

## Intravenous Labetalol in management of Hypertensive Emergencies in Pregnancy

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### Abstract

**Background:** To study the effect of IV labetalol in hypertensive emergencies in pregnancy and their effects on maternal and Perinatal outcome. Pregnant women with blood pressure >160/110 mmHg were subjected to the trial. Patients were randomized to receive intravenous labetalol injection (in an escalating dose regimen of 20, 40, 80, 80 and 80 mg) every 15 minutes until the target blood pressure of <150/100 mmHg was achieved. Addition of nifedipine treatment was done if the initial treatment regimen was unsuccessful. Primary and secondary outcomes like the time interval and number of doses required to achieve a blood pressure of ≤150/100 mmHg and adverse effects of the antihypertensive agents were reported.

IV Labetalol is effective in sustaining therapeutic level.

**Objective:** To study the efficacy of IV Labetalol in management of hypertensive emergencies in pregnancy and adverse effects of labetalol.

**Materials and methods:** A prospective observational study of 60 cases with hypertension in pregnancy, treated with Labetalol, was conducted over a period of one and half years

**Results:** The effective control of blood pressure with the use of Labetalol in the dosage used, was observed in cases of moderate to severe pregnancy induced hypertension.

**Conclusion:** Intravenous labetalol is an effective and safe drug in the management of hypertension in pregnancy.

**Keywords:** Hypertension, Pregnancy, Labetalol.

### Introduction

Hypertensive disorders represent the most common medical complications of pregnancy, with a reported incidence between 5-10%.<sup>(1)</sup> The term hypertension in pregnancy is commonly used to describe a wide spectrum of patients who may have only mild elevations in blood pressure (BP) or severe hypertension with various organ dysfunctions. However hypertensive crisis is particular challenge to treat which brings immediate risk to both the mother and fetus.<sup>(3,4)</sup> The current American College of Obstetricians and Gynecologists (ACOG) taskforce on HTN during pregnancy has modified several components of diagnostics and management of HTN during pregnancy and have simplified classification into only 4 categories: (1) preeclampsia (2) eclampsia (3) chronic HTN; (4) chronic HTN with superimposed preeclampsia; and (5) gestational HTN.

These disorders are a major cause of maternal and perinatal mortality and morbidity worldwide. It is associated with 30% all maternal deaths and as much as 22% of all perinatal deaths.<sup>(5)</sup> It has been estimated by the WHO (World Health Organization) that worldwide approximately 50,000 women will die each year from hypertensive disorders of pregnancy.<sup>(6)</sup>

Mild hypertension is defined as diastolic BP of 90–99 mmHg and systolic BP 140–149 mmHg. Moderate hypertension is defined as diastolic BP of 100–109 mmHg and systolic BP of 150–159 mmHg. Severe hypertension includes diastolic BP of 110 mmHg or greater and systolic BP 160 mmHg or greater.

These levels represent cut off levels of overcoming cerebral auto regulation. It requires prompt treatment because of risk of cardiovascular accident, to prevent intracerebral hemorrhage, hypertensive encephalopathy and other target organ damage.<sup>(7,8)</sup> It also presents an increased risk of complications for the foetus, including prematurity, low birth weight, NICU involvement and even fetal death.<sup>(8-10)</sup>

In addition to the risk they present to the pregnancy, hypertensive disorders of pregnancy have been linked to future high blood pressure and cardiovascular disease in women.<sup>(11)</sup>

It is imperative to treat severe hypertension in pregnancy, mandating hospitalization.

It is common practice to stabilize severe maternal hypertension prior to delivery by labour induction or caesarean section to avoid dangerous fluctuations or exacerbations of blood pressure during labour or anesthesia.<sup>(12)</sup> Hence speedy but safe blood pressure control will allow the definitive treatment of delivery of the baby to be carried with minimum delay in many cases of severe hypertension in pregnancy.

Most antihypertensive agents used in pregnancy are designated as “category C,” which states that human studies are lacking, animal studies are either positive for fetal risk or are lacking, and the drug should be given only if potential benefits justify potential risks to the fetus.<sup>(13)</sup>

The actions of labetalol on both  $\alpha_1$  and  $\beta$  receptors contribute to the fall in blood pressure observed in patients with hypertension.  $\alpha_1$  receptor blockade leads

to relaxation of arterial smooth muscle and vasodilation, particularly in the upright position. The  $\alpha_1$  blockade also contributes to a fall in blood pressure, in part by blocking reflex sympathetic stimulation of the heart. In addition, the intrinsic sympathomimetic activity of labetalol at  $\beta_2$  receptors may contribute to vasodilation.<sup>(15)</sup>

The National Guideline Clearinghouse,<sup>2</sup> regarding treatment of hypertensive disorders of pregnancy has recommended that the initial antihypertensive therapy should be started with labetalol (IA evidence) or nifedipine, to bring down the target BP to 160 systolic and 110 diastolic.<sup>(16)</sup>

**Materials and Methods**

The study got ethical approval by Institutional review board of Sri Siddhartha medical college, Agalkote, Tumkur, Karnataka on October 2012.

The subjects for the study had got selected from pregnant women with a systolic BP >160 mm of Hg and/or diastolic BP >110 mm of Hg who came to labour room or OPD have been admitted to Sri Siddhartha Medical College and Hospital, Tumkur from 1st October 2012 to 30th March 2014 were included in trial. It is a randomized controlled trial. Assignment of the participants was done by allotting the subjects to IV Labetalol.

**Inclusion criteria:**

1. Gestation age more than or equal to 28weeks,
2. Pregnant women with a systolic BP of more than 160mm Hg or more and diastolic BP of 110mm Hg or more, maternal heart rate > 60 and < 120 beats per minute

**Exclusion criteria:**

1. Patient with history of heart rhythm abnormality and/ or heart failure,
2. Exposure to either study medication within 24hrs of enrolment,
3. Asthma or allergic disorders with predisposition to bronchospasm, severe Hepatic/ Renal impairment, secondary hypertension and hypovolaemic shock.

The purpose of the trial was to study the role of labetalol as a first-line drug for hypertensive disorders in pregnancy in an open prospective trial, the primary efficacy parameter being control of blood pressure (BP) and secondarily studying tolerability and effects on labor and fetus.

**Method of data collection**

The patients were administered IV Labetalol based on the randomization.

Patients randomized to intravenous Labetalol, received 20 mg initially, followed by escalating doses of 40 mg, 80 mg, & then 80 mg every 15 minutes until the therapeutic goal blood pressure systolic  $\leq 150$  mmHg & diastolic  $\leq 100$  mmHg was achieved, or for a maximum of five doses. Inj labetalol was infused at a slow rate over 2-5 minutes.

Participants were rested in bed in a semi recumbent position, vital signs were recorded. Blood pressure measurement done by a mercury sphygmomanometer in the right arm.

Clinical examination was carried out. Important hematological, urine, serological and radiological investigations were carried out for the purpose of diagnosis and for knowing the severity of the disease. Necessary investigations like Obstetric ultrasound, Color Doppler study to know status of placental perfusion, Non stress test, and fetal biophysical profile were carried to assess the fetal wellbeing.

Once blood pressure was <150/100 mmHg, no further trial medication was given unless there were two consecutive blood pressure readings >160/110 mmHg, in which case the trial medication was restarted.

The primary outcome of our study was the time interval required to achieve the therapeutic goal of systolic blood pressure of  $\leq 150$  mmHg & diastolic  $\leq 100$  mmHg. Secondary outcomes analyzed included adverse effects of the drugs, maternal outcome, and perinatal outcome.

**Results and Observations**

The randomized sixty pregnant women with hypertensive disorders were subjected to IV Labetalol. All participants were started on allocated treatment. Table 1 shows the baseline characteristics of the participants stratified according to their randomization. All baseline characteristics were similar across the groups.

**Table 1: Characteristics of participants to intravenous labetalol for acute blood pressure control in hypertensive emergencies in pregnancy**

Characteristics	IV labetalol (n=60)
Age in years (Mean±SD)	23.80±3.09
Primigravida	56.7%
Gestational age(Mean±SD)	35.40±3.27
Previous history of PPH	30%
Proteinuria *	86.2%
Systolic BP**	172.13±15.28
Diastolic BP	112.80±13.13
Distribution of hypertensive disorders	17.2
A.Gestational hypertension	
B.Severe Preeclampsia	75.9
C.Eclampsia	6.9
D.Chronic hypertension	0.0
E.Chronic hypertension superimposed with preeclampsia	3.4

\*proteinuria by urine dipstick at randomization: proteinuria is considered to be present if dipstick analysis is at least 1+.

\*\*systolic and diastolic blood pressure at randomization prior to starting treatment.

There was no statically difference in the complete blood count, liver function and renal function parameters of the group (data not shown).

**Table 2: Primary and secondary outcomes of study of intravenous labetalol for acute blood pressure control in hypertensive emergencies in pregnancy**

Primary outcome	IV lbetalol
Time(minutes) taken to achieve blood pressure≤150/100mmhg	25.17±12.76
Secondary outcome	
Number of doses required to achieve target blood pressure	2.53±0.97
Maternal complications	
1.hypotension	0.0
2.palpitation	6.0
3.nausea and vomiting	13.8
4.Sweating and flushing	0.0
5.Chest pain	0.0
6.headache	6.9
7.Fetal tachycardia	10.0
Other complications	6.9
• HELLP syndrome	0.0
• Renal failure	0.0
• Eclampsia	6.9

This table shows there is significant reduction in blood pressure within 25.17±12.76. There were no maternal complications like hypotension, sweating, flushing, chest pain, HELLP syndrome and renal failure.

**Table 3: Table showing systolic and diastolic blood pressure before and after IV Labetalol**

Pair	Mean	Standard deviation	p value
1.Systolic BP before and systolic BP after	35.033	13.662	<0.001
2.Diastolic BP before and diastolic BP after	24.900	10.515	<0.001

p value is statistically significant. This table shows there is significant reduction in both systolic and diastolic blood pressure after treatment with labetalol infusion in cases of severe preeclampsia.

**Discussion**

A total of 60 patients were included in the study. During the study all enrolled patients were in antepartum period. In our study, data indicated that labetalol regimens are effective in controlling severe hypertension in pregnancy with target blood pressure achieved in all cases.

In our study there were no complications of hypotension and chest pain.

In our study, the mean systolic blood pressure before treatment was 172.10mmhg and diastolic blood pressure was 114.27. After labetalol infusion systolic

blood pressure was 137.07 mmhg and diastolic blood pressure was 89.37mmhg. Target blood pressure of <150/100mmhg. This target blood pressure of keeping blood pressure between 140 to 155mmhg and diastolic blood pressure between 90 and 105mmhg in severe pre eclampsia was according to Sibai’s suggestions.

Comparison of various methods of administration of IV labetalol used by us in severe hypertension showed that graded incremental infusion was least likely to cause a precipitate decrease in blood pressure and least prone to induce side effects. Effective blood pressure reduction, without a steep drop, as achieved in all, in none was serious side effects encountered.

In our study, all the patients enrolment were in antepartum period and delivery expedited very shortly after achieving target blood pressure.

Time taken to achieve blood pressure less than 150/100mmg was 25.17±12.76 and which is significant.

In a Kuwaiti trial<sup>3</sup> involving 104 primigravidas with mild-moderate PIH, the investigators compared alpha-dopa with labetalol for antihypertensive management, and concluded that labetalol is quicker, more efficient and better tolerated.<sup>(18)</sup>

Our trial also implies that there was no statistically significant adverse maternal outcome or neonate outcome due to use of these antihypertensive agents but attributed to severe preeclampsia.

**Conclusion**

Labetalol is a non-selective beta-blocker and a post-synaptic alpha-1 blocking agent. Intravenous Labetalol is also used for treatment of severe hypertension in pregnancy as a first line drug and has a better side effect profile but specific concerns have been raised about the risk of neonatal bradycardia.

A total of 60 patients were included in the study. In our study, data indicates that intravenous labetalol regimen is effective in controlling severe hypertension in pregnancy with the target blood pressure 80% of cases with labetalol group within five doses of commencing treatment.

**Disclosure of interests**

None declared. Completed disclosure of interests form available to view online as supporting information.

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