

A prospective observational study to compare efficacy and safety of methyldopa and nifedipine in management of moderate gestation hypertension

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ABSTRACT

Background: Hypertensive disorder in pregnancy is one of the most common complications of pregnancy worldwide. It is associated with maternal mortality and morbidity as well as perinatal mortality. Antihypertensive drugs are often used to lower blood pressure with the aim of preventing its progression to adverse outcomes for the mother and the fetus. The risk of developing severe hypertension is reduced to half by using antihypertensive medications. Studies have been done using various antihypertensive in hypertensive disorders of pregnancy. But there are very few studied comparing nifedipine and methyldopa in hypertensive disorders of pregnancy where majority of the studies are evaluated for short duration. Hence we have undertaken this study to compare the efficacy and safety of methyldopa and nifedipine in patient with moderate gestational hypertension.

Methods: This is a prospective observational study where pregnant patients with moderate gestational hypertension either on oral nifedipine 10 mg t.i.d. or on methyl-dopa 250 mg t.i.d. were enrolled during 6 month period. Data at week one and week four were observed along with side effects. Reduction in systolic and diastolic blood pressure from baseline and occurrence of side effects were studied. The statistical significance was at $P < 0.05$.

Results: The mean reduction of systolic/diastolic BP with methyldopa in four weeks was 17/13 mmHg as compared to nifedipine being 18.5/14.5 in four week. There was significant reduction in systolic blood pressure in nifedipine group compared to methyldopa group at four weeks ($p=0.04$). Both treatments were well tolerated with minimal side effects.

Conclusions: Methyldopa and Nifedipine are equally effective in controlling blood pressure in moderate gestational hypertension with minimal side effects. However, nifedipine can be preferred over methyldopa as it showed significant reduction in systolic blood pressure at four weeks.

Keywords: Moderate gestational hypertension, Methyldopa, Nifedipine

INTRODUCTION

In pregnancy until 22-24 weeks, there is a fall in blood pressure caused by active vasodilatation achieved through the action of local mediators such as prostacyclin and nitric oxide. After this, there is a gradual increase in blood pressure until term when pre-pregnancy levels are attained.¹

The prevalence of hypertensive disorder in pregnancy varies according to geographic regions of world and ranges from 1.5% in Sweden's to 7.5% in Brazil.²

Hypertensive disorders of pregnancy are common in developing countries like India where it complicate approximately 10% of pregnancies.³ They are important causes of maternal and fetal morbidity and mortality.⁴ Young primigravidae under 20 years and all patients over 30 years have an increased chance of gestational hypertension.⁵

There is no consensus about the definition of hypertensive disorders during pregnancy and several classifications have been suggested.⁶⁻⁸ Nevertheless, there is now general agreement about the broad categories.

Hypertensive disorders of pregnancy are classified into 4 categories: chronic hypertension, preeclampsia-eclampsia, Preeclampsia superimposed on chronic hypertension and Gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy).⁹

According to NICE guidelines, in pregnancy mild hypertension means diastolic blood pressure 90-99 mmHg, systolic blood pressure 140-149 mmHg. Moderate hypertension means diastolic blood pressure 100-109 mmHg, systolic blood pressure 150-159 mmHg. And severe hypertension means diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater. Antihypertensive treatment is not needed in mild hypertension but need to given in all cases of moderate to severe hypertension.⁹

In a multicentre study, approximately 30% of hypertensive disorders of pregnancy were due to chronic hypertension while 70% of the cases were diagnosed as gestational hypertension/preeclampsia.³

Hypertension in pregnancy will predispose to acute or chronic utero-placental insufficiency that may lead to fetal death, intrauterine growth retardation (IUGR) and preterm delivery.^{10,11} It is proven that control of hypertension reduces these complications.¹² The commonly used antihypertensive drugs in pregnancy are nifedipine, methyldopa, labetalol and hydralazine.¹³

Methyldopa has been used extensively and appears to be effective and safe both for mother and fetus.^{14,15} Methyldopa is a centrally acting antihypertensive agent. It is a pro drug that exerts its antihypertensive action via an active metabolite.¹⁶ Maternal side effects include lethargy, drowsiness and depression, and drug-induced hepatitis.

Redman CW, Beilin LJ, Bonnar J et al showed that hypotensive effect of methyldopa in pregnancy was similar to its action in non-pregnant individuals and greatly reduced the frequency of severe hypertension occurring antenatally and in labour. No serious side effects were encountered.¹⁴

Marked fall of both systolic and diastolic pressure generally between 24 and 48 hours from the start of using methyldopa was noticed by S. F. Hans et al.¹⁷

Subheddar V et al showed that treatment of hypertension in pregnancy with methyldopa will reduce Mean Arterial Pressure.¹⁸

Nifedipine a type 2 calcium channel blocker inhibits the inward flow of calcium across the L-type slow channels of cellular membranes and used as antihypertensive treatment in pregnancy since years, proved its efficacy in treatment of high blood pressure along with safety to mother and fetus.¹⁹

Nifedipine has been shown to cause relaxation of the uterine smooth muscle and hence its use as a tocolytic agent. In vitro studies have shown the ability of nifedipine to inhibit myometrial contraction in pregnant and non-pregnant women.²⁰

Sibai et al. compared bed rest with oral nifedipine in 200 women with pre-eclampsia between 26 and 36 weeks of gestation. They showed a significant reduction in the systolic and diastolic blood pressures with nifedipine, as well as reduction in the number of deliveries for severe hypertension.²¹

Study conducted by Bharathi K N et al showed rapid fall in systolic blood pressure at 6 hours in both methyl dopa and nifedipine groups and continued to be in normal range till 72 hours but was significant with only in nifedipine group ($p < 0.01$).²²

A prospective clinical trial conducted by Jayawardana J, Lekamge N. et al Srilanka in 126 pregnant hypertensive patients showed that nifedipine 30 to 90 mg/day and methyldopa 750 to 2000 mg/day had average systolic blood pressure of 148 and 152 mmHg respectively during pregnancy, average diastolic blood pressure 102 and 104 mmHg respectively.²³

Both methyldopa and nifedipine may cause intra uterine growth retardation by producing systemic hypotension- a harmful effect that may compromise fetoplacental blood flow.²⁴ Other side effects include headache, palpitation and insomnia.

Studies have been done using various anti-hypertensives in hypertensive disorders of pregnancy. But there are very few studies comparing nifedipine and methyldopa in hypertensive disorders of pregnancy where majority of the studies are evaluated for short duration. Hence we have undertaken this study to compare the efficacy and safety of methyldopa and nifedipine in patient with moderate gestational hypertension.

METHODS

This is a prospective observational study conducted at Basaveshwara Teaching and General Hospital attached to M.R. Medical College, Kalaburagi. Ethical clearance was obtained from Ethics committee, M.R. Medical College, Kalaburagi. Study was conducted according to Good Clinical Practice.

Inclusion criteria

All pregnant patients with more than 20 weeks of gestation diagnosed to have moderate gestational hypertension attending obstetrics and gynecology (OBG) department at Basaveshwara Teaching and General Hospital between 1st July 2015 to 31st December 2015 were included in the study. Written consent was taken before enrolment.

Exclusion criteria

- Hypertensive disorder in pregnancy with preeclampsia/eclampsia.
- Heart diseases including Ischemic Heart Disease, Rheumatic Heart Disease, Dilated cardiomyopathy.
- Haematological disorders, renal disorders and hepatic diseases.
- History of intolerance/hypersensitive to methyldopa/nifedipine.
- Patient with less than 20 week and more than 36 week gestation.
- Patient not willing to give consent.
- K/c/o hypertensive disorder in pregnancy already on antihypertensives.

Procedure

Moderate gestation hypertension is defined as sitting systolic blood pressure of 150 to 159 mm of Hg and a diastolic blood pressure of 100 to 109 mm of Hg on two occasions four hours apart after 20 weeks of gestation as per National Institute for Health and Clinical Excellence (NICE) 2011 revised guidelines for the management of hypertensive disorders of pregnancy.⁹

The blood pressure was measured using the validated Mercury sphygmomanometer in sitting position and observed for the appearance and disappearance of Korotk off sounds 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 resting state for 10 minutes.

Data collection

All pregnant patients with moderate gestational hypertension either on oral nifedipine 10mg t.i.d. or on methyl-dopa 250mg t.i.d. 6 month during study period were included in the study based on inclusion and exclusion criteria. These patients were further categorized in two groups based on antihypertensive (Methyl dopa/nifedipine) given. Nifedipine group consists of 53 patients. Methyl-dopa group consist of 52 patients. Data was collected using standard case record form. All outpatients were seen at week one and at week four after starting treatment. Side effects of the drugs were also recorded during study period.

The primary outcome was mean reduction in Systolic Blood Pressure and Diastolic Blood Pressure without using additional drugs at week 4. Secondary outcomes included maternal side effects such as hypotension, maternal tachycardia, headache, flushing, nausea and vomiting, dizziness or cardiovascular accidents after starting the antihypertensive medication.

Statistical analysis

Descriptive data was presented as mean with standard deviation (SD). Two tailed ‘t’ test was used to compare reduction in systolic and diastolic blood pressure in one week and four weeks with respect to baseline between two groups. The Statistical Package for the Social Sciences (SPSS) version 20.0 software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 105 pregnant patients with moderate gestational hypertension were enrolled in the study during 6 month period (1st July 2015 to 31st December 2015). 10 patients, 4 in methyldopa and 6 in nifedipine group didn’t comply with the follow up and were excluded from the analysis. We present analysis of 95 patients who completed the study.

The demographic and clinical characteristics of the two groups at the time of enrolments Table 1. In the present study, about 17 (35.4%) of the pregnant women in methyldopa group and 18 (38.3%) in nifedipine group were primigravidae (Table 1).

Table 1: Clinical characteristics of study population.

Characters	Group	n	Mean±SD	P-value
Age (years)	Methyl dopa	48	25.6±1.84	0.60
	Nifedipine	47	25.8±1.97	
Weight (kg)	Methyl dopa	48	55.6±2.28	0.64
	Nifedipine	47	55.3±2.31	
Gestational age at enrolment (weeks)	Methyl dopa	48	27.6±2.43	0.69
	Nifedipine	47	27.4±2.42	
Initial systolic blood pressure (mm Hg)	Methyl dopa	48	153.6±3.14	0.62
	Nifedipine	47	153.2±3.57	
Initial diastolic blood pressure (mm Hg)	Methyl dopa	48	102.6±3.43	0.08
	Nifedipine	47	103.8±3.51	

In the present study, the mean systolic blood pressure in patients treated with methyldopa on admission was 153.6 mmHg, while in one week it reduced to 143.7 mmHg and in four weeks it reduced to 136.2 mmHg. With nifedipine the mean systolic blood pressure on admission was 153.2 mmHg which reduced to 142.5 mmHg in one week and to 134.5 in four weeks.

Similarly, the mean diastolic blood pressure in patients treated with methyl dopa on admission was 102.6 mmHg, while in one week it reduced to 96.3 mmHg and in four week it reduced to 89.4 mmHg. With nifedipine the mean

diastolic blood pressure on admission was 103.9 mmHg which reduced to 96.1 mmHg in one week and to 89.2 in four weeks (Table 2).

Table 2: Comparison of blood pressure control among the two groups.

Parameters	Drugs	Baseline	One week	P	Four week	p
Systolic BP	Methyl dopa	153.6±3.1	143.7±3.5	0.11	136.2±3.5	0.04
	Nifedipine	153.2±3.5	142.5±3.9		134.5±4.5	
Diastolic BP	Methyl dopa	102.6±3.43	96.3±3.5	0.78	89.4±3.4	0.78
	Nifedipine	103.9±3.51	96.1±3.7		89.2±3.7	

The methyl dopa group shown mean systolic blood pressure reduction of 10 mmHg by one week and 17 mmHg by four weeks as compared to nifedipine group which shown reduction of 10.5 mmHg in one week and 18.5 mmHg in four weeks. There was significant reduction in systolic blood pressure in nifedipine group compared to methyl dopa group in four weeks (p=0.04) (Table 2).

The methyl dopa group shown mean systolic blood pressure reduction of 10 mmHg in one week and 17 mmHg in four weeks as compared to nifedipine group which shown reduction of 10.5 mmHg in one week and 18.5 mmHg in four weeks. There was significant reduction in systolic blood pressure in nifedipine group compared to methyl dopa group in four weeks (p=0.04) (Table 2).

The methyl dopa group shown mean diastolic blood pressure reduction of 6 mmHg by one week and 13 mmHg by four weeks as compared to nifedipine group which shown reduction of 7.5 mmHg in one week followed by reduction of 14.5 mmHg in four weeks. No significant difference between two groups. There were no cases of eclampsia or imminent eclampsia during treatment in either group (Table 2).

The methyl dopa group shown mean diastolic blood pressure reduction of 6 mmHg in one week and 13 mmHg in four weeks as compared to nifedipine group which shown reduction of 7.5 mmHg in one week followed by reduction of 14.5 mmHg in four weeks. No significant difference between two groups (Table 2).

The adverse effects of two groups were mild and generally well tolerated; the most common were headache, palpitation and insomnia (Table 3).

Redman CW, Beilin LJ et al showed that methyl dopa did control moderate hypertension in 242 pregnant women with no serious side effects.¹⁴

Table 3: Side effects of Nifedipine and Methyl Dopa group.

Side effects observed	Methyl dopa group (n = 48)		Nifedipine group (n = 47)	
	Number of patients	%	Number of patients	%
Headache	13	27%	22	47%
Palpitation	11	23%	05	11%
Dizziness	06	13%	00	
Weakness	02	04%	00	
Insomnia	03	06%	05	11%

Subhedar V et al compared methyl dopa 250 mg tid and labetalol 100 mg tid in 180 patients with PIH in South India showed fall of mean arterial pressure from 109.86 mmHg to 98.15 mmHg at 7 day of methyl dopa administration with a statistically significant p value <0.05 and with labetalol, fall of mean arterial pressure from 109.48 mmHg to 96.90 mmHg at 7 day.¹⁸

Sibai et al. showed significant reduction in the systolic (p <0.0001) and diastolic blood pressure (p <0.0001) with oral nifedipine in 200 women with pre-eclampsia between 26 and 36 weeks of gestation.²¹

DISCUSSION

We analysed 95 women with gestational hypertension during 6 month study period. Mean age of participants in both groups was 25 years among which one third of them were primigravida. Study conducted by Aparna et al had same age distribution as our study but two third of them were primigravida (Table 1).²⁵

Whereas study conducted by Bharathi K N et al at South India in 50 patients showed both nifedipine (systolic blood pressure reduction from 160 mmHg to 139 mmHg, diastolic blood pressure from 105 mmHg to 91 mmHg) and methyl dopa (systolic blood pressure reduction from 156 mmHg to 138 mmHg, diastolic blood pressure from 105 mmHg to 92 mmHg) are equally effective in reducing the blood pressure in pregnancy induced hypertension at 72 hours.²²

Adverse effects in our study were mild, well tolerated and similar in both groups. They include headache, palpitation and insomnia. Adverse effects profile was similar to study conducted by Subhedar V et al and El-Qarmalawi et al (Table 3).^{18,26}

Our study reported the effectiveness of methyldopa and nifedipine among 95 patients with moderate gestational hypertension with a follow up of four weeks. Nifedipine having an additional tocolytic action showed significant reduction of systolic blood pressure at one month compared to methyldopa.

This was single centre study and patients were followed up only for four weeks and patient with moderate gestational hypertension already on antihypertensive are not included in study. Further study is needed to evaluate effectiveness of these drugs in large sample size for longer period during pregnancy.

Monotherapy with either methyldopa or nifedipine could be used safely in pregnant patients with moderate gestational hypertension. However, nifedipine is slightly better compared to methyldopa because it showed significant reduction systolic blood pressure at one month with minimal side effects.

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