A Study Of Efficacy Of Labetalol In Pregnancy Induced Hypertension

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Abstract : **Background:** Pregnancy induced hypertension is a common medical complication associated with pregnancy. When untreated ,it has serious implications on maternal and fetal health. Labetalol is a new an anti hypertensive agent with alpha adrenergic and non selective beta –adrenergic receptor blocking actions. **Objectives:** 1)To assess the effect of labetalol on control of blood pressure in moderate to severe Pregnancy induced hypertension2)To study the side effects of labetalol 3)To analyze the maternal and perinatal outcome. **Material and Methods**: A prospective observational study of 50 cases of moderate to severe Pregnancy induced hypertension, treated with Labetalol ,was conducted over a period of two years. Cases were divided in Labetalol-respondent and non respondent group. Pregnancies from non-respondent group were terminated either by induction of labour or by caesarean section .Cases who responded to labetalol, were treated with oral Labetalol. Obstetric and perinatal outcome in both the groups was analyzed. **Results**: Fifty six percent cases did not respond to intravenous labetalol therapy (maximum dose 120 mg over 30 minutes) and thus pregnancy was terminated. Forty four percent cases responded to labetalol therapy and pregnancy was continued for average of 8 days .Forty eight percent cases were delivered by caesarean section. Seventy eight percent babies were live born .There were twelve stillbirths and five neonatal deaths .Twenty percent cases had mild and transient side effects related to labetalol. **Conclusion**:The effective control of blood pressure with the use of Labetalol in the dosage used ,was observed in less than fifty percent cases of moderate to severe pregnancy induced hypertension.[Bangal V B et al NJIRM 5(3): 57-61]

Keywords- Labetalol , Maternal morbidity , Perinatal outcome, Pregnancy induced hypertension.

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Introduction: Hypertensive disorders of pregnancy are common medical complications observed during pregnancy and are an important cause of maternal and perinatal mortality and morbidity worldwide, later being mainly due to preterm delivery and fetal growth restriction. Hypertensive disorders of pregnancy complicate around 3 to 10 percent of pregnancies and accounts for approximately a quarter of all antenatal admissions.[1,2,3] There is evidence that such pregnancies are commonly associated with reduced utero-placental blood flow. A number of antihypertensive medications are in use for control of blood pressure, but not all have proven to be safe during pregnancy. Various drugs available to treat PIH are central alpha agonists, alpha-blockers, beta-blockers, calcium channel blockers, direct acting vasodilators, diuretics etc. Methyldopa is the oldest drug used for pregnancy-induced hypertension. But there are certain disadvantages of methyldopa regarding adverse effects, onset of action, and overall control of blood pressure. There is theoretical risk of reduced placental perfusion when the maternal blood pressure is effectively reduced. Labetalol is an adrenergic receptor-blocking agent that has both selective alpha-adrenergic and nonselective beta-adrenergic receptor blocking actions.[4] It is an oral and intravenous antihypertensive agent. In view of the additional advantages of labetalol as reported in the literature, in regards to its availability for oral as well as intravenous use, effectiveness in control of blood pressure, less number of side effects and beneficial effect on utero-placental blood flow,[5] present study was conducted at tertiary care teaching hospital.

Material And Methods:

A) Prospective analytical study

B) Place Of Study: Study was carried out in a 750 bedded tertiary care teaching hospital located in rural area of central India for a period of two years.

C) Duration Of Study: Two years. (October 2011 to September 2013)

D) Study Subjects: Women as per inclusion and exclusion criteria mentioned below, who were admitted with moderate (150/100-159/109 mm hg) to severe ($\geq$ 160/110 mm hg) pregnancy induced hypertension [6] in third trimester of pregnancy.

E) Inclusion Criteria: Women admitted to tertiary care hospital with pregnancy-induced hypertension beyond 28 weeks of pregnancy and till 40 completed weeks of pregnancy

F) Exclusion Criteria: Women with serious complications of PIH like eclampsia , HELLP syndrome, Hepatic & renal failure etc.Women already taking antihypertensive agents other than Labetalol. Women having contraindications for the use of Labetalol. Women with intrauterine fetal death.

G) Sample Size: Consecutive fifty cases having moderate to severe pregnancy induced hypertension in third trimester.

H) Methodology: All pregnant women with moderate to severe degree of Pregnancy induced hypertension in third trimester of pregnancy were admitted in the obstetric critical care unit of Dept. of Obstetrics and Gynaecology. They were given complete bed rest. Blood pressure were recorded every four hourly. Complete history was obtained.

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. After confirming the diagnosis of moderate to severe PIH, antihypertensive treatment in the form of either intravenous or oral Labetalol was started as per the guidelines. Treatment with intravenous labetalol was started in severe hypertension, in the dose of 20 mg i.v. over 2 minutes, blood pressure was monitored after 10 minutes, if there was no control of blood pressure, then 40 mg i.v. was repeated, followed by 80 mg i.v. . Depending on control of blood pressure, total of 140 mg i.v. labetalol was used. The dose was adjusted as per the blood pressure response. The starting dose of oral labetalol was 100 mg twice a day and was increased to maximum of 2400 mg per day, [7], [8], [9] this was increased at half weekly intervals until control of blood pressure was achieved. The patients who responded to initial oral or intravenous labetalol, were allowed to continue pregnancy, and were named as labetalol-respondent group, and the patients whose blood pressure continued to remain high in spite of the doses mentioned above were named as labetalol-non-respondent group. The reduction in blood pressure below 140/90 mm hg was labeled as satisfactory controlled of blood pressure. Cases were strictly monitored for the evidence of side effect of Labetalol. All minor and major side effects were noted down. Patient's condition was monitored, counseling regarding the same was done and written and informed consent was taken.

Following administration of labetalol, cases were monitored for the changes in the blood pressure. Cases were kept in the hospital till delivery. Important investigations like renal function test, liver function test, platelet count, were repeated on weekly basis. Tests for fetal well-being like NST, obstetric USG, obstetric color doppler were repeated as per necessity. Time of delivery and mode of delivery was individualized. All newborn babies were managed by neonatologist. Low birth weight babies, IUGR babies and babies suffering from other complications were managed in neonatal intensive care unit (NICU). Women were discharged from the hospital after satisfactory control of blood pressure. They were asked to come for follow up after 15 days of discharge. Information of all cases was entered in a structured proforma and then was transferred to master chart. Statistical analysis of important data was done with Z- test. Institutional ethics committee approval was obtained before initiation of the study, (Reference no- PMT/PMIS/RC/2011/140).

Results : Majority of the women were young primigravidae and were unbooked. The average gestational age at presentation was around 34 weeks. Cases were treated either with intravenous labetalol or by oral labetalol in divided doses. Out of total 50 cases of moderate to severe hypertension, 28 cases (56%) did not respond to intravenous labetalol therapy .In view of the risk of serious maternal complications,decision of termination of pregnancy taken. Remaining 22 cases (44%) responded through satisfactory reduction of blood pressure.

Table 1: Distribution Of Cases As Per Severity Of Blood Pressure And Response To Labetalol Therapy

Severity of hypertension	Number of cases	Pregnancy terminated due to failure of control of blood pressure with I.V. labetalol	Pregnancy continued with oral labetalol
Moderate HTN (>150/100-159/109 mm hg)	28	13	15
Severe HTN 160/110 mm hg)	22	15	07
Total	50	28	22

TABLE 2: Comparison Between Mean Fetal Age On Admission And At Delivery

Mean fetal Gestational age	
On admission	241+/-2 days
At Delivery	248+/-7 days

The average duration of continuation of pregnancy was 7-8 days**.**

TABLE 3: Distribution Of Cases As Per Obstetric Management

Obstetric management	Number of cases (n =50)	Percentage
Spontaneous onset of Labour	09	18
Induction of labour	17	34
Caesarean section	24	48

The average dose of oral labetalol required to control blood pressure was 500 mg/ day in divided doses. Rate of caesarean section was 48 %. The common indications for caesarean section being features of eminent eclampsia (uncontrolled hypertension) not responding to intravenous labetalol, failure of induction, fetal growth restriction, protracted labor and fetal distress.

There was no serious maternal morbidity in the study group. Minor morbidities included superficial surgical site infections, post-partum febrile illness, need for blood transfusion etc. There was no maternal mortality in the present study. Perinatal outcome was satisfactory. There were 44 (78.5%) live births and 12 (21.4%) stillbirths.

TABLE 4: Perinatal Outcome In Relation To Gestational Age

Perinatal outcome (n =56)	Gestational age			%
	>28-34 wks (n =32)	35-37 wks (n =10)	>37 wks (n =14)	
Live birth (n=44)	20	10	14	78.5
Still birth (n=12)	12	-	-	21.4

The causes of stillbirths were severe birth asphyxia, extreme prematurity, severe placental insufficiency, very low birth weight baby and meconium aspiration syndrome. All 12 stillbirths were seen in pregnancy of less than 34 weeks duration. The average gestational age in these babies was 31.5 weeks and average birth weight was 1100 Gms. Out of 44 live born babies, 37 babies were low birth weight, majority of these babies required admission in intensive neonatal care unit for varied duration. There were 5 neonatal deaths; causes of neonatal deaths were respiratory distress syndrome, severe birth asphyxia, meconium aspiration syndrome, neonatal sepsis etc. Overall perinatal mortality was seen in 17 babies (30.3%) out of 56 babies born.

Ten cases (20%) experienced some minor side effects related to labetalol. Common being nausea, vomiting, dizziness, headache, etc. they were transient, minor and did not require discontinuation of treatment or termination of pregnancy.

Discussion: A prospective observational study was carried out to find out the effect of labetalol on moderate to severe hypertension in 50 pregnant women in third trimester. Cases were divided into labetalol- respondent and labetalol non-respondent group for analysis.

There were 22 cases of severe hypertension that were treated with intravenous labetalol. Out of 22 cases, fifteen (68%) did not respond to intravenous labetalol given in incremental doses upto 140 mg,as per schedule till 30 minutes. The mean systolic blood pressure in this group was 171+/-4 mm hg and mean diastolic pressure was 112+/-2 mm hg. There was no satisfactory control in terms of reduction in blood pressure in 15 cases. Pregnancy was terminated in these cases. Remaining seven cases (32%) were shifted to oral therapy after satisfactory control of blood pressure. The control of blood pressure occurred in 44% cases within 48 to 72 hours of starting labetalol therapy in labetalol respondent group. D. J. Cruickshank a, et al [7] observed satisfactory control of blood pressure in 45 of the 51 treated women (88%) within 24 hours. Several other workers, Lardoux group and C. A Michael reported satisfactory control of blood pressure within 24 hours in 82% and 92% of their cases respectively [8,9]

There were 28 cases of moderate hypertension with mean systolic blood pressure of 154+/-3 mm hg and diastolic blood pressure of 104+/- mm hg. Out of 28 cases, 15 cases were also treated with intravenous labetalol, out of 15 cases, 13 cases did not respond intravenous labetalol given in incremental doses up to 30 minutes same as described above for cases with severe hypertension. Remaining 15 cases were treated with oral labetalol therapy. Thus, out 50 cases of moderate to severe hypertension, 28 cases (56%), labetalol- non- respondent group required termination in the form of caesarean section or induction of labor, whereas in remaining 22 cases (44%), labetalol- respondent group pregnancy was continued with oral labetalol therapy. In the present study, the blood pressure control could be achieved in 44% cases. Michael C. A, in his study of 25 cases of use of labetalol in cases of severe hypertension in pregnancy reported effective reduction in blood pressure in 88% cases.[9] Cruickshank D. J., Robertson A A et al in their randomized controlled study reported satisfactory control of blood pressure in 45 of their 51 cases (88%), treated on labetalol. The effect was short-lived and required dose escalation after 3.5 days in the majority of cases. [7] In the present study 10 cases (20%) had side effects related to labetalol. Out of 10 cases, 5 cases had received intravenous labetalol and these cases had severe headache, nausea, vomiting, and dizziness. It was difficult to differentiate weather these symptoms were related to labetalol or due to severe hypertension. Remaining 5 cases had mild and transient symptoms of sweating, tremor, palpitations, and nasal congestion on oral labetalol treatment. These symptoms did not require any specific therapy. Verma et al reported minor side effects of labetalol in 4% of their cases, in the form of headache, nasal congestion, and drowsiness.[10] Qarmalawi et al reported dyspnea in 6% of cases on labetalol therapy .[11]

Conclusion: Development of hypertension during pregnancy is one of the serious complications. The maternal and perinatal outcome depends upon severity of hypertension, period of gestation and treatment received by women.

Labetalol, a new antihypertensive agent with alpha and non-selective beta-adrenergic blocking actions did not show satisfactory response in control of severe hypertension (Blood pressure > 160/110 mm hg) in the doses prescribed up to 30 minutes of admission. Labetalol by intravenous and then by oral route showed satisfactory control of blood pressure in 44% cases. Findings of the present study have been in contradiction with the findings quoted by other workers. Although there were no major side effects of labetalol, 20% cases experienced some minor side effects. High cost of labetalol therapy is another issue, in comparison with the available antihypertensive drugs in the market. The adverse perinatal outcome was mainly related to extreme prematurity, low birth weight, and utero-placental insufficiency due to moderate to severe PIH.

Due to small sample size, it was not possible to draw definite conclusion regarding efficacy as well as safety of labetalol in incremental doses as prescribed. A large multi-centric trial in Indian pregnant population is required for better understanding about labetalol as antihypertensive agent in pregnancy.

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