

# EFFECTS OF MATERNAL LABETALOL ON THE NEWBORN INFANT

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## ABSTRACT

Forty eight neonates, born to mothers suffering from pregnancy induced hypertension and receiving labetalol for control of blood pressure, were studied for the possible adverse effects of the drug. These were compared with eighty one neonates matched for gestation and weight and born to mothers with pregnancy induced hypertension treated with drugs other than labetalol. Incidence of birth asphyxia and intrauterine growth retardation (IUGR) in the study population was 10.4 and 22.9%, respectively and in the control group 5 and 19.7%, the difference between two groups was not statistically significant ( $p > 0.05$ ). However, the incidence of hypoglycemia was significantly higher ( $p < 0.01$ ) in the study group (47.9%) as compared to the control group (17.2%). Two-thirds of the hypoglycemic babies in the study population were asymptomatic and they were managed with sugar-fortified milk feeds.

In the study population, the symptomatic hypoglycemic babies had hypoglycemia for prolonged duration of  $43.3 \pm 23.3$  hours as compared to  $11.5 \pm 6.3$  hours in symptomatic hypoglycemic babies of the control group ( $p < 0.01$ ). The mothers of the symptomatic babies in the study group received higher doses of labetalol in the range of  $287.6 \pm 142.3$  mg/day while rest of the mothers in the same group whose babies had either asymptomatic hypoglycemia or normal blood glucose levels, received  $239.5 \pm 118.5$  mg/day, though the difference was not statistically

Pregnancy induced hypertension (PIH) is an important cause of maternal morbidity, poor fetal growth and increased perinatal mortality. Beta blocking agents have been used in the management of PIH for many years. Most studies pertaining to the use of beta blockers in PIH have focussed on the effects of these drugs on the maternal blood pressure and outcome of the pregnancy. Only a few studies have been done to assess the adverse effects of these drugs on the neonate. Over the past few years labetalol, a sympathetic blocking agent with predominant beta-blocking activity(1,2) and some alpha blocking effect has been claimed as a safe and effective antihypertensive agent in PIH(3,4). Labetalol like other beta-blockers has been shown to cross the placenta freely(5). It is known to cause some degree of sympathetic blockade which may result in metabolic disorders like hypoglycemia(6). It has been shown that the level of catecholamines in the cord blood at birth is elevated especially after a complicated delivery and it presumably reflects an appropriate physiological response by the fetus to the stress of labor(7). Sympathetic blockade induced by labetalol may, therefore, inter-

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significant. It is concluded that maternal labetalol therapy is associated with increased risk of neonatal hypoglycemia.

**Key words:** Pregnancy induced hypertension, Labetalol, Neonatal hypoglycemia.

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ferre with the ability of the fetus to cope with the stress of the delivery and predispose to birth asphyxia. After birth there is cessation of the maternal glucose supply to the neonate. The increased catecholamine response at birth and later due to low blood glucose levels along with other physiological mechanisms tends to increase the glucose levels. The lack of reflex catecholamine increase particularly in association with other risk factors like birth asphyxia and intrauterine growth retardation would predispose the baby to develop hypoglycemia.

The present study was undertaken to assess the incidence of birth asphyxia, intrauterine growth retardation and hypoglycemia in the neonates of mothers suffering from PIH treated with labetalol.

### Material and Methods

Neonates born to mothers suffering from PIH delivered between 1st Jan 1989 to 30th June 1991 were analyzed for the incidence of birth asphyxia and intrauterine growth retardation and hypoglycemia. PIH was defined as maternal systolic blood pressure of  $>140$  mm Hg and diastolic  $>90$  mm Hg.

These neonates were divided into two groups. Group I or the study group comprised babies born to mothers with PIH and treated with labetalol as a single drug or in combination with other antihypertensive drugs started at least one week prior to the delivery and continued till the day of delivery.

Group II or control group consisted of those neonates whose mothers also had PIH but received antihypertensive drugs other than labetalol, like alpha methyl-dopa, hydralazine, nefidipine, *etc.* given atleast one week before the delivery and continued till the day of delivery.

Neonates born to mothers suffering from PIH with established or gestational diabetes mellitus were excluded from the study.

Apgar scores at 1 and 5 minutes were recorded for all neonates by the pediatrician who attended the delivery and a 5-minute Apgar score of  $<6$  was taken as the evidence of birth asphyxia. Heart rates of these neonates were recorded at 5-minutes as part of Apgar scoring and their rectal temperature was taken on admission to the nursery.

Bradycardia was defined as heart rate of  $<100$ /min and hypothermia as rectal temperature of  $<35^{\circ}\text{C}$ . Gestational assessment of all the babies was assessed by any one of us according to the modified method proposed by Singh *et al.*(8). All the babies were weighed in the nursery on an electronic weighing scale (Airshield) with an error of  $\pm 1$  g. The babies were categorized as appropriate, small or large for dates based on the reference intrauterine growth curves(9).

Blood glucose was monitored in all babies first at 1-2 hours of age and again at 4-6 hours of age, thereafter 2-6 hourly depending on the previous blood glucose results. The monitoring was stopped once at least, two blood glucose values were above 40 mg on oral feeding (breast or formula) alone.

Estimation of blood glucose was done by dextrostix (glucose oxidase method) using the electronic Eyetone-glucometer. The procedure was followed strictly according to the instructions of the manufacturer. Hypoglycemia was defined as blood glucose value of  $<30$  mg/dl irrespective of gestational age, within the first 72 hours of life and below 40 mg/dl thereafter(11). In hypoglycemic neonates, the associated symptoms and the age at onset of hypogly-

cemia was noted along with the lowest blood glucose values.

The duration of hypoglycemia was noted as the time required to achieve the normal blood glucose values consistently for at least 24 hours. The results were subjected to statistical analysis by applying Chi-squared test, Student's t-test and Wilcoxon rank sum test.

## Results

Forty eight neonates were in Group I (study group) and eighty one in the Group II (control group). The characteristics of both groups and morbidities encountered are shown in *Table I*. Blood pressure of the babies after birth was not monitored regularly and was, therefore, not analyzed. The incidence of hypoglycemia in Group I was 23/48 (47.9%) as compared to 14/81 (17.2%) in Group II ( $p < 0.01$ ).

In Group I, out of a total number of 23 hypoglycemic neonates, 8 were symptomatic while 15 were asymptomatic (*Table II*). Among the symptomatic babies, all had

poor feeding and required intravenous dextrose infusion. Five babies manifested with jitteriness, three had lethargy and hypotonia, three babies had convulsions which responded to intravenous dextrose bolus, and one baby had respiratory distress. The age at onset of hypoglycemia in Group I was  $5.2 \pm 5.2$  hours in symptomatic sub-group and  $4.4 \pm 2.2$  hours in the asymptomatic sub-group. The mean  $\pm$  SD blood glucose values in the symptomatic sub-group was  $16.1 \pm 5.4$  mg/dl and  $24.7 \pm 3.4$  mg/dl in the asymptomatic sub-group. The duration of hypoglycemia was  $43.3 \pm 23.3$  hours in the symptomatic sub-group as compared to  $15.0 \pm 11.0$  hours in the asymptomatic sub-group. Only two asymptomatic babies required intravenous dextrose infusion; others were treated with sugar-fortified formula or expressed breast milk.

In Group II, out of a total of 14 neonates who developed hypoglycemia, 6 were symptomatic and 8 asymptomatic. Of the symptomatic sub-group, 4 had jitteriness

TABLE I— *Characteristics of the Study and Control Populations*

Characteristics	Study group (n = 48)	Control group (n = 81)
1. Birth weight (g) (mean $\pm$ SD)	2456 $\pm$ 732	2472 $\pm$ 554
2. Gestation (weeks) (mean $\pm$ SD)	36.4 $\pm$ 2.1	36.9 $\pm$ 1.6
3. Small for date babies (SFD)	11 (22.9)	16 (19.7)
4. Birth asphyxia	5 (10.4)	4 (5.0)
5. Bradycardia (5 min HR < 100)	6 (12.5)	4 (5.0)
6. Hypothermia	4 (8.3)	5 (6.1)
7. Hypoglycemia	23 (47.9)*	14 (17.2)

\*  $p > 0.01$ . For all other observations,  $p > 0.05$ . Figures in parenthesis are percentages.

TABLE II—Age at Onset, and Duration of Hypoglycemia and Blood Glucose Levels (Mean  $\pm$  SD)

Type of hypoglycemia	Age at onset (hours)	Duration (hours)	Lowest blood glucose (mg/dl)
1. Study group (n = 48)			
(a) Symptomatic hypoglycemia (n = 8)	5.2 $\pm$ 5.2	43.3 $\pm$ 23.3*	16.1 $\pm$ 5.4
(b) Asymptomatic hypoglycemia (n = 15)	4.4 $\pm$ 2.2	15.0 $\pm$ 11.0	24.7 $\pm$ 3.4
2. Control group (n = 81)			
(a) Symptomatic hypoglycemia (n = 6)	3.5 $\pm$ 1.6	11.5 $\pm$ 6.3	20.0 $\pm$ 3.6
(b) Asymptomatic (n = 8)	3.6 $\pm$ 2.2	4.0 $\pm$ 1.6	25.8 $\pm$ 2.3

p < 0.01; as compared to symptomatic hypoglycemia of control group.

and 2 had lethargy, none had convulsions but all received intravenous dextrose. Age of onset of hypoglycemia was 3.5  $\pm$  1.6 hours in symptomatic sub-group and 3.6  $\pm$  2.2 hours in asymptomatic sub-group. The mean lowest glucose value recorded was 20.0  $\pm$  3.6 mg/dl in symptomatic sub-group as compared to 25.8  $\pm$  2.3 mg/dl in asymptomatic sub-group. The duration of hypoglycemia was 11.5  $\pm$  6.3 hours in symptomatic sub-group as compared to the 4.0  $\pm$  1.6 hours in the asymptomatic babies. Duration of hypoglycemia in the symptomatic babies of study group (43.3  $\pm$  23.3 hours) was significantly prolonged as compared to the symptomatic babies in control group (11.5  $\pm$  6.3 hours).

In the study group, the maternal drug history revealed that labetalol was used as the only antihypertensive drug in 25 out of 48 cases while the rest 23 mothers received labetalol in combination with other antihypertensive drugs. The daily mean dose of labetalol in the mothers of babies of study

group, who developed symptomatic hypoglycemia, was 287.6  $\pm$  142.3 mg/day while the rest of babies who had asymptomatic hypoglycemia or normal blood glucose levels, their mothers were receiving 239.5  $\pm$  118.5 mg/day (p > 0.05). The mean duration of treatment with labetalol was 4.0 weeks with a range of 1 to 16 weeks. The other labetalol was 4.0 weeks with a range of 1 to 16 weeks. The other antihypertensive drugs received in combination with labetalol in the study group were: aldomet in 16 patients (0.5 g to 2.0 g/day), nifedipine in 9 patients (20-40 mg/day) and hydralazine (50-100 mg/day) in 4 patients. In the control group the drugs prescribed were: aldomet (0.5-2.0 g/day) in 64 patients, 35 patients received it as a single antihypertension drug while other 29 received in combination with other drugs; nifedipine (20-40 mg/day) in 35 patients, 13 received it as a single drug while 22 patients in combination with other drugs; hydralazine was given to 17 patients as

combination with other drugs (50-100 mg/day). The mean systolic blood pressure in Group I mothers was  $161.4 \pm 10.7$  mmHg and the diastolic pressure was  $109 \pm 7.2$  mmHg. In Group II, the mean systolic pressure was  $158.9 \pm 9.7$  mmHg and mean diastolic pressure was  $107.3 \pm 6.8$  ( $p > 0.05$ ).

Out of 23 hypoglycemic babies in the study group, 18 were low birth weight (<2500 g), 7 being small for date and 11 being appropriate for date preterm babies. In the control group, all 14 hypoglycemic babies were low birth weight, 10 being small for date and 4 being appropriate for date preterm.

Six babies had bradycardia at 5 minutes in the study group, of these 5 suffered birth asphyxia. One baby whose mother received labetalol had bradycardia at 5 minutes which subsided in 1 hour. In the control group, 4 babies developed bradycardia at 5 minutes but all suffered from birth asphyxia.

## Discussion

The incidence and severity of neonatal hypoglycemia was significantly increased in the study group. Maternal labetalol freely crosses the placenta and is expected to cause some degree of adrenal blockade and blunting of catecholamine response of the newborn baby at delivery and predispose the neonate to hypoglycemia, bradycardia, hypotension and birth asphyxia.

The use of propranolol, a beta blocker, has been abandoned during pregnancy because it causes significant adverse effects in the neonate like bradycardia, hypotension, intrauterine growth retardation and hypoglycemia. Since the pharmacological characteristics of beta blockade are common to both drugs, it is understandable that labetalol may cause some of the above

mentioned effects in the newborn.

Haraldsson *et al.* (13) described severe adverse effects of maternal labetalol in a preterm baby. Macpherson *et al.* (4) found mild transient hypotension in infants born to mothers treated with labetalol which disappeared after 24 hours. We found a slightly increased incidence of birth asphyxia (10.4%) in the study group as compared to the control group (5%) but the difference was not statistically significant.

Increased incidence of hypoglycemia in the neonates born to mothers receiving labetalol during pregnancy has not been reported earlier. We found a statistically significant increase in the incidence of neonatal hypoglycemia in the study group. Two-thirds of the hypoglycemic babies were symptomatic cases required intravenous dextrose. The dose of maternal labetalol in the symptomatic subgroup was higher than in the asymptomatic hypoglycemia subgroup or in euglycemic babies but the difference was not statistically significant.

It can be argued that PIH itself causes low birth weight babies, due to placental dysfunction and higher incidence of preterm induction of labor. The low birth weight babies thus born are prone to hypoglycemia but we have seen that the duration of hypoglycemia was significantly prolonged in the symptomatic hypoglycemic sub-group of the study population as compared to symptomatic babies in control group. The blood glucose level also was lower in the symptomatic hypoglycemic sub-group of study population as compared to symptomatic babies in control group or asymptomatic babies of either group though the difference was not statistically significant. Our findings suggest that higher the dose of labetalol given to the mother, more are the chances for a

prolonged and severe hypoglycemia particularly in low birth weight babies.

We conclude that care must be taken in prescribing labetalol during pregnancy and if deemed necessary due to maternal indications, the pediatrician should be forewarned to anticipate the adverse effects of this drug and monitor heart rate, blood pressure and blood glucose level in the neonate.

Further prospective studies, which should include measurement of neonatal labetalol levels, are indicated to evaluate the adverse effects of this drug in the neonates.

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