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"LABETALOL VS METHYLDOPA IN THE TREATMENT OF MILD TO MODERATE PREGNANCY INDUCED HYPERTENSION"

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ABSTRACT Pregnancy induced hypertension (PIH) is one of the major causes of maternal mortality and morbidity.

MATERIALS AND METHODS: A prospective study aimed to compare the antihypertensive efficacy of alpha methyldopa and labetalol in treatment of mild to moderate PIH patients between 20 wks and 36 wks of gestation who are randomly selected to labetalol (group I) or alpha methyldopa (group II). Duration of antihypertensive treatment required and pregnancy outcome were noted and analysed statistically.

RESULTS: Majority of the patients (91%) recruited for drug therapy belonged to 15 - 25 years. Primigravidae were 69% and multiparae 31%. Both the groups showed significantly lower MAP than pre treatment level (Labetalol group $p < 0.001$ vs Methyldopa group $p < 0.01$) after three days of treatment. Labetalol group showed significant improvement of proteinuria when compared with Methyldopa group ($p < 0.001$), there was no deterioration in this group. In Methyldopa group 8% of patients showed deterioration of proteinuria and only 4% of patients showed improvement of proteinuria. No significant difference in 1 minute Apgar score and mean birth weights in both groups.

CONCLUSIONS: Labetalol has better effect on controlling hypertension than Methyldopa with minimum dosage with decreased proteinuria.

KEYWORDS : Labetalol, Methyldopa, Mild PIH, Moderate PIH

INTRODUCTION

Hypertensive disorders of pregnancy continue to be one of the scourges afflicting womanhood. In India, even today, The maternal mortality in India is 301 per 100,000 live births and PIH was responsible for 18.9 % of total maternal mortality.

Dewhurst 1986 found that preeclampsia can affect blood glucose control in up to 8 % of cases and perinatal mortality can be doubled.Das et al observed that there was a sudden rise in perinatal mortality, where BP exceeded 180/110 mm Hg , albuminuria exceeded 5 gm/24 hrs and blood urea exceeded 40 mg.

A challenge for the obstetrician and internist is the proper prescribing of the drug to treat pregnant women with hypertension.

In recent years, a variety of drugs which lower the BP have been described to treat hypertension during pregnancy. These agents have potential adverse effects both to mother and fetus. However, it is clear from studies that mother gets benefit from such therapy, the benefits for the fetus have been less obvious. Methyldopa is a time honoured antihypertensive and it is widely used in the treatment of PIH.It causes psychic depression, orthostatic hypotension, sodium and water retention. It crosses placenta and accumulates in the amniotic fluid. Because of the poor control of blood pressure and above disadvantages, necessity is felt for better antihypertensive which can overcome the above disadvantages with additional therapeutic benefits.

Labetalol has the advantages e.g.when administered orally it acts within 1-2hrs , cardiac output is unaltered, it reduces myometrial activity, maintains uterine artery caliber, widely used in renal hypertension, improves renal function, as it crosses placenta. It stimulates pulmonary surfactant formation, which helps in early lung maturation and has proved efficacy in the refractory cases of methyldopa.

To enunciate the above facts, the present study was conducted using alpha methyldopa and alpha-beta blocker Labetalol in the drug treatment of PIH.

MATERIALS AND METHODS

A prospective study to compare the antihypertensive efficacy of traditionally used alpha methyldopa and a new drug alpha beta blocker labetalol in the drug treatment of mild to moderate pregnancy induced hypertension was carried out at G.G.H. Kurnool from June 2006 to November 2007.

MATERIALS :

The obstetric patients between 20 weeks and 36 weeks of gestation carrying a live fetus with PIH attending the antenatal clinics at GGH , Kurnool were recruited to this study. PIH was defined as sustained rise of BP to 140/90 mm of Hg or more in a previously normotensive woman or an increase by 30 mm of Hg of systolic or 15 mm of Hg of diastolic BP over baseline values on at least two occasions 6hrs apart or an increase of mean arterial pressure of more than 103.6 mm of Hg after 20th week of pregnancy. The patients with mild to moderate PIH i.e ; diastolic BP between 90 mmHg and 110mmHg or MAP > 103.6 mm of Hg were considered for antihypertensive therapy.

METHODS:

The history , clinical examination , laboratory investigations , details of the patient recruited was recorded in a designed proforma.BP was recorded with a mercury sphygmomanometer and taken at the same time each day 6th hourly whilst the patient was on treatment until delivery.All BP values in the study were recorded after rest in the left lateral position. Phase IV of the korotkoff's sound was taken for determination of the diastolic BP.

Mean arterial pressure was calculated by the formula
MAP= Systolic BP + (2x diastolic BP)/3

The patients after admission to the hospital were managed with rest in the left lateral position.Those patients requiring antihypertensive treatment were randomly allocated to labetalol (group I) or alpha methyldopa (group II) after excluding contraindications of these two drugs.

There were fifty patients who received labetalol (group I) and fifty patients who received methyldopa (group II).To start with, 100 mg bd of labetalol (group I) was given and 250mg tid of alpha methyldopa (group II) was given. In both the groups, the dose was doubled if the BP was not controlled within 48hrs. The maximum amount of drug in Labetalol was 800 mg/day in two divided doses and in case of alpha methyldopa it was 2250 mg/day in three divided doses. MAP of < 103.6 was considered to be a satisfactory BP control. The patients on drug treatment were monitored for fetal and maternal well being .The patients were considered for analysis of study after the delivery or termination of pregnancy. Duration of antihypertensive treatment required and pregnancy outcome were noted.

OBSERVATIONS AND RESULTS

A total of 100 patients of pregnancy induced hypertension were subjects for this study.

- Each category of patients were divided into Labetalol and Methyldopa group. In either group , 50 patients were subdivided

into mild and moderate PIH group according to the level of BP.

- Majority of the patients (91%) recruited for drug therapy belonged to 15 - 25 years.
- Primigravidae were 69% as compared to multiparae 31%.
- After three days of initiation of antihypertensive therapy both the groups showed significantly lower MAP than pre treatment level (Labetalol group $p < 0.001$, Methyldopa group $p < 0.01$)
- In Labetalol group 62 % of patients showed significant improvement of proteinuria ($p < 0.001$), there was no deterioration in this group. In Methyldopa group 8% of patients showed deterioration of proteinuria and only 4% of patients showed improvement of proteinuria.
- BP was controlled with minimum dose of the drug in labetalol group requiring double the dose of the drug in only 4 patients. Whereas in the methyldopa group double the dose of the drug was required in 10 patients.
- In both the groups the number of AGA babies were similar. SGA babies were found more in group I than in group II. But it is not statistically significant.
- There was no significant difference in 1 minute Apgar score in both the groups.
- In both the groups mean birth weights were similar (2.6 kg)

Drug therapy

	Gr-I (N=50)	Gr-II (N=50)	Total 100
Mild PIH	25 (50%)	26 (52%)	51
Moderate PIH	25 (50%)	24 (48%)	49

Amount of the Drug required

	Minimum dosage	Double the dose
Group – I	46	4
Group – II	40	10

Minimum doses for Labetalol - 100mg/Bid - 46 pts
Methyl dopa - 250mg/Tid - 40 pts
Double the dose :
Labetalol - 200mg/bid - 4pts
Methyl dopa - 500mg.Tid -10pts

Mean arterial pressure after treatment in mm of Hg

	Elquamalawi study	Present study
Group – I	92.5	90.3
Group – II	91.1	94.8

p-value for Gr-I: <0.001, Gr-II : <0.01

Drug Effects On Proteinuria

	On admission		After treatment	
Proteinuria	**Gr-I**	**Gr-II**	**Gr-I**	**Gr-II**
Nil	11	26	31	28
Traces	13	4	10	4
1+	16	16	7	12
2+	8	4	2	3
3+	2	0	0	3

Significant improvement of proteinuria was seen in Gr-I in 62% (31 pts) in Gr-II only 8 % (4 pts) P-Value Gr-I Is <0.001

Period of Gestation at Induction

	Mild PIH (N=51)		Moderate PIH (N=49)	
	Gr-I (N=25)	**Gr-II (N=26)**	**Gr-I (N=25)**	**Gr-II (N=24)**
Gest. Age in weeks <34 wks	-	1 (3.8%)	2 (8%)	1 (4.1%)
34-37 wks	-	-	-	2 (8.3%)
>37 wks	25 (100%)	25 (96.1%)	23 (92%)	21 (87.5%)

Pregnancy outcome

	Mild PIH (N=51)		Moderate PIH (N=49)	
	Gr-I (N=25)	**Gr-II (N=26)**	**Gr-I (N=25)**	**Gr-II (N=24)**
Normal vaginal delivery	16 (64%)	19 (73%)	20 (80%)	16 (66.6%)
Instrumental delivery	2 (8%)	2 (7.6%)	1 (4%)	-
LSCS	7 (28%)	5 (19.2%)	4 (16%)	8 (33.3%)

Neonatal outcome

Apgar score	Gr-I (N=50)	Gr-II (N=50)	Total 100
0-3	2 (4%)	-	2
4-7	7 (14%)	8 (16%)	15
8-10	41 (82%)	42 (84%)	79
No significant difference between Gr-I & Gr-II			
AGA babies	43 (86%)	46 (92%)	89
IUGR babies	7 (15.9%)	4 (8%)	11

Mean birth weight in both groups was 2.6 kg

DISCUSSION

In the present study the BP was controlled well with minimum dosage of the drug requiring 200 mg bid dose only in 4 cases in the labetalol group whereas in 46 patients the dosage required was only 100 mg bid. Whereas in methyldopa group the dosage was doubled in 10 cases i.e. 500 mg tid and in 40 patients the dosage required was 250 mg tid. In the Plouin et al study the addition of a complementary drug to achieve control of BP was less often required in the labetalol group than in the methyldopa group. BP control was achieved more frequently in hypertensive pregnancies treated with labetalol than with methyldopa as a first line of treatment. Hence the results of the present study were similar to the Plouin et al study.

In the present study no side effects were noticed in either group.) Whereas in Lamming and Symmonds study, slight breathlessness was noticed in labetalol group. Drowsiness , headache , postural hypotension was noted in methyldopa group.

In the present study no apparent detrimental effects were found on the fetus antenatally, during labour or postpartum period in the labetalol group. The results were similar to the study conducted by Lamming and Symmonds.

In the present study small for gestational age babies were more frequently found in the labetalol group than with methyldopa group. The results are comparable with the study conducted by Sibai and associates in which SGA infants were significantly higher with labetalol.

In the present study there was significant improvement in renal function with a markedly lower incidence of proteinuria in the labetalol group than with methyldopa group. The results are similar to the study conducted by Lamming et al where they have found that after two weeks of treatment with labetalol renal function had significantly improved with a markedly lower incidence of proteinuria.

CONCLUSIONS

- Labetalol has better effect on controlling hypertension than methyldopa.
- Better BP control was achieved with minimum dosage of the drug in labetalol group than in the methyldopa group. Hence labetalol is a better drug.
- Labetalol causes significant improvement in renal function as evidenced by decreased proteinuria than methyldopa.
- The only drawback of the drug observed in this study was that SGA babies were more often associated with labetalol group than with methyldopa group but it is not statistically significant.
- Hence labetalol can be recommended as a first line of drug not only for the treatment of mild to moderate PIH but also can be considered for severe PIH as it can be given intravenously also.

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