- 197.

10. Sharma KJ, Greene N, Kilpatrick SJ. Oral labetalol compared to oral nifedipine for postpartum hypertension: A randomized controlled trial. Hypertension in Pregnancy. 2017 Feb;36(1):44-47.

11. ACOG Practice Bulletin: Diagnosis and management of preeclampsia.No 33. Jan 2002. ACOG. International Journal of Obstetrics and Gynaecology 77:67-75.

12. Gestational Hypertension and Preeclampsia, Obstetrics & Gynecology: June 2020 - Volume 135 - Issue 6 - p e237-e260

13. Upadya M, Rao ST. Hypertensive disorders in pregnancy. Indian J Anaesth. 2018;62(9):675-681.

14. Kristen Duckitt et al: Risk factors of preeclampsia. BMJ 330:565, 2005.

15. Junie.P Warrington et al. Hypertension. 2013; 62:666-673.

16. Steven G.Gabbe : Obstetrics normal and problem pregnancies. 6th edition, 33:866-867.

17. Zeek PM et al: Vascular changes with eclamptogenic toxemia of pregnancy. Am J Clin Pathol 20: 1099-1109, 1950.

18. Laivuori et al: Susceptibility loci for preeclampsia . Am J Hum Genet 72:168,2001.

19. Oudejans et al: The parent of origin effect in preeclampsia. Mol HumReport 10:589,2004.

20. Sibai BM et al: Prevention of preeclampsia and eclampsia. 2009 page, 215. CLASP Trial. Lancet 343:619-623,1994.91

22. S.S.Trivedi: Management of high risk pregnancy – A Practical Approach . 1st edition 15: 301-302,2010.16

23. Morko Foloic et al: Antihypertensive drug therapy for hypertensive disorders in pregnancy. Acta Medica Medianae Vol .47, 2008.

24. PeterVon Dadelzen: Meta-analysis on antihypertensives in pregnancy, Lancet.2007.

25. Lippincot's Pharmacology. 5th edition 3:95.

26. R.S.Satoskar: Pharmacology and Pharmacotherapeutics. 22nd edition 17:276-277, 2011.

27. Gerald G. Briggs: Drugs in pregnancy and lactation. 9th edition page:797-799, 2009

28. George M. Bremer: Textbook of Pharmacology. 3rd edition 11:114-115, 2010.

29. Carl P.Weiner : Drugs for pregnancy and lactating women. 2nd edition page: 559, 2010.

30. Levin AC, et al. Use of nifedipine in the hypertensive diseases of pregnancy. 1994; 28:1371–8

31. Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomized controlled trial. Lancet. 2019;394(10203):1011-1021.

32. Dr Nilesh Dalao et al. A comparative study of oral labetalol versus oral nifedipine in hypertensive disorders of pregnancy. Int J Clin Obstet Gynaecol 2019;3(3):132- 13

33. Dhali B, Bhattacharya S, Ganguly RP, Bandyopadhyay S, Mondal M, Dutta M, et al. A randomized trial of intravenous labetalol & oral nifedipine in severe pregnancy induced hypertension. Int J Reprod Contracept Obstet Gynecol. 2012; 1:42-6.