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A randomized, double-blind, comparative trial of nifedipine and methyldopa in moderate pregnancy induced hypertension

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ABSTRACT

To assess the efficacy and safety of nifedipine compared with methyldopa in the management of moderate pregnancy induced hypertension (PIH). One hundred pregnant patients with moderate PIH were randomly allocated to receive either methyldopa or nifedipine. The dose of the drugs was doubled every 48 hours to maintain a mean systolic arterial blood pressure < 150 mmHg and mean diastolic blood pressure <100 mmHg. Maternal and fetal outcomes and frequency of side effects were studied. The statistical level of significance was taken at P < 0.05. 3 patients in methyldopa group and 5 patients in nifedipine group were excluded from the study as they were delivered other hospitals. Both drugs reduced hypertension with similar fetal and maternal outcome benefits. Nifedipine and methyldopa could both be used effectively to control blood pressure in moderate PIH.

Keywords: Pregnancy, Hypertension, methyldopa, nifedipine, pre-eclampsia.

INTRODUCTION

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 fetus. 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.

It has been clearly shown that control of hypertension reduces these complications, although the choice of antihypertensive agent is controversial. Most obstetricians agree that drug therapy has little place in the management of mild pregnancy induced hypertension (PIH) occurring late in the third trimester. When moderate or severe PIH occurs with proteinuria, mortality rates are raised and active treatment results in a lower perinatal mortality rate.

Both nifedipine and methyldopa are the drugs most commonly used by obstetricians for the treatment of PIH. Many studies have demonstrated comparable efficacy and a lower risk of overshoot hypotension and fetal distress in severe PIH, but there have not been any randomized clinical trials comparing these 2 agents in moderate PIH.

The objective of our investigation was to compare the efficacies of oral nifedipine and methyldopa in the management of moderate PIH after 32 weeks of gestational age.

MATERIALS AND METHODS

After obtaining informed and written consent and Institute ethics committee approval, one hundred women with singleton pregnancies complicated by hypertension were allocated by a series of random numbers to treatment with either nifedipine (50 women) or methyldopa (50 women). The patient and the investigator were blinded regarding treatment.

Patients with past history of hypertension, diabetes, renal disease, asthma, congestive heart failure, known atrioventricular block, other illness, or fetal congenital abnormality including intrauterine growth retardation were excluded from the study. All patients in the study were more than 32 weeks pregnant and were normotensive before 20 week of pregnancy. The criteria for entry into the study was a sitting systolic blood pressure of 150 to 169 mm Hg or diastolic blood pressure (disappearance of sounds phase V, Korotkoff sounds) of 100 to 109 mm Hg on two occasions at least 4 hours apart. On each occasion the mean of two readings taken one minute apart after the patient had been sitting quietly for 10 minutes was recorded. All patients were managed as per National Institute for Health and Clinical Excellence (NICE) 2011 revised guidelines for the management of hypertensive disorders during pregnancy.

The initial doses of the drugs were 250 mg methyldopa three times a day or 10 mg nifedipine four times a day. The target diastolic blood pressure was 80-100 mm Hg and systolic blood pressure was 140-150. If this was not reached after 48 hours treatment, the dose was doubled and then doubled again after a similar period if necessary. All patients were allowed an unrestricted salt diet. If the target blood pressure was not reached at a dose of 3000 mg methyldopa a day or 160 mg nifedipine a day, labetalol was added to the regimen.

At enrolment point-of-care dipstick (reagent-strip) urinalysis, serum creatinine and urate concentrations, liver function, hematological and coagulation state were assessed, and unstressed fetal cardiotocography (CTG) was performed at admission. If dipstick was >1+, 24-hour urine sample was collected to detect significant proteinuria (>300mg/day). Ultrasound was done used to assess fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry at enrolment. Ultrasound and CTG were repeated whenever clinically indicated. For the purposes of this study an abnormal cardiotocogram was one where there was (a) an episode of tachycardia (fetal heart rate of more than 160 beats/min) lasting more than five minutes; (b) an episode of bradycardia (fetal heart rate of less than120 beats/min) lasting more than five minutes; (c) "flattening" of the tracing (lack of variability of fetal heart rate to within five beats/min for more than five minutes); or (d) late deceleration (occurring more than 15 seconds from the peak of contraction).

Delivery was effected for either fetal or maternal indications. Maternal indications for early delivery were: a rise of 50% or more in serum creatinine concentration; the development of coagulopathy; abnormal liver function; or a rapid increase in the clinical severity of disease as assessed by blood pressure, vasospasm, hyperreflexia, hepatic tenderness, and nausea. Fetal indications were, cessation of intrauterine growth shown by ultrasonography and an unreactive cardiotocograph.

All outpatients were seen every two weeks until 36 weeks' gestation and thereafter every week until delivery. Patients were admitted to hospital if their blood pressure exceeded 110 mm Hg diastolic, if there was proteinuria (>300mg/24hr urine), or for obstetric reasons. All inpatients were assessed everyday; urine analysis was performed daily, and uric acid was measured weekly.

All study patients who did not go into spontaneous labor before term had labor induced with prostaglandin E2 gel, provided that there was no contraindication to vaginal delivery.

The primary outcome was successful control of SBP <150 mmHg and DBP <100 mmHg without using additional drugs. Secondary outcomes analyzed included, maternal and fetal side effects such as hypotension, maternal tachycardia, headache, flushing, nausea and vomiting, dizziness, abnormal cardiotocogram or cardiovascular accidents after starting the antihypertensive medication.

Continuous measurements were compared using a two tail t test. Categorical data were tested using $\chi 2$ test with allowance for paired data as appropriate. All continuous variables were expressed as means (SD). The level of significance was $P < 0.05$.

RESULTS

100 patients were randomized to the 2 treatment groups. Out of 100 patients, 8 patients were excluded from study for failure to comply regular follow up, 3 in methyldopa and 5 in nifedipine group. Further analysis will focus on the 92 patients who completed the study. The demographic and clinical characteristics of the two groups were similar (Table 1) before initiation of therapy.

Table 1: Clinical characteristics of study population

Characteristic		Methyldopa (n=47)	Nifedipine(n=45)	pvalue
Age (years)		24.09 ±4.71	23.82±3.32	.709
Weight (kg)		59.31±3.55	58.44±3.32	.226
Gestational age at enrolment (weeks)		34.36±1.25	34.31±1.41	.856
Gravidae	Primi	39(83%)	32(77.2%)	.134
	Multi	8(17%)	13(22.8%)	
Initial systolic blood pressure (mm Hg)		158.97±7.07	157.77±6.20	.390
Initial diastolic blood pressure (mm Hg)		103.25±4.29	102.46±4.07	.369
Initial heart rate (beats/min)		85.19±4.05	84.26±4.13	.282
Total duration of treatment (days)		20.02±7.36	20.28±8.21	.870

Values are expressed as mean ±standard deviation (SD), or number of patients(%). pvalue <.05 is statistically significant.

All patients in both groups achieved target blood pressure on the single, double or redouble dose of medications, none required added labetalol. There were no cases of eclampsia or imminent eclampsia during treatment in either group. Table 2 shows the fetal and maternal outcome. The duration of therapy and gestational age at labor were similar in both groups.

Table 2: Maternal and fetal outcomes

Characteristic	Methyldopa(n=47)	Nifedipine (n=45)	pvalue
Maternal outcomes			
Total duration of pregnancy	37.08±1.01	36.84±0.952	.245
Preterm labor	12(25.5%)	15(33.3%)	.270
Vaginal delivery	28(59.6%)	33(73.3%)	.120
Caesarean delivery	19(40.4%)	12(26.7%)	
Spontaneous labor	7(14.9%)	9(20%)	.542
Induction of labor	25(53.2)	26(57.8%)	
Elective caesarean delivery	15(31.9)	10(22.2%)	
Reported side effects			
Dizziness	14(29.8%)	0	.000
Nausea	14(29.8%)	8(17.8%)	.134
Headache	4(8.9%)	14(29.8%)	.001
Flushing	13(27.7%)	19(42.2%)	.007
Fetal outcomes			
Mean birth weight (kg)	2.68±0.33	2.59±0.27	.198
Apgar score at 5minutes	8.91±0.74	8.78±0.59	.335
Abnormal CTG	9(19.1%)	12(26.7%)	.271
NICU admission	7(14.9%)	8(17.8%)	.463

Values are expressed as mean ±standard deviation (SD), or number of patients(%). CTG; carditocogram, NICU; neonatal intensive care unit. pvalue <.05 is statistically significant.

The mild adverse effects like headache and flushing were more common in nifedipine group and dizziness was seen more frequently in methyldopa group (table 2). The eventual fetal outcome for all patients treated with methyldopa was the same as that for those treated with nifedipine; birth weight, Apgar score and NICU admissions were not significantly different and there were no stillbirths in either group (table 2). The most common cause for admission to neonatal intensive care unit was prematurity.

DISCUSSION

Control of blood pressure is an important strategy in the management of PIH for the prevention of both maternal and fetal adverse events. No drugs in current clinical use beneficially affect the human placenta. As a result, management involves treatment of maternal hypertension and close antenatal supervision of the mother and fetus with timely delivery to prevent deterioration of the mother and fetus.

This study demonstrated that both nifedipine and methyldopa could be used effectively in the control of blood pressure in moderate pregnancy induced hypertension, and this is consistent with the reports of the previous studies[1-3]. However, methyldopa was associated with increased incidence of dizziness whereas nifedipine was associated with increased incidence of flushing and headache. All these minor side effects did not result in the need for discontinuation of either study medication. None of the patient required labetalol; we therefore believe that both methyldopa and nifedipine are equally effective to control blood pressure.

Pregnancy induced hypertension complicates about 10% of pregnancies; pre-eclampsia affects 2-8% of pregnancies; the incidence of eclampsia greatly varies between settings, being higher in developing countries[4]. Pre-eclampsia and eclampsia increase maternal and perinatal morbidity and mortality. Many drugs are currently available for

treating pregnancy induced hypertension. Some have been used extensively and others have been used infrequently or have yet to be tried.

Nifedipine has been into antenatal antihypertensive treatment since years, proved its efficacy in treatment of high blood pressure along with safety to mother and fetus. However, Nifedipine is a potent antihypertensive agent and should not be given sublingually as it may cause a precipitate fall in blood pressure, which can lead to fetal distress.

The potential advantages of nifedipine are rapid onset of action, ability to increase urine output due to a selective renal vasodilatation, and tocolytic property. α-Methyldopa (a centrally acting α-adrenergic agonist that inhibits vasoconstricting impulses from the medulla oblongata) has traditionally been the most commonly used agent for the control of blood pressure during pregnancy. Its safety has been well established both in pregnancy and in the long-term follow-up of the infants. One of the most frequent side effects is sedation, which can be profound. In higher doses this is often poorly tolerated and leads to unpredictable compliance.

The evidence for the benefit of prophylactic antihypertensive therapy is controversial[4]. Even though, antihypertensive agents may reduce risk of developing severe hypertension, cerebral hemorrhage or hypertensive encephalopathy, a clear benefit of antihypertensive agents in mild-to-moderate chronic hypertension remains unproven, as treatment does not prevent. Apart from these, these drugs may cause intra uterine growth retardation by producing systemic hypotension- a harmful effect that may compromise fetoplacental blood flow[5]. the effect on uteroplacental circulation is more pronounced with betablockers than calcium channel blockers[6, 7].

Methyldopa is the oldest drug used for PIH. It is effective and safe for both the mother and the fetus. Drug exposure in utero does not affect later infant growth and development[8]. The main disadvantages are a delayed onset of action, drowsiness, depression, fluid retention and nasal congestion. It may also give a positive Coombs' test in 20% of patients, and may cause hemolytic anemia, systemic lupus erythematosus like syndrome and hepatic damage.

The incidence of PIH is seen more in primigravidae, 77.2 % was seen in our study[9]. The immunological etiology in 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 etiology 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.

In our study group neither methyldopa nor Nifedipine restricted fetal growth. This corrected well with the study of Moretii etal, the effect of nifedipine on fetal and placental Doppler waveforms does not affect the resistant indices[10].

Based on our findings, we conclude that both oral nifedipine and methyldopa could be used effectively and safely in the control of blood pressure in moderate PIH.

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