Research Article

A comparative study of efficacy of antihypertensive drugs and feto-maternal outcome in the treatment of pregnancy induced hypertension

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ABSTRACT

Background: Hypertensive disorders are the most common medical disorders in pregnancy contributing significantly to maternal and perinatal mortality and morbidity worldwide. The incidence is around 3-10% of all pregnancies. The aim of antihypertensives is to reduce, stabilize the blood pressure and thus minimize the risks such as placental abruption, maternal cardiac failure, cerebral hemorrhage; but they should not have any adverse effects on the utero-placental circulation and the fetus. Antihypertensive drugs are often used to lower blood pressure to prevent this progression to adverse outcomes for the mother and the fetus. The risk of developing severe hypertension is reduced to half by using antihypertensive medications. The aim and objectives of the study was a comparative study of the efficacy of methyldopa, nifedipine versus labetalol and the feto-maternal outcome in gestational hypertension in a tertiary care referral centre.

Methods: A prospective study on 240 outpatients as well as inpatients of the antenatal ward of Obstetrics and Gynaecology department of Chhattisgarh Institute of Medical Sciences, Bilaspur which is a tertiary care referral hospital. The patients randomly divided in three groups. The first group received alpha-methyl dopa 250mg tds, second 20 mg bd nifedipine and the third one labetalol 100mg bd. Mean arterial pressure calculated by systolic BP +2 DBP/3. The fall in BP calculated along with time required, dose of drug required, spontaneous/induced labour or caesarean section, adverse maternal and the fetal outcome was observed.

Results: Maximum number of patients that is 145(60.42%) patients belonged to the age group of 19 to 24 years and were primigravida (70.42%) presenting at 33-37 weeks of gestation. Significant fall in MAP was seen in patients receiving nifedipine and labetalol. Mean time to control blood pressure is 46.32 hrs in methyldopa group, 30.44hrs in nifedipine group and 37.24 hrs in labetalol group. 103 (42.9%) patients had normal delivery whereas 137 (57.1%) required a caesarian section, higher rate of spontaneous labour in nifedipine and labetalol group. Most common side-effect observed was headache; the other side effects included drowsiness, more in patients treated with methyldopa, weakness, more in patients treated with labetalol. The fetal outcome was better with labetalol and nifedipine than methyldopa group.

Conclusions: The decreased association from maternal and fetal side-effects, the comparatively better hypotensive action indicates that labetalol and nifedipine is suitable for use during pregnancy. Labetalol is safer, quicker in achieving adequate control of blood pressure with considerable prolongation of the duration of pregnancy with fewer side effects on the mother as well as the neonate when used in the management hypertensive disorders of pregnancy.

Keywords: Pregnancy, Hypertension, Methyldopa, Nifedipine, Labetalol, Efficacy
INTRODUCTION

Hypertension during pregnancy is defined as a blood pressure of 140/90 mmHg or greater on two occasions more than 4 hours apart in a previously non-hypertensive person.¹

Hypertensive disorders in pregnancy remain one of the major causes of maternal and perinatal mortality in developing as well as developed countries.² In some women, it can become more serious resulting in hospital admission due to pre-eclampsia, eclampsia and adverse fetal effects. Antihypertensive drugs are often used to lower blood pressure with the aim of preventing this progression to adverse outcomes for the mother and the fetus.

A wide spectrum of antihypertensive agents represents the key of successful pregnancy hypertension treatment and opportunity of choice, in accordance with indications and availability of drugs provided by drug tendering. The risk of developing severe hypertension is reduced to half by using antihypertensive medications. Methyldopa, labetalol and long-acting nifedipine are acceptable oral antihypertensive agents if drug therapy is required in pregnant women with mild to moderate hypertension.³

According to the National High Blood Pressure Education Program Working Group (NHBPEPWG), hypertensive disorders in pregnancy are classified as:

1. Gestational hypertension
2. Pre-eclampsia and eclampsia
3. Pre-eclampsia superimposed on chronic hypertension
4. Chronic hypertension
   a. Hypertensive disorders in pregnancy remain one of the major causes of maternal and perinatal mortality in developing as well as developed countries. The commonly used antihypertensive drugs in pregnancy with proven safety are:
5. Alpha-methyldopa
6. Nifedipine (calcium channel blocker)
7. Labetalol

Methyldopa was most commonly used for treatment of hypertension during pregnancy but it takes longer time to act and also less efficacious as hypotensive drug. It is still the most commonly used drug for long term control of blood pressure in pregnancy. Methyldopa is a centrally acting adrenergic antagonist that acts by stimulation of the central alpha 2 receptors, leading to a decrease in sympathetic nerve activity with resultant arterial dilatation and reduction in BP. Methyldopa should not be used if there is a substantial risk of maternal depression when a beta-blocking agent or calcium antagonist may be more suitable.

Nifedipine is a nondihydropyridine calcium channel blocker. Maternal adverse effects with nifedipine include tachycardia, palpitations, peripheral oedema, headaches, and facial flushing.⁵ Rapid acting nifedipine should not be used for treating hypertension or hypertensive emergencies especially in pregnancy because it has been associated with fatal and nonfatal untoward cardiovascular events as well as compromised placental perfusion.⁶

Labetalol gives better control of blood pressure compared to other anti-hypertensive agents. Labetalol is a combined alpha- and beta-blocker and has the advantage over other beta blockers due to its additional arteriolar vasodilator action that helps to lower peripheral vascular resistance with little or no decrease in cardiac output.⁷

Today, though oral medications are available and widely used for the treatment of PIH, the physicians still have to deal with many challenges. 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. A wide spectrum of antihypertensive agents represents the key of successful pregnancy hypertension treatment and opportunity of choice, in accordance with indications and availability of drugs provided by drug tendering.⁸⁹

In this backdrop, a study was designed to compare the antihypertensive drugs - methyldopa, nifedipine versus labetalol versus in pregnancy induced hypertension (PIH) in tertiary care referral institute.

The objectives of the study was to evaluate the efficacy of methyldopa, nifedipine versus labetalol in controlling blood pressure in pregnancy and to study the maternal and fetal outcome after these drugs administration in pregnancy.

METHODS

A prospective randomized study was carried out in 240 pregnant women from 2011-2014 in the Department of Obstetrics and Gynaecology, Chhattisgarh Institute of Medical Sciences Bilaspur. All pregnant women attending the antenatal clinic were screened for and hypertensive pregnant women were included in the study after obtaining informed consent. The study was approved by the institutional ethics committee of the hospital.

Inclusion criteria

The criteria for diagnosis and classification of the hypertensive disorder of pregnancy will be obtained according to the NHBPEPWG. Medical and obstetric history taking and physical examination were performed at the time of initial recruitment. Pregnant patients diagnosed with systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥ 90 mmHg requiring medication and gestational age between more than 20 weeks of pregnancy (calculated from the first day of last
menstrual period) were included in the study excluding oedema or proteinuria. Only singleton pregnancy with vertex presentation was included.

**Exclusion criteria**

Patients suffering from bronchial asthma, any pre-existing cardiovascular disorder, diabetes, Rh isoimmunisation, patients at risk of major obstetric complications - antepartum haemorrhage, malnutrition, multifetal gestation and hydranmios during the current pregnancy and patients who had already received antihypertensive drugs were excluded.

Patients (80 each) were randomised to each of the three treatment arms – methyldopa, nifedipine and labetalol, with bed rest for patients. After randomization, first group received methyldopa 250 mg t.i.d, second received nifedipine 10 mg b.d. and labetalol 100 mg b.d. Mean Arterial pressure (MAP) was calculated according to formula systolic BP +2 diastolic BP /3. Patients were subjected to 6 hourly BP monitoring. Comparison of the drugs was done daily by calculating MAP of these groups. If there was no control in BP even after 48 hrs of drug therapy, dose of the drug was doubled. Response in lowering BP was assessed over a period of 7 days. Observations were made as regards fall in BP, time required to control BP, average dose of drugs required to control BP, onset of labour-spontaneous/induced or caesarean section, adverse effects of drugs and fetal outcome.

Measurement of blood pressure (BP) was done using mercury sphygmomanometer (auscultation method) taken after 15 minutes of rest. Readings were taken at least on two occasions six hours apart before diagnosing the patient as hypertensive. The patient was made to lie in the left lateral position with the right arm well supported at the level of the heart. Systolic BP corresponded to appearance of the first tapping sounds and diastolic BP was recorded at the point where the sounds first became muffled. (Korotkoff phase IV). Patients were followed up and BP, pulse rate and fetal heart rate were recorded every 15 minutes for two hours after initiation of treatment. Patients were advised to take the minimum dose of drug which kept the BP below 90 mmHg, with advice to come for weekly follow up and get admitted if BP rose beyond the point of control. Patients who remained uncontrolled in spite of therapy in these groups were closely monitored in the hospital and attempt was made to continue the pregnancy up to 37 completed weeks followed by induction of labour and caesarean section, wherever induction was contraindicated or failed.

**RESULTS**

According to Table 1, among the total 240 patients, maximum number of patients that is 145(60.42%) patients belonged to the age group of 19 to 24 years: 51 patients (63.75%) in Group 1 and 49 patients (61.25%) in Group 2 and 45(56.25%) patients in Group 3.

<table>
<thead>
<tr>
<th>Parity</th>
<th>Methyl-dopa</th>
<th>Nifedipine</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primigravida</td>
<td>56(70.0%)</td>
<td>52(65.0%)</td>
<td>61(76.25%)</td>
</tr>
<tr>
<td>Multigravida</td>
<td>24(30.0%)</td>
<td>28(35.0%)</td>
<td>19(23.75%)</td>
</tr>
</tbody>
</table>

Table 2 states that in the present study, 169(70.4%) patients were primigravidae, 56 patients (70.0%) in methyldopa group, 52(65.0%) in nifedipine and 61 patients (76.25%) in labetalol group.

In the study 49 patients (61.25%) in group 1, 57 patients (71.25%) in group 2 and 55 patients (68.75%) in group 3 presented at 33-37 weeks gestational age (Table 3).

<table>
<thead>
<tr>
<th>Gestational age (wks)</th>
<th>Methyldopa</th>
<th>Nifedipine</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-24</td>
<td>4(5.0%)</td>
<td>5(6.25%)</td>
<td>6(7.5%)</td>
</tr>
<tr>
<td>25-28</td>
<td>2(2.5%)</td>
<td>2(2.5%)</td>
<td>3(3.75%)</td>
</tr>
<tr>
<td>29-32</td>
<td>17(21.25%)</td>
<td>16(20.0%)</td>
<td>18(22.5%)</td>
</tr>
<tr>
<td>33-37</td>
<td>49(61.25%)</td>
<td>57(71.25%)</td>
<td>55(68.7%)</td>
</tr>
</tbody>
</table>

Table 4: Dose of methyl dopa at which control of BP achieved.

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>750</td>
<td>37</td>
<td>46.25</td>
</tr>
<tr>
<td>1000</td>
<td>19</td>
<td>23.75</td>
</tr>
<tr>
<td>1500</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>2000</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 5: Dose of labetalol at which control of BP achieved.

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>300</td>
<td>14</td>
<td>17.5</td>
</tr>
<tr>
<td>400</td>
<td>39</td>
<td>48.75</td>
</tr>
<tr>
<td>600</td>
<td>11</td>
<td>13.75</td>
</tr>
</tbody>
</table>

Figure 1 shows comparison of MAP in both the groups at Day 1 and Day 8. In the present study, the mean arterial pressure on admission in patients treated with
methyldopa, nifedipine and labetalol was 109.72mmHg, 109.92mmHg, 109.56mmHg and while on day 8 it reduced to 98.2mmHg, 94.8mmHg, and 96.4mmHg respectively.

Table 6: Dose of nifedipine at which control of BP achieved.

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>9</td>
<td>11.25</td>
</tr>
<tr>
<td>30</td>
<td>17</td>
<td>21.25</td>
</tr>
<tr>
<td>40</td>
<td>34</td>
<td>42.5</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

The average time to control blood pressure is 46.32 hrs in methyldopa group, 30.44hrs in nifedipine group and 37.24 hrs in labetalol group (Figure 2). The dose of methyldopa to control blood pressure is 750mg/day in 37 patients (46.25%), 40mg/day in 28 patients (42.5%) by nifedipine and 400mg/day in 39 patients (48.75%) by labetalol (Table 4, 5, 6).

The fetal outcome revealed not much difference in the three treatment arms as correlated with other similar studies.

DISCUSSION

The primary objective of management in women with pregnancy-induced hypertension is to protect the safety of the mother and the fetus and the subsequent delivery of a healthy baby. Age distribution shows maximum patients between 19-24 years in three groups (63.75% in methyldopa group, 61.25% in nifedipine and 57.77% in labetalol group) and there was no significant difference in age distribution in the groups. Majority of the pregnant women presenting to our health facility are illiterate with
only rudimentary medical knowledge of their own pregnancies with majority had no prior antenatal check-up. Age has an important influence on the incidence of hypertensive disorders of pregnancy. Young primigravidae under 20 years and all patients over 30 years have an increased chance of hypertension. Approximately half of PIH cases occur at term (≥37 weeks' gestation), including most cases of gestational hypertension. The mean gestational age at presentation was 32.7 weeks which is comparable with other study (i.e. 37 weeks).

In the present study, the mean arterial pressure in patients treated with methyldopa on admission was 109.72 mmHg, while on day 8 it reduced to 98.2 mmHg, with nifedipine the mean arterial pressure on admission was 109.92 mmHg which reduced to 94.68 mmHg on day 8 and with labetalol, the mean arterial pressure on admission was 109.56 mmHg which reduced to 96.4 mmHg on day 8. On comparing these drugs, MAP on admission was comparable but on day 8, significant fall in MAP was seen in patients receiving labetalol and nifedipine. The comparable effect of methyldopa, nifedipine and labetalol on BP control in hypertensive disorders of pregnancy is supported by previous studies. (Pickles CJ et al, Sibai BM et al). However, one study says that labetalol provides more efficient control of BP than methyldopa in the treatment of mild hypertension in pregnancy and had a significant fall in MAP as against 68.5% in patients taking methyldopa.

In the present study, the mean time required to control BP in group 1 was 46.32 hours, in group 2 it was 30.44 hours and in group 3 it took 37.24 hours. The difference between the groups was with nifedipine and labetalol showing earlier control of BP than methyldopa.

The dose of methyldopa to control blood pressure is 750 mg/day in 37 patients (46.25%), 40 mg/day in 34 patients (42.5%) by nifedipine and 400 mg/day in 39 patients (48.75%) by labetalol. Lardoux et al found that the average daily dose of labetalol required for satisfactory blood pressure control was 600 mg.

9 patients in group 1 went in spontaneous labour while 14 patients were induced in group 2, 17 patients went in spontaneous labour and 20 patients were induced and in group 3, 20 patients went in spontaneous labour and 23 patients were induced. The rate of spontaneous labour was more in patients treated with labetalol. This may be accounted to the fact that labetalol has ripening effect on the cervix. Lamming et al too reported a higher incidence of spontaneous labour in the labetalol group.

The commonest adverse effects noted were occipital headache (3-9%), postural hypotension (3-8%), tachycardia (4-11%), and depression (2-7%). Tachycardia (11%) and occipital headache (9%) were more common with nifedipine compared to methyldopa and labetalol groups. Postural hypotension drowsiness and depression were more commonly reported side effects with methyldopa group (8%) compared to nifedipine and labetalol but weakness more in patients treated with labetalol. The incidence of side-effects such as nausea, vomiting, myalgia was similar in the three groups. Study conducted by Verma et al. states that adverse events...
observed were lower in the labetalol treated group compared to the methyldopa group. In another study patients receiving methyldopa complained of side-effects such as drowsiness (22.2%), headache (14.8%), nasal congestion (7.4%), and postural hypotension (5.6%).

The effect on fetal and maternal outcomes like the incidence of prematurity, intrauterine growth retardation, perinatal death, need for NICU, incidence of eclampsia and incidence of elective or caesarean section in the mother must be considered before pronouncing that labetalol may be preferred in PIH on account of equal efficacy and better tolerability.

The fetal outcome revealed that there was not a major difference due to the choice of antihypertensive. Unlike other antihypertensive drugs labetalol reduces peripheral resistance without significantly reducing maternal cardiac output and pulse rate. This may be an additional factor in maintaining adequate placental perfusion and therefore foetal oxygenation in the treatment of pregnancy hypertension with labetalol. Drug treatment of mild chronic or pregnancy-induced hypertension improves maternal outcomes but does not clearly improve perinatal outcomes.

All forms of antihypertensive therapy were associated with a higher risk for SGA, preterm birth and admission to the NICU, and multiple therapies had the strongest association with these events.

CONCLUSIONS

Treating the hypertension does not alter the progression of disease but early treatment decreases not only the frequency of hypertensive crisis, but also the rate of neonatal complications. Antihypertensive medications are mainly used to prevent or treat severe hypertension, to prolong pregnancy for as long as safely possible thereby maximizing the gestational age of the infant, and to minimize fetal exposure to medications that may have adverse effects.

This study confirms the previous findings that labetalol is an effective and safe drug for use in the control of blood pressure in pregnancy-induced hypertension. The low incidence of maternal and foetal side-effects together with the excellent perinatal outcome in a condition usually accompanied by a high maternal and foetal mortality and morbidity confirms its suitability for use during pregnancy. Nifedipine is equally efficacious and better tolerated compared to methyldopa in the treatment of new onset hypertension during pregnancy. However, the effect on fetal and maternal outcomes must be considered before selecting any drug in the treatment of hypertensive disorders of pregnancy.

Awareness regarding PIH and availability of easily accessible and affordable health care services to rural population and poor people is important which shall be helpful in reducing the PIH related morbidity and mortality.

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