

## EFFICACY AND SAFETY OF LABETALOL IN THE MANAGEMENT OF MODERATE GESTATION HYPERTENSION - A PROSPECTIVE OBSERVATIONAL STUDY

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### ABSTRACT

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. Antihypertensive drugs are often used to lower blood pressure with the aim of preventing its progression to adverse outcomes for the mother, at the same time they should not have adverse effects on the uteroplacental circulation and the fetus. The risk of developing severe hypertension is reduced to half by using antihypertensive medications. The objective of this study is to study efficacy and safety of Labetalol in lowering blood pressure in patients with moderate gestational hypertension.

### METHOD

This is a prospective observational study where fifty six pregnant patients with moderate gestational hypertension on labetalol are included in the study. Reduction in hypertension and frequency of side effects were studied. The statistical level of significance was taken at  $P < 0.05$ .

### RESULT

The result showed labetalol is effective in control of blood pressure and well tolerated with free of side effects.

### CONCLUSION

Labetalol is a safe, well tolerated and effective in controlling blood pressure in moderate gestational hypertension.

### KEYWORDS

Moderate Gestational Hypertension, Labetalol.

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### INTRODUCTION

Hypertensive disorders of pregnancy are an important cause of severe morbidity and mortality among both mother and fetus.<sup>1</sup> 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).<sup>2</sup> Hypertensive disorders of pregnancy are common in developing countries like India. Hypertensive disorders seem to complicate approximately 10% of pregnancies and are important causes of maternal and fetal morbidity and mortality.<sup>3</sup> International guidelines define severe pregnancy hypertension as systolic blood pressure (SBP)  $\geq 160$ -170 mmHg and/or diastolic BP (DBP)  $\geq 110$  mmHg.<sup>4,5</sup> Severe hypertension is the only modifiable end-organ complication of pre-eclampsia, the most dangerous of the hypertensive disorders of pregnancy.<sup>6</sup> It is widely accepted that women with severe hypertension are at increased risk of stroke and as such must have their BP lowered.<sup>7,8</sup>

The hypertensive disorders of pregnancy are very important disorders, because if not treated they may adversely affect both the mother and the fetus.<sup>9,10</sup> They predispose to acute or chronic uteroplacental insufficiency that may lead to fetal death, Intrauterine Growth Retardation (IUGR) and preterm delivery.<sup>11</sup> It is proven that control of hypertension reduces these complications.<sup>12,13</sup>

All international pregnancy hypertension guidelines recommend immediate treatment of severe pregnancy hypertension, a recommendation endorsed as 'strong' by the World Health Organization (WHO).<sup>14</sup> While severe pregnancy hypertension is a 'hypertensive urgency' that requires treatment, it is appropriate to lower BP over hours (and certainly within 24 hours) and this could be achieved with oral or parenteral antihypertensive therapy. Traditionally, severe hypertension has been treated with short-acting parenteral antihypertensive agents, most frequently, intravenous hydralazine or labetalol.<sup>15,16,17</sup> These agents have been most widely studied in Randomized Controlled Trials (RCTs), although systematic reviews have failed to reveal clear differences between agents.<sup>18,19</sup>

Once blood pressure rises above a certain level; however, there is a risk of direct damage to the blood vessel wall, regardless of what caused the rise. This risk is not specific to pregnancy, as it is similar for non-pregnant people with very high blood pressure. The level at which this risk merits mandatory antihypertensive therapy is usually considered to be 170 mmHg systolic blood pressure or 110 mmHg diastolic.<sup>20</sup> If the woman has signs and symptoms associated with severe pre-eclampsia (such as hyperreflexia, severe

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headache, sudden onset of epigastric pain or lowered platelets), a lower threshold for treatment may be recommended.<sup>21</sup> The possible consequences of such high blood pressure for the mother include kidney failure, liver failure and cerebrovascular haemorrhage (stroke).

In the UK, for example, stroke resulting from severe hypertension was the single most common cause of maternal death associated with preeclampsia. For the baby, risks include fetal distress due to impaired blood supply across the placenta and placental abruption (separation of the placenta from the wall of the womb before birth).

The commonly used antihypertensive drugs in pregnancy are Nifedipine, methyldopa, labetalol and hydralazine.<sup>22,23</sup> Most of these drugs are quite safe for mother and foetus.<sup>24</sup>

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.<sup>25</sup> According to National Collaborating Centre for Women's and Children's Health (NICE) guidelines, antihypertensive treatment is not needed in mild hypertension, but need to be given in all cases of moderate-to-severe hypertension.<sup>26,27</sup>

A prospective study conducted in 2012 evaluated the effectiveness and safety of oral Labetalol and oral Nifedipine in pregnant women with Pregnancy Induced Hypertension (PIH) and concluded that Labetalol is more effective than Nifedipine in controlling blood pressure, whereas tachycardia (11%) and occipital headache are more common with Nifedipine.<sup>13</sup>

Hence, the present study focuses on an assessment of efficacy and safety of Labetalol in lowering blood pressure in patients with moderate gestational hypertension.

## MATERIALS AND METHODS

The study was a prospective observational study conducted at Basaweshwara Teaching and General Hospital attached to M.R. Medical College, Kalaburagi. Ethical clearance was obtained from Ethics Committee, M.R. Medical College, Kalaburagi.

### Inclusion Criteria

All pregnant patients with systolic blood pressure in range of 150 to 159 mmHg and a diastolic blood pressure in range of 100 to 109 mmHg on two occasions four hours apart after 20 weeks of gestation attending OBG Department, Basaweshwara Teaching and General Hospital between July 2015 to December 2015.

### Exclusion Criteria

1. PIH with preeclampsia/eclampsia.
2. Heart diseases including IHD.
3. Haematological disorders.
4. Liver diseases.
5. History of intolerance/hypersensitive to Labetalol.

The criteria for entry into the study was a sitting systolic blood pressure range of 150 to 159 mmHg and a diastolic blood pressure (disappearance of sounds phase V, Korotkoff sounds) in range of 100 to 109 mmHg 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 study group consists of 118 pregnant patients selected on the basis of inclusion and exclusion criteria with moderate gestational hypertension. Labetalol in the dose of 100 mg BD. Detailed medical and obstetric history was taken along with complete obstetric examination. Blood pressure was recorded using Mercury Sphygmomanometer. All outpatients were seen week after starting treatment with Labetalol 100 mg BD and then one month after starting treatment. Side effects of the drugs were also recorded during study period. The primary outcome was successful control of SBP <150 mmHg and DBP <100 mmHg without using additional drugs. Secondary outcomes included maternal side effects such as hypotension, headache, flushing, nausea and vomiting, dizziness or cardiovascular accidents after starting the antihypertensive medication.

## STATISTICAL ANALYSIS

For parametric data, Student's t-test and Chi-square goodness-of-fit tests were used, whereas for non-parametric data RIDIT analysis was used.

## RESULTS

Out of 117 patients, 6 patients were excluded from the study because they failed to comply regular followup. Further analysis will focus on the 111 patients who completed the study.

In the present study, about 15.31% of the pregnant women were primigravidae. The rest of the patients were multigravidae.

Comparison or Outcome	Mean
Age (Years)	24.23±3.64
Primi's	17
Weight (kg)	55.56±2.28
Gestational age at enrolment (weeks)	27.64±2.43
Initial systolic blood pressure (mmHg)	162.36±20.72
Initial diastolic blood pressure (mmHg)	105.62±12.46
Pulse Rate	87.94±4.39

**Table 1: Clinical Characteristics of Study Population**

All patients achieved target blood pressure on the twice daily dose of medications; none required added other antihypertensive medications. The mean difference in the fall of the systolic/diastolic BP with Labetalol by one week was 10.74/6.48 mmHg and by one month it was 18.72/13.79 mmHg. There were no cases of eclampsia or imminent eclampsia during treatment.

Blood Pressure	Outcome	Mean mmHg
Systolic BP	Fall in one week	10.74 mmHg
	Fall in one month	18.72 mmHg
Diastolic BP	Fall in one week	6.48 mmHg
	Fall in one month	13.79 mmHg

**Table 2: Comparison of Blood Pressure Control in the Study Group**

On an individual assessment of the adverse effects like headache (12%) is more common. Other adverse effects like

pedal oedema (9%), sweating (6%), orthostatic hypotension (1%), blurred vision (1%) and facial oedema (1%).

Side Effects Observed	Number of Patients	Percentage
Headache	14	12.61%
Pedal Oedema	11	9.9%
Sweating	06	5.4%
Orthostatic Hypotension	03	2.7%
Blurred Vision	02	1.8%
Facial Oedema	10	9.0%

**Table 3: Side Effects of Labetalol Recorded During the Treatment**

## DISCUSSION

The Cochrane review on drugs for the treatment of high blood pressure in pregnancy concluded that until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug.<sup>28</sup>

The appropriate selection of antihypertensive in pre-eclampsia is controversial in the literature. Most commonly preferred choice of antihypertensive is Labetalol, Methyldopa and Nifedipine in pre-eclampsia.<sup>29</sup>

As per the National Institute for Health and Clinical Excellence [NICE] guidelines for hypertension in pregnancy, the preferred choice of drug is oral labetalol to Nifedipine and Methyldopa.<sup>30</sup>

Labetalol is an alpha-blocker with nonselective beta-blocking properties. It is available in oral as well injectable forms. Its safety in the first trimester of pregnancy has been documented.<sup>31</sup>

A recent prospective study conducted by Nita K. Patela et al in 2012.<sup>7</sup> to evaluate the comparative effectiveness and safety of Nifedipine, Methyldopa and Labetalol monotherapy in patients with Pregnancy Induced Hypertension (PIH) concluded that Labetalol was more effective than Methyldopa and Nifedipine in controlling blood pressure in patients with Pregnancy Induced Hypertension (PIH).<sup>32</sup>

In the present study, efficacy was assessed based on control of blood pressure in 7 days and 1 month after treatment. There was no major adverse event attributed to drug regimen. It was found that Labetalol is effective in controlling blood pressure in moderate gestational pregnancy and is suitable first-line antihypertensive for hypertensive emergencies of pregnancy.

Our study showed that Labetalol significantly reduced systolic BP and diastolic BP by one month. There were no serious side effects in study period. Side effects of Labetalol were minimal and well tolerated. Headache (12.61%) is more common as side effects, but none of the patients required addition treatment.

Based on our findings, we conclude that oral Labetalol could be used effectively and safely in the control of blood pressure in moderate gestational hypertension.

Limitation of our study was we did not include patients with severe hypertension in pregnancy, who had more chances of developing complications.

## CONCLUSION

From our study, we observed that oral Labetalol is more efficacious in controlling blood pressure in patients with

moderate gestational hypertension with less side effects. However, further study is needed to evaluate safety of these drugs during later stages of pregnancy, during labor and during postpartum period.

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