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THE COMPARATIVE STUDY OF NIFEDIPINE AND LABETALOL IN THE MANAGEMENT OF PREGNANCY INDUCED HYPERTENSION.

Obstetrics & Gynaecology

Dr. Aparna J* Associate professor, Shadan Medical college, Hyderabad. *Corresponding Author
Dr. B. Jyothirmayee Professor, Shadan Medical college, Hyderabad.
Dr. K. Saraswathi Professor, Shadan Medical college, Hyderabad.

KEYWORDS

INTRODUCTION

Hypertensive disorders represent the most significant complication in pregnancy, affecting as many as 10% of the pregnant women and they contribute second leading cause of maternal.[1] The fetal outcome is directly proportional to the quality of obstetric care in the community. Severe hypertension in early pregnancy increases the maternal mortality by 15-20%. Hypertensive disorders constitute 10% of all perinatal deaths. Hypertensive disorders complicating pregnancy are common and form one of the deadly triad along with hemorrhage and infection that results in much of the maternal morbidity and mortality related to pregnancy. Although maternal hypertension is diagnosed in approximately only 7% of all deliveries, 1.5% in private hospitals and upto 15% in university hospitals, it is associated with as much as 22% of all perinatal deaths and 30% of maternal deaths.[2]

How pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research and hypertensive disorders remain among the most significant unsolved problem in obstetrics.[3] In India preeclampsia / eclampsia impact 30% of all deliveries with 50,000 cases of woman having this serious complication each year. These women are at higher risk for complications like abruptioplacentae, thrombotic microangiopathy, coagulopathy, cerebral hemorrhage and multi organ injury.

The hypertensive disorders of pregnancy constitute the most widely studied, discussed and analyzed condition, because of the fact that they adversely affect both the mother and foetus. They predispose to acute or chronic uteroplacental insufficiency resulting in ante or intrapartum anoxia that may lead to fetal death, intrauterine growth retardation both asymmetrical as well as symmetrical thereby, compromising the intellectual abilities of the child in future especially in symmetrical intra uterine growth retardation (IUGR); and preterm delivery.[4]

Because the etiology of the disease still poses an enigma, management is necessarily symptomatic and empirical and mainly directed towards the prevention or arrest of seizures and the reduction of blood pressure. Hence the ultimate management in hypertensive disorder of pregnancy is termination of pregnancy. This can be postponed until fetus is mature enough to survive exutero without jeopardizing both the mother and foetus, balancing between benefits and risks of continuing the pregnancy.

Hence the role of antihypertensive drugs does play a role in the management of hypertensive disorders of pregnancy. Many trials had been conducted in non-severe pregnancy induced hypertension to prove the efficacy of the drugs in the disorder.[5-7] Few of them concluded there is still a role in starting antihypertensive treatment if diastolic blood pressure is below 110 mm Hg where the resources to adequate antenatal care are less, where regular and daily blood pressure checking is not feasible, in such circumstances we can start the pharmacologic treatment in mild PIH too.

AIMS AND OBJECTIVES OF THE STUDY

1. To study the effects of Nifedipine and labetalol in patients of PIH
2. To study the comparative efficacy of these two drugs on the hypertension.
3. To study the impact of Nifedipine and labetalol on maternal and perinatal outcome.

MATERIALS AND METHODS

A total number of 100 patients were randomized into two groups. Fifty patients were given oral Nifedipine and the other 50 patients were given oral Labetalol for non-severe pregnancy induced hypertension. These patients were taken up from the labor or antenatal ward for the study.

Patients with gestational age ≥ 32 weeks and sustained rise in blood pressure ≥ 140 mm Hg to 160 mm Hg, diastolic blood pressure ≥ 96 to 106 mm Hg and were included in the study. Patients with systolic blood pressure ≥ 170 mm Hg diastolic blood pressure ≥ 110 mm Hg, gestational age < 32 weeks were excluded from the study. Blood pressure was recorded in the left lateral position or right upper arm in sitting posture after 5 minutes of rest. All the patients included in the study were hospitalized, investigated and treated.

All the patients were treated indiscriminately with nifedipine or labetalol, both orally. In the nifedipine group, an initial dose of 10mg was administered every 20 min until the blood pressure (BP) was reduced under 150/95 mmHg. In the labetalol group (L), the process was the same, with 100mg doses, until reaching the BP target. When the target was not achieved, a new dose was administered, up to a maximum of 4 doses, before switching to another antihypertensive drug.

Statistical analysis

All data were analyzed by student t test (independent samples *t* test) and Chi-squared test where ever applicable. Nonparametric tests (wilcoxon signed rank tests (2-tailed)) were used when ever mean value is less than two times standard deviation (SD). A p-value < 0.05 was considered statistically significant. The statistical analysis was performed with SPSS® 17.0 software (SPSS® Inc., Chicago, IL, USA).

RESULTS

100 cases were randomized to 50 cases of Nifedipine and 50 cases of labetalol each; matching age, gestational age, parity, socio-economic status, blood pressure recordings, keeping these variables constant among these two divided groups (table 1-3).

TABLE – 1: Incidence of PIH in various age groups

Incidence of PIH in various age groups				
Age (yr)	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
18- 20	18	36	15	30
21-23	22	44	19	38
24-26	7	14	13	26
27-30	0	0	1	2
> 30	3	6	2	4

*P value <0.05 was considered statistically significant.

Table 2 emphasizes the fact that PIH is primarily disorder of young primigravidae which is reflected by high incidence (74%). This shows

incidence of PIH decreases as parity increases.

TABLE 2: Distribution of cases according to the parity.

Parity	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
Primi	40	80	34	68
G2	9	18	10	20
G3	1	2	6	12

$\chi 2 = 4.11$; *P value <0.05 was considered statistically significant.

TABLE 3: Distribution of cases according to the Socio Economic status

Socio Economic group	No of cases (n=100)	Percentage (%)
Class IV & V	92	92
Class III	8	8

* p value <0.05 was considered statistically significant.

TABLE 4: Distribution of cases according to the pedal oedema.

pedal edema	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
Grade 0	20	40	23	46
Grade I	10	20	12	24
Grade II	20	40	15	30
Grade III	-	-	-	-

* p value <0.05 was considered statistically significant.

Table 4 shows that most of the cases around 57 % had pedal oedema there by confirming a relation between PIH and pedal oedema. There is no significant difference between pedal oedema incidence between the two study groups. There by showing neither of the two drugs, Nifedipine or labetalol predisposed to peripheral oedema.

TABLE – 5: Distribution of cases according to Proteinuria.

Proteinuria	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
Nil or <300 mg	23	46	20	40
+	15	30	16	32
+ +	12	24	14	28
≥ + + +	Nil	Nil	Nil	Nil

* p value <0.05 was considered statistically significant.

Our results shows that 57% of study cases had preeclampsia i.e. proteinuria and hypertension and around 43% showed only hypertension during pregnancy (table 5). The severity of PIH increased with proteinuria, +2 proteinuria was seen only in cases of diastolic blood pressure between 100 – 110 mm Hg where as +1 was seen in both between 90- 100 mm Hg and as well as 100 – 110 mm Hg .

There is no significant difference between the study groups in relation to proteinuria showing both Nifedipine and labetalol had almost same impact on proteinuria.

TABLE 6: Time taken to achieve targeted blood pressure.

Time taken for fall in B. P.	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
0 – 30 mts.	9*	18	1*	2
31 – 60 mts	33*	66	18*	36
61 – 90 mts.	6*	12	13*	26
91 – 120 mts	2*	4	10*	20
>2 hrs.	Nil*	0	8*	16

* p value <0.05 was considered statistically significant.

Both Nifedipine and labetalol equally reduce blood pressure, Nifedipine achieves the targeted blood pressure much earlier (table 6). Almost 84 % of Nifedipine group achieved with in 1 Hr where as same % of labetalol group took 2 Hrs to reach targeted blood pressure. The mean time to achieve required blood pressure for Nifedipine is 40 ±15.6mts and labetalol is 75±25.3mts.

TABLE – 7: Adverse effects observed during the study period.

Adverse Effects	Nifedipine group		Labetalol group	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
Nausea, Vomiting	20	40	10	20
Headache	18	36	6	12
Flushing	10	20	-	-
Dizziness	20	40	12	24
Tachycardia	4	8	-	-
Bradycardia	-	-	1	2
Transient hypotension	15	30	-	-
Dyspnea	-	-	1	2

* p value <0.05 was considered statistically significant.

Nifedipine group had more maternal side effects compared to labetalol group (table 7). Almost 40 % of Nifedipine patients complained of nausea, headache, dizziness where labetalol group had none. Labetalol had minimal maternal side effects in our study group, one had maternal bradycardia with irregular pulse and one had dyspnea.

TABLE – 8: Number of cases according to birth weight (kg)

Birth weight	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
≥ 3 Kg.	5	10	9	18
2.5 – 3.0 Kg.	40	80	32	64
2.0 – 2.5 Kg.	3	6	8	16
< 2 Kg.	2	4	1	2

* p value <0.05 was considered statistically significant.

Since our study group includes only mild PIH cases birth weight has not been affected significantly. Most of the delivered babies fell under 2.5 – 3.0 kg birth weight category (table 8). Both Nifedipine and labetalol had almost same range of birth weight babies showing neither of them restricted intrauterine growth of fetus.

TABLE – 9: No. of cases according to Apgar Score.

Apgar Score	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
8,10	40	80	34	68
6,8,10	10	20	14	28
4,6,8	-	-	1	2

* p value <0.05 was considered statistically significant.

Both Nifedipine and labetalol groups had almost same apgar scores (table 9). Only one baby of labetalol group had low apgar score that was due to premature rupture of membranes with obstructed labour. The novel drug labetalol too has got good perinatal outcome.

TABLE – 10: No. of cases according to mode of delivery

Mode of Delivery	Nifedipine		Labetalol	
	No of cases (n=50)	Percentage (%)	No of cases (n=50)	Percentage (%)
Spontaneous Vaginal delivery	14	28	20	40
Induction of Labour	6	12	2	4
Acceleration of Vaginal Delivery	1	2	4	8
Instrumental Delivery	9	18	4	8
Caesarean Section	20	40	20	40

* p value <0.05 was considered statistically significant.

More patients (34%) in labetalol group were delivered by spontaneous vaginal delivery 9table 10). Caesarean section was done in 40 % of the cases. Both Nifedipine and labetalol showed equal incidence in LSCS rate.

TABLE – 11: Indication of Caesarean Section.

Indication of Caesarean Section	Nifedipine		Labetalol	
	No of cases (n=20)		No of cases (n=20)	
	Emergency	Elective	Emergency	Elective
Failure of Induction	6	0	-	-
Premature rupture of membranes with prolonged labour	2	-	5	-
Cephalopelvic disproportion	1	0	2	1
Foetal distress	4	-	5	-
Previous Section	1	2	1	1
Other causes				
A) Malpresenation, Breech	0	1	-	2
B) Elderly Primi	1	-	-	1
C) precious Pregnancy	-	2	-	2

* p value <0.05 was considered statistically significant.

There were 15 emergency, 5 elective LSCS in Nifedipine group (table 11). In labetalol 13 emergency and 7 elective LSCS were done. Most of the cases were done for fetal distress, PROM, failed induction. Both the study groups had almost equal incidence of fetal distress. None were done for uncontrolled PIH. Elective LSCS was done for malpresentation, previous LSCS, precious pregnancy, CPD.

DISCUSSION

In our study, PIH and hypertensive disorders of pregnancy have been extensively studied starting with etiological factors of PIH to the management of it. The role of antihypertensive drugs, labetalol and Nifedipine is evaluated in the management of non-severe hypertension in pregnancy.

Our study revealed that teenage primis constituted nearly 33% of total study group. The immunological aetiology in teenage primi is responsible because a lot of studies have shown that exposure to chorionic villi for the first time leads to accelerated rejection of allograft which is normally blocked by blocking antibodies. Paternal antigen has also been incriminated in the aetiology and in subsequent pregnancies the incidence of PIH comes down proving this hypothesis. Also the change of partner can also lead to PIH in subsequent pregnancy.

The incidence of PIH is seen more in primigravidae. Low socioeconomic group comprised about 92% of the cases hypertensive disorders. This is in comparison with other studies which says that preeclampsia is more common in low socio economic group because of a combination of poor dietary habits with ignorance and apathy leading to poor antenatal care.[8, 9]

The incidence of severe PIH is decreased because of earlier diagnosis and proper management and timely induction of labour for the study cases. The presentation of cases according to trimester is important for the foetal outcome in the hypertensive disorders of pregnancy. In our study, 87% of the patients presented after 35 weeks of gestation. The cause being that increased surface area of placenta, which is the site of pathology. The same phenomena i.e. increased placental size which occurs multi foetal pregnancy, diabetes mellitus, hydatiform moles, fetal hydrops, leads to early development of preeclampsia.

In our study, both nifedipine and labetalol equally reduce the mean arterial pressure with a significant difference in their effect of duration of onset of their antihypertensive action to peak effect. Our study consisted of groups between 140-169 mm Hg systolic blood pressure and 90-106 mm Hg of diastolic blood pressure. Accordingly dosage was given and incremented with regard to their antihypertensive action. Nifedipine tablets (10mg) form were administered which have sustained duration of action as compared to 5mg /10mg capsule forms. The onset of 10mg tablet form was seen within 30 minutes and peak effect within 1 hour of the administration of the drug. There was effective fall of diastolic blood pressure of about 10-15 mm Hg within 30minutes to 1 hour. In whom there has been no fall, capsule form or the dosage of the drug was increased and administered to achieve the targeted blood pressure, but there was no switch over or cross over therapy in both the study groups.

Labetalol too reduced the mean arterial pressure effectively but took a little longer time to achieve the target. The maximum dose administered in our study group was 800mg of labetalol for diastolic up to 109 mm Hg. Their onset of action was within 30minutes to peak effect of 1.5 -2 hours. There was effective fall in blood pressure like Nifedipine with delayed onset and peak. But the effect lasted for longer duration compared to Nifedipine requiring tid/qid dosage since the plasma half-life of the drugs were 8-12 hours and 4-6 hours respectively.

About 27 cases of Nifedipine and 35 cases labetalol were treated for total duration including ante and postpartum for less than 10days. About 16 cases of Nifedipine and 6 cases of labetalol were treated for 11 to 20 days. About 7 cases of Nifedipine and 9 cases of labetalol were treated for total duration of more than 21 days (21-28 days). Treatment duration was increased in response to duration of the pathology but not due to the individual effects of the drugs. Hence form antepartum to postpartum, treatment duration in our study group not lasted for more than a month.

We have not noticed any significant decreases in proteinuria and increased in urinary output in Nifedipine as compared to labetalol. Both of the groups showed almost same results as against the observation of Stephenetal in their randomized double blind trial of Nifedipine and labetalol (1999) in hypertensive emergencies of pregnancy.[10]

In our study, we observed that maternal side effects were minimal in labetalol. This correlates well with the study done by el-Qarmalwi etal (1995) labetalol vs. methyldopa in the treatment of pregnancy induced hypertension.[11] Labetalol was better tolerated to methyldopa in frequency of side effects like headache, drowsiness, nasal congestion, postural hypotension. There was one case of maternal bradycardia with irregular rhythm with only 200mg of statum dose, which was given for diastolic blood pressure of 109 mm Hg in labour room. Thereafter patient pulse was regained with time, and atropine was given postoperatively. In one patient, there was dyspnea, chest pain, dizziness and palpitations. Whether this was due to labetalol or anemia was confirmed in postpartum, where the patient symptoms disappear after she regained her hemoglobin.

Side effects were observed more with increased or high dosages. Maximum dose of Labetalol in our group was 800mg per day and Nifedipine was 60mg per day. Nifedipine has 15 cases of transient hypotension and about 40% cases experienced headache, nausea, dizziness. These side effects were observed in patients of diastolic blood pressure of 109 mm Hg where capsules were given as and when required.

In our study group neither Labetalol nor Nifedipine restricted fetal growth. Moreover the drugs were administered for very short period of time where fetal outcome cannot be predicted conclusively. This corrected well with the study of Moretii etal (1990) the effect of Nifedipine on fetal and placental Doppler waveforms does not affect the resistant indices.[12]

The mode of delivery in both the study groups gave an equal incidence of LSCS rate. LSCS rate was not due to severe PIH and uncontrollable PIH but due to fetal distress, PROM with prolonged labour and failed induction. 40% of cases went for caesarean section. Spontaneous vaginal delivery were seen more in Labetalol as compared to Nifedipine, though it is only marginal. This correlates well with A.M Elqarmalawi etal study in Kuwait (1995) where they found labetalol went into spontaneous onset labor due to favorability on cervix, had a better bishop score for induction compared to methyldopa group.[11] Labetalol has been speculated in cervical ripening. Hence the novel drug, Labetalol had almost the same effect on mode of delivery as compared Nifedipine.

There was one intrauterine death in Labetalol group of 32 weeks gestation that was an un-booked case admitted in view of fetal demise with hypertension complicating pregnancy. Otherwise the apgar scores at birth gave same outcome in both the study groups.

In essence, this study has evaluated the efficacy between the two drugs, Nifedipine and Labetalol, in controlling blood pressure along with maternal and foetal outcome.

The aim being, to evolve a pattern of management of cases of mild PIH where there is very narrow margin of difference between mild and severe PIH of only 1 mm Hg difference in diastolic blood pressure which would result in cerebrovascular complications if the blood pressure is left untreated. Hence serial record of blood pressure readings every 4th hourly during day is obviated for blood pressure readings of diastolic above 100 mm Hg with hospital admission and antihypertensive treatment.

Nifedipine has been into antenatal antihypertensive treatment since years, proved its efficacy in treatment of high blood pressure along with safety to mother and foetus. The newer drug α plus β blocker labetalol too is equally effective in controlling blood pressure with minimal maternal and foetal side effects.

In conclusion, the control of pre-eclampsia hypertensive emergency is faster with nifedipine than with labetalol and, in addition, no major adverse events in mothers or foetus were found with nifedipine. Labetalol scores over Nifedipine in that twice a day administration is more convenient rather than every four hourly. However, Nifedipine remains a better alternative because of its rapidity in action in controlling blood pressure even in hypertensive emergencies very efficiently. In a resource poor setup like our hospital Nifedipine remains a very cost-effective option in comparison to labetalol which is very expensive and not within the reach of poor patient. For these reasons, nifedipine is an alternative as safe and effective as labetalol for the management of hypertensive emergency during pregnancy.

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