Original Article

Intravenous Labetalol Usage among Hypertensive Pregnant Women Admitted to a Tertiary Care Hospital: A Prospective Observational Study

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Abstract

Background: Hypertensive disorders complicating pregnancy are one of the deadly triad. Objectives :1) To assess the efficacy of intravenous (IV) labetalol in severe hypertension of pregnancy. 2) Determine the various adverse effects of IV labetalol on mother. 3) To find out the Foetal outcome to the use of IV Labetalol in the study group. **Materials & Methods**: It was a prospective observational study which was conducted for a period of 1 year among the Pregnant women. Total sample size was 100.

Results: The rate of fall of systolic and Diastolic blood pressure occurred during first 40 min for drug. It is apparent that the target SBP & DBP was reached by the study groups in less than 20 minutes. Out of 100 cases only 14 patients had adverse effects . 94 were live,6 stillborn. Out of 94 live born babies 5(5.3%) had asphyxia, 4(4.3%) had HIE, 2(2.1%) were IUGR and 6(6.4%) were preterm.

Conclusions: We found that labetalol regimen is highly effective & can safely be used due to its rapid onset of action, no significant adverse reaction and no adverse effects on foetus.

Keywords- Hypertension, Labetalol, Pre-Eclampsia, Pregnancy, SBP, Severe.

Introduction

Hypertensive disorders in Pregnancy represent the most common medical complications with a reported incidence between 5-10%.(1)

Globally, the incidence has increased from 16.30 million to 18.08 million from 1990 to 2019, a total increase of 10.9% over two decades. The incidence of preeclampsia in hospital practice in India varies from 5% to 15%, and that of eclampsia is about 1.5%. Every year, over 5.2 million women die from pregnancy-related complications worldwide. With an estimated 62,000–77,000 deaths each year, Hypertensive disorders in Pregnancy account for approximately 18.1% of maternal mortality.(2)

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Hypertension is considered severe if there are sustained elevation in SBP ≥ 160 mmHg and /or DBP ≥110mmHg. [3] It requires prompt treatment as there is risk of cardio-vascular accident, to prevent intracerebral hemorrhage, hypertensive encephalopathy and other target organ damage.[4, 5] It also presents an increased risk of complication for the fetus including prematurity, low birth weight, NICU admission and even fetal death .[5]

The most commonly used antihypertensive agents for severe hypertension in pregnancy are Nifedipine, Labetalol and Hydralazine. Recent guidance from the National Institute for Health and Clinical Excellence, UK, recommends inpatient treatment of severe hypertension of pregnancy with labetalol (oral or intravenous), intravenous hydralazine or oral nifedipine as first-line alternative antihypertensives within the critical care setting.[3]

Labetalol appears to be a safe, effective alternative to hydralazine & nifedipine for treating hypertension in the peripartum period. It results in good and sustained control of BP. There is no tachycardia and BP is stabilized. Labetalol has no effect on utero-placental blood flow. Although it crosses placenta, there is no evidence of intrauterine growth retardation (IUGR), perinatal death and neonatal hypoglycemia. These additional benefits are important characteristics expected of an ideal therapeutic agent for the treatment of hypertensive emergencies complicating pregnancy to control hypertension and to prevent end organ damage.[6]

But few studies in our setup have assessed the intravenous labetalol in terms of efficacy, rapidity, tolerability and safety in the control of severe hypertension of pregnancy. So we had conducted this study with the following

Objectives: 1) To assess the efficacy of intravenous labetalol in severe hypertension of pregnancy. 2)To determine the various adverse effects of IV labetalol on mother. 3) To find out the Fetal outcome to the use of IV Labetalol in the study group.

Material and Method

It was a prospective observational study which was conducted for a period of 1 years (December 2015-December 2016) among the Pregnant women who had blood pressure ≥ 160/110 mm Hg, & was admitted to the labor room, Dept of O & G of VIMSAR(VSS Institute of Medical Sciences and Research), Burla . Total sample size was 100. We have included all the pregnant women who had came to the labor room. Universal sampling technique was used.

Inclusion criteria: Pregnant women with severe hypertension after 20weeks of gestation

Exclusion criteria: Medical disorders like- H/O Cardiac disease, Bronchial asthma, Diabetes mellitus, hematological disorder, Liver disorders, Renal disorders , allergy to drugs, Maternal heart rate <60 or >120 beats per minute and Antihypertensive treatment in the preceding 72hours

Study instrument & Data collection method: All patients with sustained systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥ 110 mm Hg were included in the study after satisfying inclusion and exclusion criteria. A proper history was taken from the patients and/or from the relatives after taking consent. General examination, systemic examination & obstetric examination were performed. Demographic and standard laboratory data were collected on the time of admission. The patients were randomized to receive IV labetalol after taking proper informed consent. Injection labetalol 20 mg IV bolus over 2 minutes repeated every 10 min increasing to 40, 80, 80, to a maximum of 220mg .[2] After successful blood pressure control, sustained release tablet of labetalol started 2hours after the last trial medications.

During the study period maternal vital signs were recorded. Mean arterial pressure was calculated. Treatment was considered as failure if blood pressure did not decrease even after increasing the dose to maximum. Additional antihypertensive agent was added & managed accordingly. Fetal monitoring was done by manual auscultation. After successful delivery of the baby with controlled hypertension of mother. Fetal outcomes were assessed by APGAR SCORE, morbidity (asphyxia, prematurity, IUGR, HIE), NICU admission, stillbirths etc.

Data analysis: Data was compiled & statistical analysis was done by applying paired 't' test & Repeated measures of Anova. for the differences in pre- and post treatment values using SPSS (statistical

package for social sciences) 17 statistical software. A p –value <0.05 was considered as significant with 95% confidence limits.

Results

Out of total 100 cases majority of the cases (44%) belonged to the age group 21-25years followed by 26-30years (33%). The incidence of hypertensive disorders was (57%) in primigravida and (43%) in multigravida. Majority of the patients were between 37-41 weeks of gestation that was 74%. 24 cases belonged to ≤36 weeks gestation and 2 were >41weeks. Mean gestational age was 37.85±1.92 years. 85 cases had no past history of hypertensive disorders, only 15 cases had history of hypertensive disorder, out of which 9 cases had severe Pre-eclampsia and 6 cases had h/o of eclampsia.

From **figure 1**; it was apparent that, in **gestational hypertension group** after 1st dose,2nd dose mean SBP was 149.3± 31.85, 129.2±25.23mmHg respectively .Mean difference between pre and post 1st dose, was 29.3±32.68mmHg,1st dose to 2nd dose 20.1±29.86mmHg, 2nd to 3rd dose was 4.95±14.74mm of Hg & 3rd to 4th dose was 5.95±14.22mm of Hg .This was statistically significant (p=0.01) using Repeated measures of Anova whereas **In Eclampsia Group** initial SBP was 182 ± 14.14 mmHg. Mean difference of SBP between 1st and 2nd dose was 24.8±30.92mmHg which was found to be statistically significant(p=0.03). Maximum cases controlled within 2nd dose.

Figure 2 illustrates that in case of **gestational hypertension** group initial DBP was 122.25±4.33mmHg. after 1st dose mean DBP starts to decrease and after second dose DBP reduced to 84.50±3.96mmHg. Mean difference between pre and post 1st dose and 1st dose and 2nd dose show significant decrease which was found to be significant statistically with P value=0.001. No patients in this group required more than 2 doses. In **severe Pre-eclampsia group**, mean difference of MAP between pre and post 1st dose was 23.09±25.49mmhg, 1st and 2nd dose was 16.22±23.62mmHg, 2nd-3rd dose was 3.92±11.71 and 3rd to 4th dose 4.39 ±11.37. This difference with usage of IV labetalol on DBP was found to statistically significant with P<0.05.

In case of **eclampsia** only after 2dose mean difference of MAP reduced significantly from 24.6 ± 21.64mmHg to 19.6±25.27 mmHg which found to be significant seen in **Figure 3.**

Initially mean± S.D of heart rate was 89.83±6.70 beats/min in the study group. After giving labetalol mean± S.D of heart rate was 81.12±5.92 beats/min. Statistically the difference was found to be significant as seen in **(Table 1**) but clinically it didn't reduces the heart rate much. It was observed that the *mean number of doses & mean duration in minutes* required to achieve target blood pressure was [1.38±0.51, 13.75±5.17]in gestational hypertension group,[1.79±0.93 ,17.93±9.39] in severe preeclampsia group and [1.60±0.96 , 17.93±9.39] in eclampsia group.

It was observed in**(Table 2)** that; out of 100 cases only 14 patients had adverse effects.4 (28.6%) cases had nausea and vomiting,5(35.7%) cases had headache,4(28.6%) cases had hypotension and only one(7.1%) case had sweating.

Mean APGAR score at 1 minute and 5 minute were 6.12±1.24 and 8.37±1.40 in gestational hypertension group, 6.04±2.23 and 8±2.62 in severe preeclampsia group and 7.1±1.1 and 9.5±0.84 in eclampsia group respectively as seen in **Table 3(a).**

Table 3(b) shows out of 100 babies born 94 were live,6 stillborn. Out of 94 live born babies 77(81.9%) babies were normal, 5(5.3%) had asphyxia, 4(4.3%) had HIE, 2(2.1%) were IUGR and 6(6.4%) were preterm.

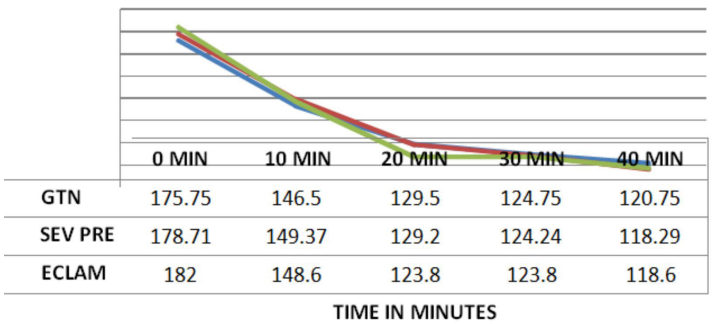
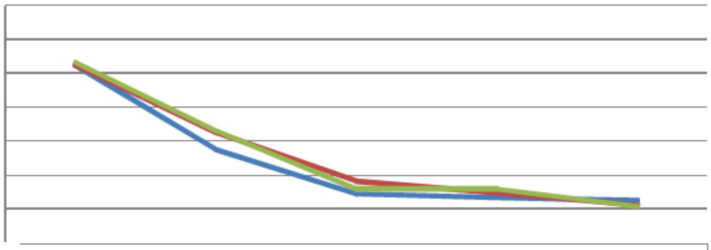


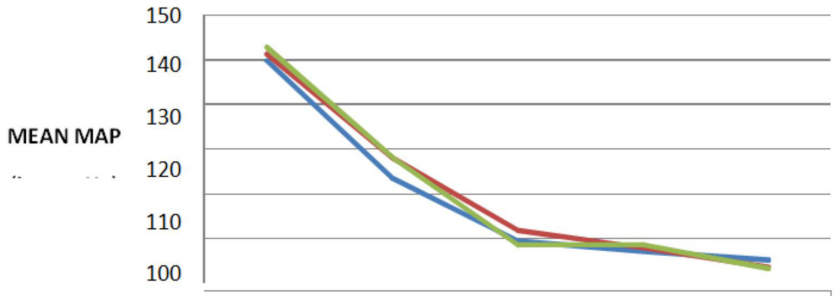
Figure 1: Effect of Labetalol on Systolic BP in patients with time (n=100)



	0 MIN	10 MIN	20 MIN	30 MIN	40 MIN
GTN	122.25	97.5	84.5	83.5	82.5
SEV PRE	122.49	102.51	88.27	84.85	81.2
ECLAM	123.2	103	86	86	80.8

TIME IN MINUTES

Figure 2: Effect of Labetalol on Diastolic BP in patients with time(n=100)



	0 MIN	10 MIN	20 MIN	30 MIN	40 MIN
GTN	139.75	113.5	99.5	97.25	95.25
SEV PRE	141.2	118.1	101.88	97.95	93.56
ECLAM	142.8	118.2	98.6	98.6	93.4

TIME IN MINUTES

Figure 3: Effect of Labetalol on Mean Arterial Pressure(MAP) in patients with time (n=100)

Table 1: Profile of Mean Heart Rate of Study Group (n=100)

Heartrate	Mean	SD	SE	Mean difference	95% CI		P value
					Lower	Upper	
Initial	89.83	6.70	0.67	8.71 ± 9.25	6.87	10.54	0.001*
After labetalol	81.12	5.92	0.59				

[*indicates p<0.05]

Table 2: Adverse Effects observed in Study Group(n=100)

Adverse Effects	Gestational Hypertension (N=8)	Severe Pre-Eclampsia (N=82)	Eclampsia (N=10)	TOTAL (n=100)
No	8(100%)	70(85.3%)	8(80%)	86
Nausea & vomiting	0	4(4.87%)	0	4
Headache	0	4 (4.8%)	1(10%)	5
Hypotension	0	3(3.6%)	1(10%)	4
Sweating	0	1(1.2%)	0	1

Table 3(a): Fetal outcomes Parameters

FETAL OUTCOMES	N	MEAN ±SD
Birth weight (in kgs)		
Gestational Hypertension	8	2.3±0.29
Severe Preeclampsia	82	2.25±0.35
Eclampsia	10	2.25±0.25
APGAR at 1 min		
Gestational Hypertension	8	6.12±1.24
Severe Preeclampsia	76	6.04±2.23
Eclampsia	10	7.1±1.1
APGAR at 5 mins		
Gestational Hypertension	8	8.37±1.40
Severe Preeclampsia	76	8±2.62
Eclampsia	10	9.5±0.84

Table 3(b) Perinatal Mortality & Morbidity among Study Group (n=100)

Perinatal Mortality	**Gestational Hypertension (N=8)**	**Severe Pre-Eclampsia (N=82)**	**Eclampsia (N=10)**	**Total (n=100)**
Live birth	8 (100%)	76 (92.6%)	10 (100%)	94
Still born	0	6 (7.31%)	0	6
Perinatal Morbidity	**Gestational Hypertension (N=8)**	**Severe Pre-Eclampsia (N=76)**	**Eclampsia (N=10)**	**Total (n=94)**
Nil	6(75%)	62(81.5%)	9(90%)	77
Asphyxia	0	5(6.5%)	0	5
HIE	1(12.5%)	3(3.9%)	0	4
IUGR	0	1(1.3%)	1(10%)	2
Pre term	1(12.5%)	5(6.5%)	0	6

Discussion

Hypertensive disorders of pregnancy remain one of the greatest unsolved mysteries in obstetrics. In this study the mean age of the cases in the study group was 25.22±4.09 years. Majority of cases (82%) belonged to the group of severe preeclampsia, only 8% of cases belonged to gestational hypertension and 10% patients to eclampsia group. Comparable to Murthy K et al[7], where 17.2% were gestational hypertension, 75.9% severe preeclampsia, 6.9% were eclampsia and 3.4% were chronic hypertension superimposed withpreeclampsia.

In the present study the mean SBP was 178.8±11.30 mm Hg for study group (175.75mm Hg in gestational hypertension, 178.71mm Hg in severe preeclampsia and 182mm Hg in eclampsia) and the mean diastolic blood pressure values for study group 122.54 ± 8.59 mmHg.(122.25mm Hg in gestational hypertension, 122.49mmHg in severe preeclampsia and 123.2mmHg in eclampsia). The rate of fall of systolic and Diastolic blood pressure occurred during first 40 min for drug. It is apparent that the target systolic blood pressure (≤150 mmof Hg) & diastolic blood pressure (≤ 100 mm of Hg) was reached by the study groups in less than 20 minutes. That mean the patients in the study group took considerably less time i.e (20 minutes) to reach the target SBP and DBP.

The mean MAP values for study group 141.24 ± 8.83 mmHg.(139.75mm Hg in gestational

hypertension, 141.2mmHg in severe preeclampsia and 142.8mmHg in eclampsia). Mean heart rate was 89.83±6.70 beats per minute in study group before intravenous labetalol. The patients in the study group showed a tendency towards bradycardia with a gradual decline of maternal heart rate from 89.83 to 81.12 beats per minute after intravenous labetalol.

Raheem et al [8] had a similar finding where the maternal heart declined in the first hour in the labetalol group. But not that much that it can affect life so clinically holds no significance.

It is apparent that 100% of total cases responded well to drug within the stipulated treatment regimen. Only 16 patients, took more than 2 doses, so drug is highly effective in controlling hypertension. There is no resistant cases, no additional antihypertensive used in our study.

In a study conducted by Ashe et al , had maximum treatment failure i.e 60%, [9], Whereas Raheem et al [8], Marbie et al[6] , Michael et al [10] had less rate of failure(20%,10% and 7% respectively) whereas in our study there was no treatment failure which was similar with the study conducted by Vermillion et al. [11]

Similarly Omkara Murthy et al[7] had 80% success rate. D.J. Cruickshank A, et al[12], Lardoux group[13] and Michael et al[10] reported satisfactory control of blood pressure within 24 hours in 88%,82%,and 92% of their cases respectively.

The mean total number of doses required for labetalol was 1.74±0.91.The average time taken for control of BP for labetalol was considerably less 17.4±9.17, this shows that labetalol controls BP more rapidly . Our study is comparable with MurthyK et al [7] , in which time taken to achieve blood pressure <150/100mm Hg was 25.17±12.76 and number of doses required to achieve target blood pressure is 2.53±0.97.

This is in contrast with the two studies. Vermillion et al [11] in their trial found that to achieve target blood pressure the labetalol regimen took 43.6±25.4minutes. Raheem et al[8] conducted a similar trial and found that the time taken for intravenous labetalol was 45 minutes and doses required were 3 doses. However in the present study, we found that labetalol required lesser number of doses (statistically significant) and has more rapid onset of action (statistically significant).

Of the 100 patients ;86 cases had no adverse reactions. Only 14 cases had adverse reactions. Naden and Redman[14] also reported that labetalol either parenterally or orally appears to be an effective and safe antihypertensive. Verma et al reported 4% cases with headache, nasal congestion and drowsiness.[15] Qarmalawi et al[16] reported 6% cases with dyspnea. Lamming et al [17] also reported in a series of 19 patients of severe preeclampsia that labetalol had no apparent detrimental effect on fetus antenatally during labor or post partum.

In our present study we found out that out of 100 cases live births were 94 & 6 were stillborn. Mean APGAR score at 1minute was 6.16±2.09 and APGAR score at 5 minute was 8.24±2.45. Maximum babies had APGAR score between 7 -10. This shows a better standard of health care and proper neonatal resuscitation facilities in the hospital. Out of 94 live births only 17 had perinatal morbidity (like birth asphyxia, HIE, prematurity, IUGR etc). In a study conducted by Michael et al[10] concluded that ,BP is better controlled which may influence perinatal outcome. Mabie et al[6] found no significant fetal and neonatal problems ascribed to labetalol. Ashe et al[9] concluded there are no harmful effects on fetus/ neonate. .Thus from the adverse effect profile it is quite apparent that the drug are quite safe for both mother and fetus in hypertensive emergencies of pregnancy.

Conclusion

In this study the time taken to reach the target blood pressure was less (17.4 minutes) with the mean dose of 1.74. The mean heart rate of patients showed a gradual decline though it's statistically significant but clinically not found to be significant. Similarly regarding adverse reactions, nausea & vomiting, headache and hypotension were more common in the study group. But the overall perinatal outcome was good by the usage of the drug. So drug was found to be effective.

Limitation: This study was a small study taking 100 patients for the drug. Large multicentric trials are required to highlight & prove the superiority of Labetolol.

Conflict of interest: No

Funding: Nil

Ethical Clearance no: Virec No.2015/P-1-RP/124.date 31.10.15

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