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A Comparative Study of Nifedipine, Labetalol and Methyldopa in P.I.H.

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ABSTRACT

Background: Hypertension is one of the most common medical problems encountered during pregnancy. This study aim to identify the incidence and demographics aspects of pregnancy induced hypertensive disorders and to compare the antihypertensive drugs like Nifedipine, Methyldopa and Labetalol on various aspects such as control of BP, gestational age on admission and delivery, maternal and perinatal outcome. **Methods:** This randomized prospective study was conducted in the antenatal ward of State Referral Hospital, Falkawn Mizoram. 150 patients divided into three groups, each of 50 patients were given Nifedipine, Methyldopa and Labetalol. Comparision of groups on the basis of age, parity, control of BP, gestational age, maternal and perinatal outcome were analyzed. **Result:** The incidence of P.I.H was more in primigravida with the incidence decreasing as parity increases,with no significant diferrence in the 3 treatment groups(p=0.0890). Labetalol has the best control of BP (137.40/87.80 mmHg) followed by methyldopa (141.0/91.20mmHg) and Nifedipine (148.40/95.40mmHg).The difference is found to be statistically significant.,and Labetalol has better result though not statistically significant (p>0.05) in the maternal complication among the treatment groups. **Conclusion:** Labetalol has a slight advantage over Methyldopa and Nifedipine for better maternal and fetal outcome.

Keywords: Nifedipine, Methyldopa, Labetalol, Pregnancy-induced-hypertension.

INTRODUCTION

Pregnancy induced hypertension is one of the commonest cause of maternal and fetal morbidity and mortality in developing and developed countries. It is a disease unique to pregnancy and a multisystem disorder characterised by hypertension, proteinuria, generalized oedema and at times coagulation and or liver function abnormalities. It is a sign of underlying pathology, which can be preexisting or appear for the first time during the course of pregnancy.

Hypertension in pregnancy is diagnosed when blood pressure is 140/90mmHg or greater, using korotkoff phase 5 to define diastolic pressure. Gestational hypertension is a condition when blood pressure reaches 140/90 or greater for the first time in pregnancy, but where proteinuria has not developed or blood pressure has returned to normal by 12 weeks post-partum. Pre-eclamsia is diagnosed when blood pressure reaches 140/90 or more after 20weeks gestation with proteinuria [300mg or more of urinary protein/24 hours or persistent 30mg/dl (1+dipstick) in random urine sample]

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The incidence of Pregnancy Induced Hypertension is cited to be 5-10%, but remarkable variations are reported. It is common in extremes of reproductive ages, its incidence is influenced by parities, race and ethnicity-and thus to genetic predisposition and environmental factors. Other risk factors include multiple pregnancies, history of chronic hypertension, diabetes mellitus, kidney diseases, first pregnancy maternal age over 35 years, obesity and African-American ethnicity.

The exact aetiology of Pregnancy Induced hypertension is still unknown.It is a multisystem disorder in which the intra vascular volume is contracted to that of non pregnant woman rather than expansion in normal pregnancy and the severity of intravascular volume contraction generally parallels the severity of the disease(Cunningham FG et al,2001).[1]

The trend of using antihypertensive agents in Pregnancy Induced Hypertension became common in the 1980s. The main objective of giving Antihypertensive agent in pregnancy induced hypertension is to prevent cerebrovascular accidents and congestive heart failure in mothers without compromising uteroplacental blood glow. The main benefit of antihypertensive is to allow safe

prolongation of pregnancy, which has to be balanced against potential fetal side effects of the drugs. (Singh A and Verma R,2003).[2]

The search for ideal antihypertensive still continues, and at present the gold standard in managing Pregnancy Induced Hypertension remained an early diagnoses, single or combination of anti hypertensives in pre-eclampsia and in understanding the precise cut off point to terminate pregnancy, as it is said that delivery is the definitive treatment for pre-eclampsia.

The commonly used antihypertensive agents in Pregnancy induced Hypertension are Methyl Dopa, Nifedipine, Labetalol, Hydralazine and Nimodipine (Singh A and Verma R,2003).[2]

Such studies are not yet reported from Mizoram, a small state in Noth East India, so this study has been conducted to find out the most effective and safest antihypertensive agent as well as to compare the efficacy of Methyldopa, Nifedipine and Labetalol in the management of Pregnancy induced Hypertension.

MATERIALS AND METHODS

A prospective randomized study among Pregnancy Induced Hypertension patients attending Ante Natal Clinic of State Referral Hospital, Falkawn, Mizoram was conducted after obtaining the approval of the ethics committee and other appropriate authority.

Exclusion Criteria

Patients suffering from pre-existing cardio vascular disorder, diabetes, Rh-iso immunizations were firstly and patients who are already on anti hypertensive excluded. Patients with risk of obstetrics complications like ante partum hemorrhage, multi fetal gestation, hydramnios were also excluded from the study.

Materials

The study is based on a feasible sample size of 150 patients with Pregnancy Induced Hypertension who are admitted in the department of obstetrics and Gynaecology, SRHF, Mizoram. The study group of 50 patients for each drug will be randomly allocated to treatment with Methyldopa, Nifedipine and Labetalol respectively.

Methods

The diagnoses of Pregnancy induced Hypertension used for the study includes:

-An absolute rise of blood pressure of at least 140/90mmHg or more, if the blood pressure is not known or a rise in systolic pressure of at least 30mmHg, or a rise in diastolic pressure of at least 15mmHg over the previously known blood pressure, at least on two occasions 4 or more hours apart. Presence of protein in 24 hours urine of more than 0.3mg/L or more than 1gm/L in two or more midstream specimens obtained 6hours apart in the absence of urinary tract infection.

A complete history was taken. A thorough general physical examination, systemic examination including the abdominal examination, pelvic examination is carried out.

Investigations includes; Blood for Hb, TLC, DLC, ESR, platelete count, ABO and Rh, BT, CT, Serum uric acid, creatinine, Liver enzymes, Fundoscopy, Urine –Routine (physical, chemical, albumin and sugar and microscopic) examinations, Volume of urine-24hrs urinary output and urinary protein, Ultrasonography-Fetal wellbeing and Umbilical artery flow velocimetry.

Specific Treatment

Nifedipine group: Nifedipine 5mg orally every 8 hourly was given, till effective control of blood pressure is achieved. The dose may be increased to 10 mg 12 hourly or 8 hourly if needed.

Methyl dopa group: Methyldopa 250mg was given orally 8 hourly, dose may be increased to 500mg 8 hourly if necessary.

Labetalol Group: Labetalol at a dose of 100 mg 8 hourly was given, and the dose increased to 200mg 8 hourly if necessary.

The patients were followed till delivery and the efficacy of antihypertensive agents will be assessed by the following criteria:

Maternal

1. Gestational age of pregnancy
2. Previous history of P.I.H
3. Side effects of the drugs
4. Prolongation of pregnancy
5. Blood pressure control after treatment
6. Volume of urine output in 24 hours
7. Laboratory interaction-hematocrit and liver function ,proteinuria ,uric acid level
8. Incidence of eclampsia
9. Onset of labour-induced or spontaneous
10. Maternal complications
11. Incidence of preterm labour and delivery
12. Incidence of intrauterine death
13. Mode of delivery

Fetal

1. Maturity of foetus and gestational age at delivery
2. Birth weight
3. Apgar score
4. Small for gestational age or prematurity
5. Admission to Neonatology unit
6. Perinatal death

Statistical Analysis –t test and chi-square are used

RESULTS

The present study sample consist of 150 patients with P.I.H, and are divided into 3 groups, each of which receive one of the antihypertensive drugs-Nifedipine, Methyldopa and Labetalol.

Table 1: Clinical Profile Of The Patient

Parameters	Nifedipine	Methyldopa	Labetalol
Age in Years (Mean ± SD)	23.5 (6.7)	27.6 (0.7)	26.8 (7.4)
Low Socio Economic	13 (26%)	10 (20%)	7 (14%)
Middle Socio Economic	37 (74%)	40 (80%)	43 (86%)
Primigravida	26 (52%)	26 (52%)	30 (60%)
Multigravida	24 (48%)	24 (48%)	20 (40%)
Previous history of PIH	5 (10%)	2 (4%)	2 (4%)
Gestational age (days) on admission (Mean ± SD)	251.18±17.88	251.46±12.88	255.14±6.23

From [Table 1] it is observed that the variation in diferrent age group among the three groups was not statistically significant (p>0.05). Regarding socioeconomic status of the patients P.I.H was found more in middle class family, with no significant difference among the 3 groups (p=0.325). The incidence of P.I.H was more in primigravida with the incidence decreasing as parity increases,with no significant diferrence in the 3 treatment groups(p=0.0890). And regarding past history of P.I.H., the variation is found insignificant at at 5% probability level as p>0.05. And the gestational age on admission were found to be similar in the three groups.

Table 2(a): Outcome of different treatment group.

Variables	Antihypertensive agents		
	Nifedipine [50]	Methyldopa [50]	Labetalol [50]
	Mean ± SD	Mean ± SD	Mean ± SD
B.P Before treatment	150.96/97.65 ± 9.95/5.85	149.98/92.32 ± 8.12/6.85	150.65/98.12 ± 1.30/7.31
B.P after treatment	148.40/95.40 ± 9.11/5.78	141.00/91.20 ± 7.35/5.58	137.40/87.805 ± 0.64/6.15
Gestational age of the fetus at delivery	258.80 ± 0.70	266.16 ± 14.86	269.09 ± 6.27
Birth Weight	2.84 ± 0.70	2.88 ± 0.53	3.18 ± 0.40
Apgar Score	7.72/10±2.52/10	8.34/10±1.58/10	8.82/10±0.43/10

Table 3(b): Statistical Analysis of the Efficacy of Drugs

		t-value	df	P-Value
B.P after treatment	Nifedipine & Methyldopa	4.468/3.692	98/98	0.000/0.000
	Nifedipine & Labetalol	7.254/6.359	98/98	0.000/0.000
	Methyldopa & Labetalol	2.746/2.892	98/98	0.007/0.005
Gestational age of the fetus at delivery	Nifedipine & Methyldopa	2.275	98	0.025
	Nifedipine & Labetalol	3.924	98	0.000
	Methyldopa & Labetalol	1.271	98	0.207
Birth Weight	Nifedipine & Methyldopa	0.305	98	0.761
	Nifedipine & Labetalol	2.937	98	0.004
	Methyldopa & Labetalol	3.140	98	0.002
Apgar Score	Nifedipine & Methyldopa	1.471	98	0.145
	Nifedipine & Labetalol	3.037	98	0.003
	Methyldopa & Labetalol	2.063	98	0.042

Table 3: Side Effects.

Side Effects	Antihypertensive Agents		
	Nifedipine [50]	Methyldopa [50]	Labetalol [50]
Mild drowsiness	19 (38%)	9 (18%)	3 (6%)
Mild Headache	6 (12%)	4 (8%)	4 (8%)
Total	25 (50%)	13 (26%)	7 (15%)

Table 4: Maternal complications.

Maternal Complications	Antihypertansive Agents		
	Nifedipine [50]	Methyldopa [50]	Labetalol [50]
Postpartum Hemorrhage	3 (6)	2 (4)	Nil
Abruptio Placenta	2 (4)	Nil	Nil
X2 = 7.066; df = 4 ; P = 0.132			

[Table 2] shows the control of blood pressure with the antihypertensive given. Here, it is seen that Labetalol has the best control (137.40/87.80 mmHg) followed by methyldopa (141.0/91.20mmHg) and Nifedipine (148.40/95.40mmHg).The difference is found to be statistically significant.

Table 5: Neonatal Outcome.

	Nifedipine [50]	Methyldopa [50]	Labetalol [50]	X2	df	P
Preterm Delivery	7 (14%)	5 (10%)	4 (8%)	0.881	2	0.05
Intra Uterine Fetal Death	3 (6%)	1 (2%)	1 (2%)	-	-	-
Small for Gestational age	8 (16%)	7 (14%)	5 (10%)	0.709	2	0.05
Admission to NICU	13 (26%)	9 (18%)	8 (16%)	1.500	2	0.05
Neonatal Death	2 (4%)	1 (2%)	1 (2%)	-	-	-

The period of gestation at delivery was lowest in the Nifedipine group (258.80 days) and 269.06 days in Labetalol group. Similar trend was found in case of birth weight, seen lowest in Nifedipine group followed by methyldopa group and Labetalol group. Apgar score was also seen highest in labetalol group. Regarding the side effects of the drugs, minor side effects like mild headache and drowsiness were seen

with all the drugs in some cases, the difference in the incidence of side effects was significant (p>0.009). Thus this implies that Labetalol is better tolerated than Nifedipine and methyldopa.

[Table 4] show the maternal complication in the treatment groups,and Labetalol has better result though not statistically significant (p>0.05).

It is observed from the above table that the difference in preterm delivery, intrauterine death, small for gestational age, admission to NICU and neonatal death was not statistically significant.

DISCUSSION

Pregnancy complicated by pregnancy induced hypertension remote from term is associated with an increased risk of maternal and fetal morbidity and mortality. A number of antihypertensive have been tried, but not all have been found to be safe in pregnancy. Methyldopa (centrally acting adrenergic antagonist) is the oldest drug used for PIH, it is safe but has a delayed onset of action, and causes depression and drowsiness. Labetalol, an alpha and beta adrenergic blocker is rapidly absorbed. It has rapid action with minimal side effects on maternal cardiac output. The sustained effect on blood pressure is mainly due to lowering of peripheral resistance (EL Qarmalawi et al, 1995).[3] Nifedipine is a calcium channel blocker causing peripheral vasodilatation. It is fast and long acting with minimal side effects .It lowers blood pressure without apparent reduction in uteroplacental blood flow (Fenakel K etal 1991).[4]

The study sample of 150 patients are divided into three groups with the mean age 23±4.0 yrs (nifedipine), 27 ±0.7yrs (methyldopa), and 26.8 ±7.4 yrs in Labetalol group. The same were found in the study of Sibai BM et al (1992, 1994),[5,6] 21.9 ±4.4 yrs(nifedipine), 30.9±0.7yrs(methyldopa) and El Qarmalawi et al 25.2±1.7yrs (methyldopa), 24.3±1.7yrs (nifedipine).

The Mean and SD of blood pressure after treatment is 148.40/95.40 ± 9.11/5.78 (nifedipine), 141.00/91.20 ± 7.35/5.58 (methyldopa) and 137.40/87.805 ± 0.64/6.15 (labetalol); another study conducted by Plouin PF et al observed the mean BP after treatment with methyldopa and labetalol to be 146/94±13.4/7.5 mmHg and 133/84±14/11 mmHg respectively. Shivakumar V (2017),[7] observed BP after treatment 132.70/89.50±14.40/9.41 with nifedipine and 132.46/87.95±14.08/9.19 with methyldopa. Sibai BM et al observed no significant difference between methyldopa and labetalol with the mean of 139/91±0.9/0.7 for methyldopa and 139/91±0.8/0.6 for labetalol.

Regarding the side effects, mild drowsiness is observed more in Nifedipine (38%) followed by Methyldopa (18%) and Labetalol (6%). Mild Headache is observed in the group of Nifedipine (12%), Methyldopa (8%) and Labetalol (8%). The finding is in agreement with El Qarmalawi et al (1995)[3], where they observed that Labetalol has fewer side effects and better tolerated than Methyldopa, and more adverse effects like headache and drowsiness are found more in Methyldopa. Jayawardana J et al (1994),[8] found that there is no significant difference in the incidence of side effects like drowsiness, headache etc. between Nifedipine and Labetalol treated groups and both were well tolerated. Babbar K et al (2015),[9] noted that Headache and tachycardia were more common with Nifedipine group as compared to Methyldopa and Labetalol group.

CONCLUSION

Nifedipine, Methyldopa and Labetalol are safe and effective agents in the management of pregnancy induced Hypertension. However, considering all the maternal and fetal parameters applicable in the study, Labetalol has a slight advantage over Methyldopa and Nifedipine for better maternal and fetal outcome.

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