Original Article

Effectiveness and safety of intravenous labetalol in severe pre-eclampsia and eclampsia at a teaching institution in Chhattisgarh

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Abstract

Introduction: Severe hypertension in pregnancy deserves prompt recognition and urgent effective reduction in order to reduce the risk of complications such as eclampsia and HELLP syndrome and to achieve desirable neonatal outcomes. There is a need for effective and safe parenteral antihypertensive treatment. **Subjects and Methods:** We studied the effectiveness and safety of intravenous labetalol use in severe hypertension in pregnancy and post-partum period in a teaching hospital in Chhattisgarh in 101 women. IV labetalol was given as bolus doses till the blood pressures were controlled. Neonatal outcomes were recorded, and adverse effects such as hypotension, hypoglycemia, and neonatal asphyxia were documented. **Results:** Intravenous labetalol given as a single bolus of 20 mg was efficacious in controlling blood pressures in 93 out of 101 (93%) women, and the rest were controlled with 1 or 2 additional doses in 1–3 hours. No neonatal deaths happened beyond the 13 intrauterine fetal deaths at presentation. No women developed any episodes of hypotension, tachycardia of more than 100, or nausea or vomiting on labetalol. **Conclusion:** Intravenous labetalol, even as a single bolus dose, is highly efficacious and is free of any major adverse effects.

Keywords: Eclampsia, intravenous labetalol, labetalol, obstetric emergency, pregnancy-induced hypertension, severe pre-eclampsia

Introduction

Hypertension, either chronic or pregnancy-related, is a common complication of pregnancy. When severe, it can lead to eclampsia and HELLP syndrome and cerebrovascular complications including stroke and death, but prompt recognition and treatment can reduce the risk of these complications.[1] There is consensus that women with severe hypertension (defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >110 mmHg) persisting for more than 15 minutes should be treated to reduce the risk of eclampsia, HELLP, maternal stroke, and heart failure and other serious maternal complications.[2] Treatment should be initiated as soon as reasonably possible and within 30 to 60 minutes.

Magnesium sulfate has been used for seizure prevention in severe preeclampsia for many years with demonstrated efficacy in eclampsia prevention and treatment.[3] Its use was reported to be associated with a significant reduction in maternal mortality, and nowadays, it is considered the standard of care for seizure prophylaxis in severe preeclampsia.[4] However, it does not reduce blood pressure substantially, which limits its sustained benefit.

Labetalol is a nonselective, competitive β-adrenergic blocker and a selective, competitive α1-adrenergic blocker. It produces a rapid yet dose-dependent decrease in blood pressure without

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causing reflex tachycardia or a significant reduction in heart rate. Furthermore, labetalol has many important nonantihypertensive effects that may be beneficial in preeclampsia. It has an antiplatelet aggregation action, a thromboxane-reducing effect, and a fetal lung maturation-accelerating influence,[5] and currently, it is recommended as the first-line treatment for blood pressure control in preeclampsia by the American College of Obstetricians and Gynecologists (ACOG). Several studies have suggested similar effectiveness between intravenous labetalol and oral nifedipine,[6–8] though some have opined better effectiveness for labetalol.[9,10]

While efficacy has been documented with one or more doses of bolus and infusions of labetalol, safety concerns have also been expressed with respect to maternal complications like hypoglycemia,[11] tachycardia, and hypotension.

Given such a scenario, we wish to study the effectiveness and safety of intravenous labetalol use in severe hypertension in pregnancy and postpartum period in a teaching hospital in Chhattisgarh that draws women from marginalized rural communities such as tribals and Dalits.

Methods

We enrolled all consecutive women who presented with severe hypertension and evidence of severe preeclampsia in the second or third trimester of pregnancy from January 1, 2022 till December 31, 2022 at the Chhattisgarh Institute of Medical Sciences, Bilaspur, in Chhattisgarh. Women were admitted from either the emergency or outpatients' department. Written Consent for participating in this observational study was taken. All women enrolled were managed as per FOGSI_ICOG guidelines, that is, anyone with blood pressure of >160/110 mg Hg or >140 systolic and/or 90 diastolic pressure with danger signs of severe pre-eclampsia. History and previous medical records of all women were examined for previous diagnosis of preeclampsia and for any treatment that may have been offered. IV labetalol, if decided, was administered as the treatment of choice in all women with severe PET or eclampsia. Blood pressures were recorded every 10 minutes or more frequently in the first hour and then hourly till it reached a level of less than 160 mm Hg systolic and less than diastolic BP less than 100 mm Hg. Pulse rate, any postural dizziness, any sweating, or effects on fetal heart rate were also monitored every hour. Blood sugars were examined if there are any symptoms and at baseline, at 1 hour, and at 4 hours post admission. The decision for expediting birth of the child was taken on the basis of the gestational age, fetal distress, and summary assessment of the maternal risk due to continued pregnancy. IV labetalol was continued till the delivery is completed and/or till the blood pressure is controlled and switch to oral medicines (amlodipine postpartum or oral labetalol antepartum) if required. If 1 hour of use of intravenous labetalol or use of a ceiling dose of 300 mg was unable to control the pressures to the target level, it was labeled as failed treatment and use alternative additional drugs such as intravenous hydralazine was done. Neonatal outcomes were recorded as per standard methods. Adverse effects such as hypotension, hypoglycemia, and neonatal asphyxia were documented in a protocolized way.

Results

One hundred and one (101) women with severe hypertension and severe preeclampsia or eclampsia were enrolled in this prospective case series. 63/101 (63%) women had never received a diagnosis of severe hypertension nor treated outside, and an additional 8 had been diagnosed less than 24 hours prior to referral and sent to us. 38/101 had been diagnosed prior to arrival and had been put on variable treatment such as oral labetalol, nifedipine, magnesium sulfate, and phenytoin, but they still presented with severe PET or eclampsia.

Forty-six women (47%) presented at term gestation, and another 28% between 33 to 37 weeks gestation, and another 25% between 24th and 32nd weeks' gestation.

Systolic blood pressures ranged from 200 to 130 mm Hg and diastolic pressures from 140 to 90 mm Hg. Four women had tachypnea on admission. 13 women had absent fetal heart at presentation, and another 25 had a fetal heart rate between 120 and 140 per min. None had a fetal tachycardia more than 180 per min [see Table 1].

72/101 had albuminuria of 2 + or more at presentation, which cleared in 93% to less than 2 within 24 hours of hospitalization and treatment. Five women had blood sugar less than 60 mg/dl at admission, and no one developed hypoglycemia after treatment with labetalol. 24 of 99 (25%) women in whom we did serum alanine aminotransferase (ALT) had an abnormal value. 13 (13%) women had a platelet count of less than 100,000 per microliter.

Thirty (30%) of 101 women presented in eclampsia, 69 had severe PET, and 2 had chronic hypertension with headache. HELLP syndrome was diagnosed in 25 of 101 women. Intravenous labetalol was administered within 30 minutes in 82 of these 101 women and within 60 minutes in the remaining 19. 93 of these 101 women required only one bolus dose of 20 mg labetalol, and only 4 required 2 doses of 20 mg bolus and another 4 required a 3rd dose [see Table 2 and Figure 1].

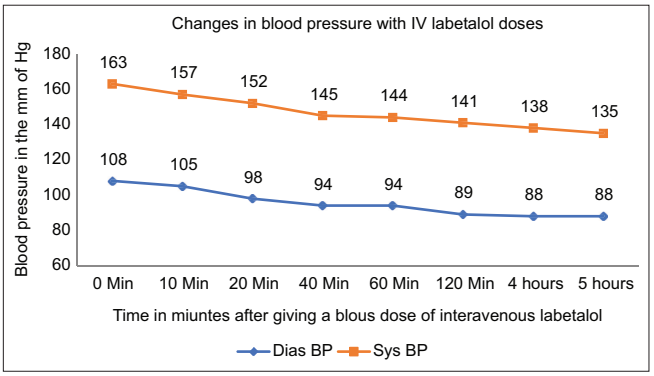

Figure 1: Pattern of blood pressure control after administration of labetalol

28/101 (28%) could be delivered by a vaginal route, and the rest required some assistance. 57 of these 101 were delivered by operative routes through lower segment cesarean section (LSCS). Most births happened within 4 hours of hospitalization.

13 of these 101 women delivered a stillborn baby, and all these had presented with absent fetal heart at admission. Thus, there was not even a single fetal death after treatment initiation. Fetal distress was documented in 57 of 101 pregnancies. Only 2 of 101 neonates had Apgar scores of 4 to 6 at 5 minutes and none lower than 4 at 5 minutes, even though 26 of 88 livebirths had a less than 7 Apgar score at 1 minute [see Table 3].

Only 36 newborns had a birth weight of 2500 g or more.

No women developed any episodes of hypotension, tachycardia of more than 100, or nausea or vomiting on labetalol. Almost all of them required an antihypertensive drug in the form of amlodipine or nifedipine.

Table 1: Presentation of pregnant women with severe PET/eclampsia

Variable	Number	Percentage (%)/ medians
Diagnosis of severe PET before admission	63	63
Term (37-42 weeks) gestation	47	47
Mean Systolic blood pressure	160	
Mean diastolic blood pressure	110	
Absent fetal heart at admission	13	13
>= 2+albumin in urine	72	72
Hypoglycemia (60 mg/dl glucose) at admission	5	5
Raised ALT	24	25
Decreased platelets	13	13

Table 2: Use of intravenous labetalol

Variable	Numbers	Proportion
Indication- eclampsia	30	30
Indication- severe PET	69	69
Number requiring 1 bolus of 20 mg	93	93
Numbers requiring 2/3 doses	8	7
Control of hypertension	101	100%

Table 3: Neonatal and obstetric outcomes

Variable	Numbers	Proportions
Livebirths	88	87
Still births	13	13
Fetal deaths after administration of rx	0	0
Birth weight	2500 g for >37 weeks	
Correction of urine albumin to <2	93	93
Hypotension post treatment	0	0
Severe nausea/vomiting	0	0
Tachycardia	0	0
Any congenital malformations	0	0

Discussion

Intravenous labetalol given as a single bolus of 20 mg was efficacious in controlling blood pressures in women with severe preeclampsia and eclampsia and in preventing neonatal deaths. There were no adverse effects on the mother or on the fetus observed in its use.

Women with severe PET/eclampsia present late, and diagnosis of their hypertension is also made late in an emergency situation. Thirty percent women in our study presented with eclampsia. In that situation, use of a rapidly effective drug like intravenous labetalol makes an ideal choice since it preserves uteroplacental blood flow to a greater extent than traditional beta blockers and other drugs like methyldopa and nifedipine.

Labetalol can be given as a series of intravenous bolus injections[12] or as a constant-dose infusion. We found that even a single bolus of 20 mg was highly effective in controlling blood pressures. The desired blood pressures were achieved within an hour [see Figure 1]. There was not even a single patient who did not respond to labetalol, and only 4 each out of 101 women required a second or third dose of 20 mg labetalol. The FOGSI-ICOG guidelines in fact simply suggest the target pressures to be less than 140/90 mm Hg. We acknowledge the lack of clinical trial data to support these recommendations and the need to individualize therapy based on maternal and fetal factors. In our study, we found a 19 mm Hg median fall in the systolic blood pressure and 14 mm Hg in the diastolic pressure within 1 hour of the drug administration. Systolic hypertension appears to be more predictive of adverse cerebral events than diastolic hypertension.[13]

In some parts of the world and most of rural India, oral therapy may be available, but access to parenteral therapy is limited. Oral nifedipine retard and labetalol can be used where parenteral therapy is not possible,[14] but where one can use, it is preferable to use intravenous labetalol for best outcomes. High proportion of women presenting as eclampsia, as in our study, makes a strong case for intravenous labetalol. Given the vulnerability of women to peripartum stroke, we recommend lowering blood pressure with parenteral agents like intravenous labetalol when the blood pressure is >160/110 mmHg.

Despite the widespread use of labetalol in pregnancy, the safety of beta blockers has been controversial[15] due to inconsistent reports of preterm birth, fetal growth restriction/small for gestational age infant,[16] perinatal mortality,[17] neonatal apnea,[18] bradycardia,[19] and hypoglycemia. Even though higher rates of congenital malformation are seen in fetus of those women treated with antihypertensives, a consistent association with labetalol is not seen.[20] In our study, we did not observe even a single instance of any of these possible adverse events.

Intravenous labetalol started being used in severe preeclampsia and eclampsia in pregnancy without any formal studies of its

efficacy and safety in Indian women. The results of our study should settle the questions of efficacy and safety of this drug in both the mother and the newborn child, especially among those with lower body weights and malnutrition. We found that even a single dose of 20 mg intravenous labetalol was sufficient to control severe hypertension, whereas it may require 3 or more doses in other studies.[21]

There are a few limitations in the study. There was no control group receiving an alternative drug like oral nifedipine, even though that comparative effectiveness has already been demonstrated. This was a single-center study in central India.

The fact that even a single bolus dose of intravenous labetalol safely brought the blood pressures to acceptable levels within an hour in over 90% makes it possible for us to consider its administration as a prereferral drug for women with severe hypertension even at peripheral centers before they are referred to a higher center.

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Conflicts of interest

There are no conflicts of interest.

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