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Original Research Article

A prospective, parallel group, open label, observational study to compare efficacy and feto-maternal outcomes in treatment of pregnancy induced hypertensive patients

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ABSTRACT

Background: Pregnancy induced hypertension (PIH) is defined as elevation in blood pressure 140/90 mmHg or greater after 20 weeks of gestation on two occasions more than 4 hours apart in a newly diagnosed patients. Complications of pregnancy are the major health problems leading to maternal and perinatal mortality and morbidity. Some anti-hypertensive drugs are commonly used to control hypertension.
Methods: A prospective, parallel group, open label observation study was carried out at SVS Medical Hospital, Mahabubnagar. Patients were divided into three groups based on severity of hypertension and the drug used for treatment.
Results: Of 120 patients diagnosed with PIH majority (50%) of women were in the age group of 21-24 years with 33-37 gestational age. In the present study there was a significant reduction in BP after the treatment with Labetalol when compare to Nifedepine and Methyldopa. Although, all the three groups have shown significant reduction in BP during 24 hrs treatments and the mean time to achieve target BP was shown less in Labetalol group when compare to Methyldopa and Nifedepine and the maximum doses required to achieve target BP was in between 4-6 doses/day. 40% of complication observed was HELLP syndrome.
Conclusions: Our study coincides with the previous findings that labetolol is an efficacious and safer drug for use in control of PIH and mean time required to achieve target BP is low when compared to nifedipne and methyldopa.

Keywords: Anti-hypertensive, Perinatal, Pregnancy induced hypertension

INTRODUCTION

Pregnancy Induced Hypertension(PIH) is defined as increase in systolic and diastolic blood pressure to (≥140/90 mmHg) with or without proteinuria (≥300 mg/24 hours) after 20 weeks of gestation and resolving after 12 weeks postpartum.[1] According to the Canadian Hypertension Society, PIH refers to one of four conditions: a) pre-existing hypertension, b) gestational hypertension and pre-eclampsia, c) pre-existing hypertension plus superimposed gestational hypertension with proteinuria and d) unclassifiable hypertension.[2] Leading cause of maternal deaths due to hypertensive disorders ranges from 6 to 10% for which the leading risk factor is intra cerebral hemarrohage.[3] Complications due

to hypertension in pregnancy can be categorized as fetal and maternal complications.

Fetal complications

Intrauterine growth retardation (IUGR) and fetal death.[4]

Maternal complications

HELLP syndrome, temporary blindness, abruptio placentae, disseminated intravascular coagulation (DIC), acute renal failure (ARF), pulmonary edema, arrhythmias, liver lesions, intracranial or hepatic hemorrhage, adult respiratory distress syndrome (ARDS), hypervolemia and risk of recurrent preeclampsia.[5]

Treatment of PIH can be attributed to low/high blood pressure levels, gestational age, severity of symptoms and risk factors. After adequately evaluating all the anti hypertensives for their use during pregnancy some drugs are used to prevent maternal and fetal complications and many other drugs are contraindicated due to their adverse effects.[6-8] Most frequently used anti-hypertensives to treat PIH are methyldopa, labetalol, acebutolol, metoprolol, pindolol, propranolol and calcium channel blockers such as nifedipine. The society of obstetrician and gynecologists of Canada has suggested labetalol, nifedipine and hydralazine as the first line therapy for severe hypertension.[9]

Methyldopa a centrally acting adrenergic agonist decreases BP by decreasing sympathetic nerve activity which results in arterial dilation, at high doses it causes sedation and depression. Labetolol has advantages over other Beta blockers due to its additional arteriolar vasodilation activity that helps to lower peripheral vascular resistance with little or no decrease in cardiac output, however it causes foetal bradycardia[10.]

Calcium channel blockers (CCBs) such as Nifedipine are commonly used during pregnancy and lactation to treat hypertension, arrhythmia, and preeclampsia and also to prevent premature labour and its complications.[11]

As PIH is one of the root cause for many feto-maternal complications, the present study was planned to evaluate the safe and efficacious anti-hypertensive option for managing PIH and also to assess feto-maternal outcomes for the choosen drugs in Mahabubnagar, India.

METHODS

A prospective, parallel group, open label observational study was conducted in the Department of Obstetrics and Gynecology from august 2017 to January 2018 at a 300 bedded super specialty teaching hospital at Mahabubnagar comparing Nifedipine, labetalol and methyldopa in the management of pregnancy induced hypertension.

120 women with pregnancy induced hypertension with a gestational age more than 28 weeks gestation were in included in the study.

Inclusion criteria

Patients with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg with a pregnancy greater 28 weeks gestation.

Exclusion criteria

Patients with asthma, heart disease, allergic to nifedipine, labetalol or methyldopa, liver disease, diabetes, heart rate 120 beats/min.

All the patients included in the study were randomized into three treatment groups.

- Group A-treated with nifedipine (40 cases)
- Group B-treated with a labetalol (40 cases)
- Group C-treated with Methyldopa (40 cases)

Patients randomized to the nifedipine group were administered 10 mg of oral hydralazine. At regular intervals of 1 hour BP was monitored. The dose was repeated until the target blood pressure that is systolic blood pressure <160 mmHg and diastolic blood pressure> 110mmHg was achieved. Patients in the labetalol group were administered with 20mg of oral Labetalol. At regular intervals of 1 hour BP was monitored. The second dose of 100 mg inj. labetalol was given if the target blood pressure was not achieved. Patients in the Methyldopa group were administered with 250mg of oral Methyldopa. Blood pressure was monitored at every 1 hour interval.

The time required for blood pressure to reach the target value was noted. The number of doses required to achieve the target value was noted. Adverse effects like maternal hypotension, tachycardia, nausea, abruptio placentae were noted if any were reported. The patients were followed up and complications arising as a result of severe hypertension were noted. Data obtained was analysed statistically. Two way ANOVA was used to analyse the data. Probability values less than 0.05 were considered significant.

RESULTS

A total of 120 patients participated in the study with mean age of 24.85 for nifedipine, 24.17 for labetolol and 24.25 for methyldopa. The majority of participants were between the age group of 21-24 (49.1%).

There was no significant difference with respect to age distribution between the groups. Similarly majority of participants in all treatment groups are primiparous (35%) and primigravidas (55.83%) as seen from Table 1.

Table 1: Age wise, parity, gravida distribution.

Age(yrs)	Nifedipine (%)	Labetalol (%)	Methyldopa (%)
<20	1 (2.5)	0 (0)	3 (7.5)
21-24	20 (50)	20 (50)	19 (47.5)
25-29	15 (37.5)	19 (47.5)	14 (35)
>30	4 (10)	1 (2.5)	4 (10)
Mean age	24.85	24.17	24.25
Parity distribution of cases			
Parity			
P0	6 (15)	5 (12.5)	7 (17.5)
P1	20 (50)	15 (37.5)	14 (35)
P2	8 (20)	5 (12.5)	8 (20)
P3& above	6 (15)	15 (37.5)	11 (27.5)
Gravida distribution of cases			
Gravida			
Primi gravida	21 (52.5)	23 (57.5)	23 (57.5)
Gravida-2	9 (22.5)	6 (15)	8 (20)
Gravida-3	7 (17.5)	9 (22.5)	7 (17.5)
Gravida 4 and above	3 (7.5)	2 (5)	2 (5)

When gestational age was compared In all the groups, about more than 50% of PIH patients were in the 33 to 37 weeks of gestation. Next highest percentages of patients were found in 38 to 40 weeks of gestation followed by 29 to 32, 25 to 28, and 21-24 weeks as seen in Table 2.

As given in Table 3 and 4 when efficacy was compared between the groups of all the three drugs there was a significant reduction in systolic and Diastolic BP observed after 24 hours, but the level of significance was higher in Labetalol group (117.6±8 -systolic), (72±10.79-diastolic) compared to methyldopa (128.5±9.8-systolic), (78.5±9.75-dastoilc) and nifedepine groups (125.6±9.9-systolic), (79.67±8.47-dastolic).

Table 2: Gestational age of cases.

Gestational age (weeks)	Nifedipine (%)	Labetalol (%)	Methyldopa (%)
21-24	3 (7.5)	0	0
25-28	0	4 (10)	5 (12.5)
29-32	1 (2.5)	6 (15)	4 (10)
33-37	29 (72.5)	24 (60)	22 (55)
38-40	7 (17.5)	6 (15)	9 (22.5)

Table 3: Mean systolic BP (before and after 24 hrs treatments).

Group	Pre-treatment value of mean SBP	Post 24 hrs treat-ment mean SBP	P value	Inference
Nifedipine	146.1±10.1	125.6±9.9	0.0228	Significant
Labetalol	148.25±13.18	117.6±8		
Methyldopa	150±21	128.5±9.8		

Table 4: Mean diastolic BP (before and after 24 hrs treatments).

Group	Pretreatment value of mean DBP	Post 24 hrs treatment mean DBP	P value	Inference
Nifedipine	98.56±9.58	79.67±8.47	0.0250	Significant
Labetalol	98.76±8.33	72±10.79		
Methyldopa	98.25±12.57	78.5±9.75		

Table 5: Mean time required to achieve target BP.

Group	Mean (hrs)	SD	P value
Nifedipine	86.4	31.59	0.0187
Labetalol	65.96	29.51	
Methyldopa	75	34.5	

All the three drugs were found to be significant with P value 0.0228 for mean systolic BP and for diastolic BP P value was found to be 0.0250. Similarly when mean time required to achieve target BP was compared, the least time required to achieve the target BP is seen in labetalol group (65.96 hrs with SD 29.51) followed by Methyldopa(75 hrs with SD 34.5) and nifedipine (86.4 hrs with SD 31.59). The P value for all the three groups were 0.0187 and statistical results found to be significant as seen in Table 5.

Table 6: No. of doses given to achieve target BP.

No. of doses (mg/day)	Nifedipine	Labetalol	Methyldopa
1-3	2	5	2
4-6	21	23	19
7-9	12	9	9
>10	5	3	10

Table 7: Classification of PIH distribution of patients.

Type of PIH	Nifedipine	Labetalol	Methyldopa
Mild	33	23	24
Moderate	3	3	1
Severe	4	14	15

4-6 doses were given in maximum number of patients 63(52.25%) to achieve target B.P among all treatment groups as shown in Table 6.When severity of PIH was assessed maximum number of mild cases were seen in nifedipine treatment group whereas maximum number of severe cases were seen in Methyldopa treatment group as seen in Table 7.

Table 8: Maternal complications.

Maternal complications	Nifedipine	Labetalol	Methyldopa
HELLP syndrome	6	5	5
Renal failure	3	2	2
Pre-eclampsia	3	2	5
Eclampsia	3	2	1
Abrupto placenta	1	1	2
Oligohydromnios	2	2	3
Pulmonary oedema	4	3	4
Postpartum hemorrhage	2	2	3
Pre term delivery	3	2	5
No complications	15	19	14

When maternal complications were compared our study revealed HELLP syndrome as most common complication followed by pulmonary edema, preeclampsia, renal failure, oligohydrominios, abruptive placenta and postpartum haemorrhage. Eclampsia and preterm delivery were also seen. No maternal complications were seen in 48 cases. Maximum numbers of complications were observed in methyldopa group and least in labetalol group as seen in Table 8.

Table 9: Maternal obstetric outcome & onset of labor.

Maternal obstetric outcome			
Onset	Nifedipine	Labetalol	Methyldopa
Caeserean (LSCS)	32 (80%)	30 (75%)	31 (77.5%)
Norma (NVD)	8 (20%)	10 (25%)	9 (22.5%)
Onset of labour			
Onset	Nifedipine	Labetalol	Methyldopa
Spontaneous	37 (92.5%)	36 (90%)	34 (85%)
Induced	3 (7.5%)	4 (10%)	6 (15%)

Table 10: Indications of LSCS.

Indications	Nifedipine	Labetalol	Methyldopa
Foetal distress	4 (12.5%)	3 (10%)	6 (19.35%)
Severe pih	7 (21.875%)	14 (46.67%)	15 (48.38%)
Eclampsia	6 (18.75%)	2 (6.67%)	1 (3.22%)
Imminent eclampsia	5 (15.625%)	6 (20%)	5 (16.12%)
Oligo hydromnios and IUGR	10 (31.25%)	7 (23.33%)	4 (12.90%)

When maternal obstetric outcome was compared maximum number of LSCS and NVD were seen in nifedipine (80%) and labetalol (25%) treatment group respectively. Among them maximum number of spontaneous and indeced labors were seen in nifedipine and methhyldopa group as seen in Table 9. When indications for LSCS were studied patients with severe PIH elicited highest rate followed by oligohydromnios and IUGR, imminent eclampsia, fetal distress, eclampsia in decreasing order as seen in Table 10.

Table 12: Mean diastolic BP before and after delivery.

Group	Mean DBP (before delivery)	Mean DBP (after delivery)	P value	Inference
Nifedipine	92±9.92	76.78±14.83	0.0181	Significant
Labetalol	93.5±10.27	68.06±17.43		
Methyldopa	95±7.51	78.08±15.16		

Mean systolic (SBP) and diastolic (DBP) blood pressure after delivery shows reduction in systolic and diastolic blood pressure which was extremely significant in labetalol group (119.5±9.46-systolic), (68.06±17.43-diastolic) when compared to nifedipne (123.24±10.57-syatolic), (76.78±14.83-diastolic) and methyldopa group (129.5±15.35 –systolic) (78.08±15.16-dastolic) P values for SBP was 0.0132, and for DBP was 0.0132 respectively. The P value for all the three groups and statistical results were found to be significant as seen in

Table 11 and 12. When perinatal outcomes was compared there was no significant difference seen between treatment groups with respect to parameters such as birth weight, and gestational age at birth, cases of IUGR and number of infants admitted to NICU as shown in Table 13.

Table 13: Perinatal outcomes.

Perinatal outcomes	Nifedipine (%)	Labetalol (%)	Methyldopa (%)
Birth weight based on gestational age			
Appropriate for gestational age (AGA)	26 (65)	27 (67.5)	23(57.5)
Small for gestational age (SGA)	13 (32.5)	12 (30)	15 (37.5)
Large for gestational age (LGA)	1 (2.5)	1 (2.5)	2 (5)
Birth weight			
Low birth weight (LBW)	13 (32.5)	9 (22.5)	16 (40)
Very low birth weight (VLBW)	1 (2.5)	2 (5)	2 (5)
Extremely low birth weight (ELBW)	2 (5)	1 (2.5)	3 (7.5)
Normal birth weight (Nbw)	27 (67.5)	31 (77.5)	24 (60)
IUGR	8 (20)	5 (12.5)	9 (22.5)
NICU admissions	11 (27.5)	12 (30)	11 (27.5)
Perinatal death	1 (2.5)	0	1 (2.5)
Still birth	6 (15)	5 (12.5)	7 (17.5)
Total deaths	7 (17.5)	5 (12.5)	8 (20)
Live births	33 (82.5)	35 (87.5)	32 (80)
Pre term births	3 (7.5)	2 (5)	5 (12.5)
Term births	37 (92.5)	38 (95)	35 (87.5)

Table 14: Adverse effects of drugs.

Adverse effects	Nifedipine (%)	Labetalol (%)	Methyldopa (%)
Tachycardia	11 (27.5)	3 (7.5)	5 (12.5)
Occipital headache	8 (20)	10 (25)	3 (7.5)
Postural hypotension	1 (2.5)	0	5 (12.5)
Drowsiness	3 (7.5)	5 (12.5)	14 (35)
Myalgia	6 (15)	4 (10)	1 (2.5)
Weakness	8 (20)	15 (37.5)	4 (10)
Depression	3 (7.5)	3 (7.5)	8 (20)

Tachycardia 11 (27.5%) was common ADR in nifedipne group, weakness 15 (37.5%) in labetolol and drowsiness in methyldopa group 14 (35%) as shown in Table 14.

DISCUSSION

PIH is one of the major global problem which complicates foetus and mother, with the increase in Age the risk of PIH increases as maternal age is important risk factor of PIH.[12] In our present study, incidence of PIH occurs between the age group 21-24 in all the three groups (50% in nifedepine group, 50% in Labetalol group,47.5% in methyldopa group) which was similar to study conducted by Babbar et al and similarly there were no significant difference was observed in age distribution in the groups. In our study majority of them (35%) were primiparities, and (55.83%) were primigravidas which was similar to study conducted by Sajith et al.[13,14]

Most patients with PIH in all three groups belonged to 33-37 weeks gestational age which was similar to study conducted by Babbar et al.[13]

The mean time to achieve target BP was shown less in labetalol group (65.96 hrs with SD 29.51) when compare to methyldopa and nifedepine. The similar studies have been seen in Babbar et al.[13] In present study, the maximum doses required to achieve target BP were in between 4-6 doses/day among all the treatment groups.

The mean systolic and diastolic blood pressure before and after delivery were significant in all the three groups with marked reduction in blood pressure (119.5±9.46 in systolic and 68.06±17.43 in diastolic) was seen in Labetalol group (P=0.0001) after delivery, similar studies have been seen in Thakur et al.[14]

In present study HELLP (13.3%) syndrome is most common complication observed followed by pulmonary edema in 9.1% of patients. 8.3% of patients observed to have preeclampsia. 5.8% of complications were renal failure, oligohydrominios, and postpartum haemorrhage. 5% of patients was observed to have eclampsia and preterm delivery.

Only 3.33% of patients observed to have abruptive placenta represents maternal complications were absent in 45.66% of PIH patients which is compared with Reddy et al.[15] Study in which postpartum hemorrhage (13.2%) is common complication followed by imminent eclampsia 3.9%.

Adverse effects of drugs in which patients under nifedipine group shows tachycardia as common 11 (27.5%) ADR while labetalol group commonly shows weakness 15 (37.5%) methyldopa group commonly shows drowsiness 14 (35%), similar studies were observed in Babbar et al, in which most common adverse effects were occipital headache (3-9%), postural hypotension (3-8%), tachycardia (4-11%), and depression (2-7%) which was similar to study conducted by Babbar et al.[13]

CONCLUSION

Anti-hypertensive drugs are used to provide adequate measures in controlling or preventing severe hypertension/ hypertensive crisis, maximize the gestational age and to minimize the maternal and foetal complications. Present study results coincides with previous findings that labetolol is an efficacious and safer drug for use in the control of PIH.

It has very low incidence of maternal and foetal side-effects together with the excellent perinatal outcome in a condition usually accompanied by a high maternal and foetal mortality and morbidity which assures its suitability for use during pregnancy. Results of the study recommends use of nifedipine, labetolol and methyldopa in management of mild and severe PIH.

Outcome of the study can be used in developing guidelines of management of PIH. Further, well designed randomized control trials are desired to identify long term effects of these agents.

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