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Original Article

# Neurodevelopmental Outcome of Asymptomatic Hypoglycemia Compared With Symptomatic Hypoglycemia and Euglycemia in High-Risk Neonates

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ABSTRACT

**AIMS:** We assessed the neurodevelopmental outcome at one year of age of children with asymptomatic neonatal hypoglycemia and compared their outcome with that of symptomatic hypoglycemic and euglycemic neonates. **METHOD:** Seventy two hypoglycemic (plasma glucose less than 50 mg/dL) neonates, both symptomatic (n = 27) and asymptomatic (n = 45), and 70 weight- and gestation-matched euglycemic neonates of gestational age greater than 32 weeks were enrolled during the first week of life then assessed for neurodevelopmental outcome at corrected age six and 12 months (n = 67 and 62 in hypoglycemia group and 63 and 54 in euglycemia group, with the rest lost to follow-up, and death = 1). **RESULTS:** At one year, 8% (five of 62, four in symptomatic and one in asymptomatic group) of hypoglycemic neonates developed cerebral palsy. Mean motor and mental development quotients were significantly lower at corrected ages six and 12 months in any hypoglycemia ($P < 0.001$) and if blood glucose was less than 40 mg/dL ($P < 0.001$) when compared with euglycemia. Symptomatic infants had lower motor development quotient ($P = 0.004$ and 0.003) and mental development quotient ($P = 0.001$ and 0.001) at corrected ages six and 12 months than asymptomatic infants, and asymptomatic infants had lower motor development quotient ($P \leq 0.001$ and 0.004) and mental development quotient ($P = 0.001$ and 0.004) than the euglycemic group at corrected ages six and 12 months, respectively. Blood glucose of less than 40 mg/dL had high sensitivity (83% for motor development quotient and 81% for mental development quotient) for development quotient scores of less than 85. **CONCLUSION:** Hypoglycemia, both symptomatic and asymptomatic, leads to adverse neurodevelopmental outcome when compared with euglycemia, although it was worse in the symptomatic group and at blood glucose less than 40 mg/dL.

***Keywords:*** neurodevelopment, MoDQ, MeDQ, DASII score, hypoglycemia, blood glucose

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## Introduction

Hypoglycemia in neonates has been recognized for over 50 years as a cause of serious long-term neuromorbidity due to damage to both neuronal and glial cells, resulting in death or handicap.[1,2] Due to poor correlation between blood glucose levels and clinical manifestations and to controversial treatment thresholds, it is difficult to define a safe blood glucose level. The American Academy of Pediatrics in 2011 proposed a guideline of using intravenous (IV) fluids in late preterm, term small for gestational age (SGA), and infant of diabetic mother (IDM)/large for gestational age (LGA)

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infants if the blood glucose level is less than 40 mg/dL and in symptomatic patients. In asymptomatic infants, enteral feeding is attempted if blood glucose is less than 25 mg/dL within the first four hours of life and at less than 35 mg/dL between ages four and 24 hours. If no improvement has occurred by one hour after feeding, then IV glucose is recommended. In case of partial improvement, refeeding or IV glucose is recommended.[3] Cornblath et al. proposed operational thresholds of intervention at 36 mg/dL and to maintain a therapeutic level of more than 45 mg/dL in neonates.[4] Several studies have analyzed the effects of various ranges of hypoglycemia on neurodevelopmental outcome.[1,2,5-7] However, variable results regarding the effect of asymptomatic hypoglycemia on the neurodevelopmental outcome have been reported[1,5,6] without any clear conclusion. We analyzed the long-term neurodevelopmental outcome of symptomatic and asymptomatic hypoglycemic neonates when compared with euglycemic neonates.

## Methods

This prospective study was conducted in a level III neonatal unit and subsequently in a neonatal follow-up clinic after discharge, from July 2010 to June 2012 in infants of gestational age greater than 32 weeks who developed hypoglycemia during the first seven days of life. As per our neonatal unit protocol, all neonates at risk of hypoglycemia (all preterm infants, term infants who are SGA or LGA and IDM) are routinely screened for hypoglycemia during the first 72 hours of life with blood glucose monitoring every six hours. Neonates who developed hypoglycemia, as measured by glucose test strips (defined as blood glucose levels less than 50 mg/dL, confirmed by laboratory glucose) were consecutively enrolled after written informed consent from parents. Those who remained euglycemic were matched for weight and gestation and served as control subjects. In the euglycemic group, laboratory plasma glucose level was estimated within the first six hours of life. If hypoglycemia was associated with lethargy, poor feeding, seizures, jitteriness, or apnea, they were considered to have symptomatic hypoglycemia. Those with major congenital malformations, severe birth asphyxia, Rh isoimmunization, and grade III or IV intraventricular hemorrhage (IVH) were excluded.

After 72 hours, if any baby became symptomatic due to any illness or developed any symptoms suggesting hypoglycemia, blood glucose was repeated, and if found hypoglycemic was also planned to be enrolled until day seven of life.

The initial blood glucose was measured with Optium Xceed Glucometer (Abbott Diabetes Care Inc, Alameda, CA, USA) using Optium blood glucose test strips, and if it was less than 50 mg/dL, plasma glucose level was measured using hexokinase method on clinical chemistry analyzer. We used oxalate- and sodium-fluoride-containing vials for estimation of plasma glucose.

Infants with blood glucose of 40 mg/dL or less when tested by glucose strips were started on IV fluids with a glucose infusion rate of 6 mg/kg/min. Blood glucose was repeated every 15 minutes initially until stabilization, subsequently ½ hourly for two hours, and then every six hours for the next 72 hours. If blood glucose level remained below 40 mg/dL, then the glucose infusion rate was increased by 2 mg/kg/min till blood glucose of 50 mg/dL or more was achieved. Those neonates having a value greater than 40 mg/dL were given oral feeds and monitored every ½ hour until the blood glucose increased to 50 mg/dL. The neonates were monitored for the next 72 hours with blood glucose measured every six hours. In infants who were on IV fluids, oral feeds were started as soon as possible, initially at the rate of 20 to 30 mL/kg/day, and advancement of feed was done depending on the tolerance and need for glucose infusion. After observing for six more hours, if blood glucose remained in the euglycemic range ($\geq$50 mg/dL) and the baby tolerated feeds, then feeds were further increased and IV fluids tapered off. All blood glucose determination was done by Optium glucose test strips. If the baby had intermittent hypoglycemia on subsequent days, everyday one sample for laboratory plasma glucose was sent during the episode of hypoglycemia. One documented episode of hypoglycemia on each subsequent day was counted as one day and was added up for the total duration of hypoglycemia.

At birth all infants were assessed by the New Ballard Score[8] for accurate gestational assessment. Growth was categorized as AGA, SGA, and LGA as per Lubchenco's intrauterine growth chart.[9] After discharge, infants were followed up at monthly intervals for 3 months for growth and feeding pattern and then at corrected ages (CAs) of six and 12 months for neurodevelopmental assessment. Neurological assessment was done by using the Amiel-Tison Scale,[10] and developmental assessment was done by using Developmental Assessment Score for Indian Infants (DASII) scoring system, which is an Indian adaptation of the Bayley Scale of Infant Development.[11] The DASII scale was administered by the principal investigator (unblinded) who was trained by a certified and experienced trainer. Mental development quotient (MeDQ) and motor development quotient (MoDQ) were calculated as per the DASII instruction manual, and a score of less than 70 was considered delayed, between 70 and 85 borderline, and greater than 85 average. Respiratory distress was defined as tachypnea, retractions or grunt, and need for oxygen or any form of respiratory support. We included all cases of respiratory distress irrespective of causes. Sepsis included both culture positive and culture negative with septic screen positivity along with symptoms. Polycythemia was defined as packed cell volume greater than 65% sampled from a major vein. The study protocol was approved by the institute research ethics committee.

### Sample size

According to a previous study by Yamaguchi et al.,[12] development quotient (DQ) at two years was 103.8 $\pm$ 24.2 for cases of hypoglycemia and 116.8 $\pm$ 20.7 for control subjects. Based on this, to find out a difference of DQ of 10, with an SD of 20, alpha error of 5%, and a power of 80%, 128 samples were required. Anticipating 10% loss to follow-up, we enrolled a total of 142 (72 hypoglycemia and 70 euglycemia) patients. We finally assessed 130 (67 in hypoglycemia and 63 in euglycemia group) at six months CA and 116 (62 in hypoglycemia and 54 in euglycemia group) at one year CA.

We compared the outcome (DQ) in symptomatic and asymptomatic hypoglycemic infants and compared them with those of euglycemic infants at CAs six months and one year.

### Statistical analysis

Statistical analysis was done using SPSS version 19. Quantitative variables are reported as mean (SD); median (interquartile range) and qualitative variables are reported as proportions. Comparison was made by using Student *t* test or chi-square test, as appropriate.

A cutoff of blood glucose level was established by constructing a receiver operating curve (ROC) to define a normal DQ of greater than 85. A two-tailed significance level of 0.05 was applied for all analyses. Multivariate regression analysis was performed to see the independent risk factors of abnormal neurodevelopment other than low blood glucose levels.

## Results

A total of 647 infants who fulfilled the eligibility criteria were screened (Fig 1) and a final sample of 142 were