ANTIHYPERTENSIVE EFFICACY AND PERINATAL SAFETY OF METHYL DOPA, NIFEDIPINE AND METAPROLOL IN PREGNANCY INDUCED HYPERTENSION

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SUMMARY

Gestational hypertension occurs as a consequence of physiological alterations that occur in pregnancy. The three antihypertensive drugs namely methyl-dopa, nifedipine and metaprolos were studied for their antihypertensive efficacy and perinatal safety in 75 patients (25 in each group). All the drugs had considerable antihypertensive effect, but the mean percentage fall in BP was more in patients taking nifedipine. The mean gestational age in all the groups was comparable. In perinatal outcome, there was no significant difference in the mean birth weight of the babies in the three groups, the Apgar Score at 5 min was better and also the duration of stay in NICU was minimum, in nifedipine group. No perinatal death was reported in nifedipine group while 2 each were reported in other two groups.

INTRODUCTION

Pregnancy induced hypertension affects approximately 10% of all pregnant women. It is still a major cause of obstetrical and perinatal mortality accounting for 17.2% of total maternal mortality and 22.2% of total perinatal mortality in India (Sapre et al., 1996). The role of antihypertensive therapy is controversial, some advocating aggressive drug therapy, while others recommending no treatment at all. However, the current consensus is that antihypertensive therapy during pregnancy

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has potential usefulness when PIH severe enough to warrant termination of pregnancy develops before neonatal survival is likely, (Weir, 1979).

There are many types of drugs that may be used to control maternal hypertension, prevent proteinuria and improve perinatal results. Methyldopa is considered as a preference drug for treating PIH (Redman et al, 1976). The initial reservations about the safety of calcium channel blockers and beta blockers in PIH have been proved to be uncalled for by numerous favourable reports appearing during recent years with regard to efficacy and safety of these drugs.

The present study was designed for evaluating the antihypertensive effects and perinatal safety of methyl-dopa, nifedipine (calcium channel blocker) and metaprolol (beta blocker) in moderate to severe hypertension.

MATERIAL AND METHODS

The study was conducted in the Department of Gynaecology and Obstetrics in collaboration with Department of Pharmacology and Therapeutics, Govt. Medical College and SMGS Hospital, Jammu.

All hypertensive pregnant patients seen from 1.1.95 to 31.5.96 were screened for inclusion in the study. Eligibility requirements included a primigravida with a singleton pregnancy with gestational age between 20-40 weeks and diastolic blood pressure (DBP) of > 100 mm Hg with proteinuria and oedema. Multi-gravidas or patients with DBP > 90 mm Hg antedating pregnancy, previous history of antihypertensive drugs, any co-existing renal or vascular disease, diabetes, cardiac pathology, asthma and oliguria were excluded from the study.

After obtaining informed consent, these 75 patients were randomly divided into three groups namely, Group I patients were treated with methyl-dopa, 250 mg TDS to 2 gms per day. Group II patients were put on nifedipine 10 mg TDS to 120 mg per day and group III were given metaprolos, 100 mg OD to 400 mg per day.

The patients were kept on daily follow up for pulse rate, BP and proteinuria. If after initial dose, the response was unsatisfactory, the dose of drug was increased. The foetal surveillance was done by clinical examination and ultrasonography. Perinatal outcome was assessed and any adverse maternal or foetal side effects were noted.

The data was statistically analysed using students's "t" test.

RESULTS

The mean maternal age and gestational age at the start of study were comparable in all the three groups. (Table I) The mean duration of treatment was 17.28 + 11.58; 12.5 + 6.17 and 16.8 + 11.54 days with group I, II and III respectively. No maternal death was reported in the series (Table I).

The mean pre-treatment BP in three therapeutic groups was 163.76 + 7.17/110.56 + 5.08 mm of Hg in patients taking methyl-dopa (Group I), 174.48 + 17.89/112.96 +10.28 mm of Hg, in patients taking nifedipine (Group II) and 165.52 + 5.84/ 108.6 +4.24 mm of Hg in patients taking metaprolol (Group III). The mean post-treatment BP showed a significant fall in all the three groups and was 132.72 +6.4/82.72 +8.85

Table I
GESTATIONAL AGE, DURATION OF TREATMENT AND RESPONSE TO TREATMENT

	Methyl-dopa (n=25)	Nifedipine (n=25)	Metaprolol (n=25)
Mean Age of Patients (in years)	24.24 + 3.56	24.84 +4.24	25 + 4.31
Mean Gestational age at start of Rx (in weeks)	33.62 + 1.73	34.80 + 2.11	33.38 + 1.87
Mean Duration of Rx (in days)	17.28 + 11.58	12.5 + 6. 17	16.8 + 11.54
Mean Pre Rx BP (in mm Hg)			
Systolic BP	163.76 + 7.17	174.48 + 17.89	165.52 + 5.84
Diastolic BP	110.56 +5.08	112.96 + 10.28	108.6 + 4.24
Mean Post Rx BP (in mm Hg)			
Systolic BP	132.72 + 6.4	126.92 + 11.2	132.42 + 6.66
Diastolic BP	82.72 + 8.85	78.24 + 7.06	84.5 + 6.65
Maternal Deaths	nil	nil	nil

in group I, 126.92 + 11.2/78.24 +7.06 mm of Hg, in group II and 132.42 + 6.66/84.5 + 6.65 mm of Hg in Group III.

The mean percentage fall noted with methyl-dopa, nifedipine and metaprolol was 18.95/25.18; 27.2/30.74 and 20.00/22.19 respectively (Fig.1). Unsatisfactory response to drug treatment was seen in 5 patients in Group I

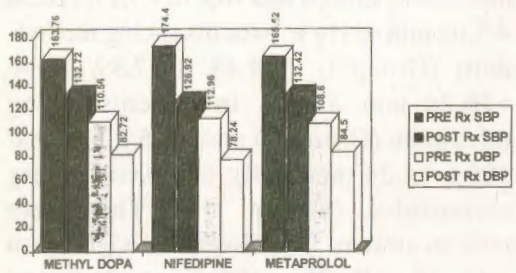

Fig. 1.: Bar diagram depicting fall in BP in three therapeutic groups

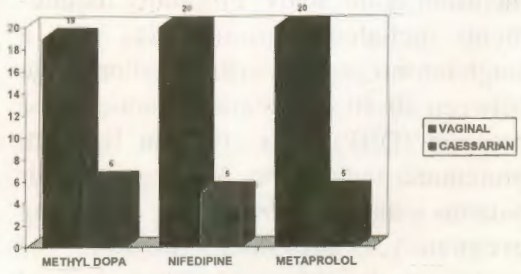

Fig. 2.: Bar diagram depicting mode of delivery in three therapeutic groups

Table II
INDICATIONS FOR THE CAESAREAN SECTION

Indication	Number of patients		
	Methyl-dopa (n=6)	Nifedipine (n=5)	Metaprolol (n=5)
Uncontrolled Hypertension	3	1	3
Failed Induction	2	-	-
Foetal Distress	1	3	2
Non progress of labour	-	1	-

out of which 3 underwent caesarean section and in the remaining 2 patients nifedipine was added. Three patients showed inadequate response to nifedipine in group II, while one was managed with emergency caeserean section and in two beta-blockers were added. Seven patients in group III had unsatisfactory response drug dosage with beta-blockers; in 4 patients nifedipine was added and in 3 patients caeserean section was done.

Majority of the patients in the study series had vaginal delivery, caeserean section was done in 6 patients in group I while 5 patients each in group II and III underwent caeserean section (Fig 2). Various

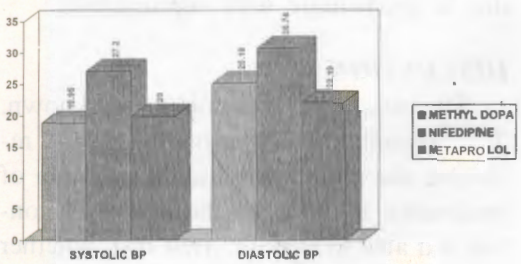

Fig. 3.: Bar diagram depicting mean percentage fall in BP in three therapeutic groups

indications for which caeserean section were done are shown in Table II.

No significant side effects were noted during the study. Only 3 patients with methyl-dopa group reported excessive sedation during the initial treatment days. Four patients taking nifedipine reported tachycardia and headache, which gradually settled without any medication and did not necessitate withdrawal of drug. None of the patients in group III showed significant maternal or foetal bradycardia.

PERINATAL OUTCOME

The perinatal outcome was better in mothers treated with nifedipine as compared to mothers treated with methyl-dopa and metaprolol (Table III). There was no significant difference in the mean birth weight in all the three groups.

In group I mean gestational age at delivery was 36.47 days. 22 (88%) babies had Apgar score (A/S) > 8 at 5 minutes, 5 (20%) neonates needed admission to NICU (Neonatal Intensive Care Unit) with mean durationof stay of 5.6 + 3.05 days. 4 babies were small for date and 2 perinatal deaths occured. One was late intrauterine death

Table III
PERINATAL OUTCOME

	Methyl-dopa (n=25)	Nifedipine (n=25)	Metaprolol (n=25)
Mean Birth Weight (in kg)	2.66 + 0.46	2.64 + 0.32	2.65 + 0.51
A/S > 8 at 5 min	22 (88%)	24 (96%)	21 (84%)
Admission to NICU	5 (20%)	4 (16%)	5 (20%)
Mean duration of stay in days) in NICU	5.6 + 3.05	3.6 + 2.41	5.2 + 2.36
Small for date (IUGR)	4 (16%)	5 (20%)	4 (16%)
Perinatal deaths	2 (8%)	nil (0 %)	2 (8 %)

at 32 weeks due to uncontrolled hypertension with IUGR, another died after two days of birth due to prematurity (Wt 1.2 kg).

In group II, mean gestational age at delivery was 36.43 weeks. 24 (96%) babies had A/S > 8 at 5 minutes, 4 (16%) neonates needed admission to NICU with a mean duration of stay of 3.6 + 2.41 days and 5 (20%) out of 25 were small for date babies. No perinatal death was seen in this group study.

In group III, mean gestational age at delivery was 36.78 days, 21 (84%) babies had A/S > 8 at 5 minutes. NICU admission was needed in 5 (20%) babies with a mean duration of stay in NICU 5.2 + 2.36 days, 4 (16%) babies were small for date and 2 perinatal deaths were observed in this group. One was IUD (Intrauterine death) at 32 weeks due to uncontrolled hypertension and proteinuria; other baby expired on 8th day due to prematurity with septicaemia.

DISCUSSION

The cause of PIH is not exactly known. The treatment is therefore aimed at relieving the symptoms and termination of pregnancy as soon as the foetus is considered able to survive. Bed rest, whether partial or absolute is important. Some women with PIH go into labour spontaneously.

For those who do not, the accepted practice is to induce labour at 37th or 38th week of gestation. If the subsequent progress is slow or if the conditions are unfavourable for induction then the baby should be delivered by caeserean section (Daftary and Daftary, 1995). The use of various antihypertensive drugs in attempt to prolong pregnancy or modify perinatal outcome in pregnancies complicated by various types and severities of hypertensive disorders has been of considerable interest.

In our study series, methyl-dopa effectively lowered the pre-treatment BP from 163.76 + 7.17/110.56 + 5.08 to 132 72 + 6.4/82.72 + 8.85 mm Hg. Comparable effects were noted with the use of methyl-dopa in various studies (Leather et. al., 1968 & Pierre et al., 1988).

Nifedipine, a calcium channel blocker was first used by Walter and Redman in 1984. Nifedipine effectively lowered BP from 174.48 + 17.89/112.96 + 10.28 to 126.92 + 11.2/78.24 + 7.06 mm Hg in our study. The main advantage noted with this drug over methyl-dopa was its rapid onset of action. Its action started within 15-20 minutes and hypotensive effect lasted for 4-6 hrs. Similar duration and efficacy in lowering BP has been reported. (Walter and Redman 1984). Majority of patients (68%) had vaginal delivery concluding that in therapeutic doses, nifedipine had no tocolytic effect on uterus. It is only very high doses which act as effective tocolytic agent (Anderson et al, 1979). No maternal or perinatal death was reported in this group.

The development of beta-blocker drugs stimulated renewed interest in controlling maternal BP in interest of improving perinatal outcome. Metaprolol used in our study series was effective in controlling BP (Mean % fall systolic/diastolic was 20.00/22.19) to safe level, with no significant foetal or maternal side effects. The incidence of perinatal loss and intrauterine growth retardation was not higher in patients of PIH treated with metaprolol than in patients treated with other anti-hypertensive drugs (Sanstrom, 1979). Statistical Analysis:- Each treatment group reported a mean fall of blood pressure after a variable period of therapy. The fall was statistically significant in all the three groups and both systolic and diastolic blood pressure witnessed stastically significant fall ($p < 0.01$ in nifedipine group, $p < 0.05$ in methyl-dopa and metaprolol group). When the three groups were compared mutually patients who received nifedipine showed a greater mean fall in BP (both systolic and diastolic) as compared to those receiving methyl-dopa and metaprolol and the difference was statistically significant ($p < 0.05$).

Neonatal outcome : Neonatal outcome was evaluated by different parameters including mean duration of stay in NICU . The outcome was better in those neonates whose mothers received nifedipine (mean stay 3.6; SD 2.41) for treatment of pregnancy induced hypertension as compared to those who received methyl-dopa (mean stay 5.6; SD 2.36) or metaprolol

(mean stay 5.2; SD 2.36); thus the neonates in nifedipine group needed to stay in NICU for a shorter period compared to those in metaprolol and methyl-dopa groups and the difference was statistically significant ($P < 0.05$).

In conclusion, all the three drugs viz methyl-dopa, nifedipine and metaprolol in our study proved effective in lowering maternal BP without significant side effects, though nifidepine group showed greater mean percentage fall in BP with no perinatal deaths as compared to other two groups.

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