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Original Research Article

Hypoglycemia occurs frequently in very low birth weight premature infants with cholestasis

Pradeep Alur[1], Sriharsha Talluri[2]*, Vishwarath Bollampalli[2], Theodore Bell[2], Jonathan Liss[2], Prabhu Parimi[3]

[1]Division of Neonatology, University of Mississippi Medical Center, Jackson, MS, USA
[2]Division of Neonatology, York Hospital, PA, USA
[3]Department of Neonatology, All Childrens Hospital Johns Hopkins Medicine, St. Petersburg, FL, USA

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***Correspondence:**
Dr. Sriharsha Talluri,
E-mail: stalluri@tcmc.edu

ABSTRACT

Background: The study purpose was to examine the incidence of hypoglycemia in very low birth weight (VLBW) infants with cholestasis while on complete enteral nutrition.
Methods: A retrospective study of 270 VLBW (<1500 grams) infants born between 2008 and 2012 at York Hospital with cholestasis was performed. A blood glucose concentration ≤50 mg/dl was used to define hypoglycemia, and hypoglycemic events were recorded while infants were on full enteral feeds. Characteristics of infants with cholestasis were compared with those without cholestasis.
Results: Cholestasis was noted in 9.6% (26/270) of VLBW infants, four babies were excluded. Twenty-two infants with cholestasis were analyzed and compared. Among those with cholestasis, hypoglycemic episodes occurred in 12 (54.5%) infants at 17±13 days (mean ±SD) after being on exclusive enteral nutrition and at a post-conception age between 31-42 weeks. Three infants (25%) needed transient reintroduction of parenteral glucose and/or alteration of feeding regimen to correct hypoglycemia. In contrast, the incidence of hypoglycemia in the control group (VLBW infants without cholestasis on full enteral feeds) was 4.5% (3/67) (P= <0.001). Receiver operating characteristic curve analysis showed a peak direct bilirubin of >4.1mg/dl (before full enteral feeds) predicts hypoglycemia while on full enteral feeds, with a sensitivity of 100%, specificity of 50%, and negative predictive value of 100%.
Conclusions: Hypoglycemia is an unrecognized complication occurring in a high percentage of VLBW infant with history of cholestatic jaundice while receiving full enteral feeds. We propose that care-givers in the neonatal ICU monitor glucose levels in this select group of VLBW infants to avoid recurrent asymptomatic hypoglycemia.

Keywords: Cholestasis, Hypoglycemia, Infants, Premature, VLBW

INTRODUCTION

Cholestasis is a complication associated with prolonged hyperalimentation (parenteral nutrition associated cholestasis PNAC), surgical conditions such as necrotizing enterocolitis (NEC), gastroschisis, intestinal atresia, small for gestation and sepsis in VLBW infants.[1-3] There is some evidence that phytsterols may be associated with cholestasis.[4-6] Current evidence suggests cholestasis suppresses gluconeogenesis by enhancing insulin sensitivity through stimulating the G protein coupled receptors.[7-9] It is suggested that bile acids may be associated with improved insulin sensitivity, and

glycemic control following gastric bypass surgery.[10] However, it is unknown if glucose homeostasis is altered during cholestasis in VLBW infants, as they achieve full enteral nutrition. Since the plasma glucose concentrations are not routinely monitored in premature infants on full enteral nutrition, unrecognized hypoglycemia may impact neurodevelopmental outcomes in this vulnerable population with cholestasis. The study purpose was to examine whether VLBW infants with a history of cholestasis, currently receiving nutrition exclusively via enteral route are at increased risk for hypoglycemia.

METHODS

Premature infants born between 2008 and 2012 at the level 3 neonatal intensive care unit at York Hospital, Pennsylvania with cholestasis (defined as direct serum bilirubin ≥2mg/dl) were included in this retrospective study.[11] The Institutional review board of the York hospital approved this original quality improvement study. All infants born at or before 36 weeks of gestation, and who developed cholestatic jaundice were included. Those infants who died or were transferred before reaching full enteral feedings, or those who had possible endocrine related issues that may contribute to hypoglycemia were excluded. Case was defined as those VLBW preterm infants with improving cholestasis, and controls comprised of VLBW infants matched for weight, and gestational age, but, without cholestasis while both groups receiving nutrition exclusively via enteral feeds. Birth weight, gestational age, sex, race, incidence of any intraventricular hemorrhage (grade 1-4), retinopathy of prematurity (Stage 0-3), culture positive sepsis (bacteremia, meningitis, urinary tract infection), duration of nil per oral status before the onset of direct component of serum bilirubin and liver function tests were collected from the electronic medical records.

All preterm infants (cases and controls) were provided with either fortified breast milk or preterm formula. Enteral feeds were initiated at 20-30 ml/kg/day via bolus feeds every 2-3 hours, and advanced every day at a similar bolus based on tolerance to feeds. The feeding intolerance was assessed by regurgitation of feeds, ≥ 30% of residual of previous feed volume or bilious aspirate. All of the study infants (cases and controls) received parenteral nutrition prior to being exclusively on enteral nutrition.

A blood glucose concentration of ≤50mg/dl was used as a threshold to define hypoglycemia beyond first few days of life in our neonatal intensive care unit. Our unit protocol dictates monitoring blood glucose levels every four hours initially while on intravenous fluids, and then every 8-12 hours until the glucose levels become stable (50-150 mg/dl) for few weeks. Blood glucose concentration is monitored at the bedside by Flexx Meter®. A point of care (POC) blood glucose levels between 45-50mg/dl is confirmed by sending a blood sample to the hospital laboratory. A POC glucose values ≤45mg/dl correlated with hospital laboratory testing (r^2=0.98). Hence, blood glucose values of <45mg/dl with Flexx Meter® were not sent for any further confirmatory testing. A blood glucose level ≤45 mg/dl was managed by either increasing the feed volume or by decreasing the interval between the feeds. An appropriate concentration of intravenous dextrose infusion was started if the blood glucose levels persisted ≤45 mg/dl an hour post-intervention. In symptomatic infants, 200 mg/kg of dextrose solution is given as a bolus, followed by initiation of dextrose containing fluids to maintain blood glucose levels between 50-150 mg/dl. We considered administration of intravenous dextrose infusion and alteration of feeding regimen to continuous nasogastric feeding as significant interventions.

Cholestasis was defined as direct serum bilirubin ≥2mg/dl.[11] Liver function tests were monitored every week starting two weeks after birth (when they typically manifest PNAC) while infants were on total parenteral nutrition. Those infants who developed cholestasis were monitored with weekly liver function tests until the laboratory values have become normal. Cholestatic jaundice secondary to prolonged total parenteral nutrition was generally treated by the attending neonatologist at his discretion, either with phenobarbital or ursodeoxycholic acid. Once cholestasis was diagnosed, routine abdominal ultrasound and urine cytomegalovirus (CMV) cultures were done to exclude congenital hepatic condition or CMV infection.

Incidence of hypoglycemia in VLBW infants while exclusively on enteral nutrition was the primary outcome of present study. Characteristics of VLBW infants with (cases) and those without cholestasis (control group) were compared. Independent sample t-test or Mann-Whitney U tests, Pearson's Chi-Square or Fishers Exact tests were used to compare the differences between the groups. ROC Receiver operating characteristic (ROC) curve analysis was used to determine a peak bilirubin level predictive for hypoglycemia. SPSS version 20.0 was used for descriptive analysis and MedCalc 12.1 was used to perform ROC curve analysis. A $p \leq 0.05$ was used for statistical significance.

RESULTS

A total of 270 VLBW infants were born during the study period, among whom 26 (9.3%) had cholestasis during their hospital course**.** Four infants were excluded from analysis due to insufficient clinical and or laboratory information or were receiving postnatal steroids. Twenty two infants with cholestasis were analyzed and compared with 67 control infants without cholestasis.

Cholestasis in all the case infants was secondary to prolonged total parenteral nutrition. No case of cholestasis was associated with either CMV infection or any other etiology. Hypoglycemia occurred in 12/22 patients (54.5%) with cholestasis and, in 3/67 (4.5%) of

control infants (P <0.001). Hypoglycemia first manifested at a mean chronological age of 63.3 days in cholestatic infants vs 31 days in the control infants after being on full enteral feeds (P = 0.066). Mean duration of full enteral nutrition was 16.8 days in cholestatic infants versus 14.7 days in the control infants, when the hypoglycemia occurred for the first time after parenteral nutrition was discontinued (p = 0.814).

None of the study infants had symptomatic hypoglycemia. There were no significant differences in gestational age, birth weights, sex, infections, ROP, chronic lung disease, and intraventricular hemorrhage between the cases and controls (Table 1). The duration of parenteral nutrition, duration of nil per oral status, maximum dextrose concentration was higher in cholestatic infants (p <0.001) (Table 2).

Table 1: Clinical characteristics.

	Cholestasis (N=22)	Control (N=67)	Significance
Females	40.90%	52.20%	0.36
Gestational age (weeks)	27 (2.4) SD	28.1 (2.2) SD	0.06
Birth weight (grams)	866.5 (376.2) SD	988.5 (211.7) SD	0.06
Race (white)	59.10%	80.60%	0.02
Chronic lung disease	55.00%	32.80%	0.07
IVH	50.00%	38.80%	0.36
PDA	81.80%	38.80%	<0.001
ROP	72.70%	49.30%	0.06
Infection	36.40%	35.80%	0.96

SD=Standard deviation

Table 2: Parenteral nutrition and hypoglycemia characteristics.

Group		N	Mean	Std. Deviation	Significance
Days on HAL (total)	Cholestasis	22	33.8	21.8	<0.001
	Control	67	15.7	5.9	
Days NPO	Cholestasis	22	8.8	4.2	<0.001
	Control	67	2.1	3.1	
Max. dextrose concentration	Cholestasis	22	15.3	1.8	<0.001
	Control	67	13.4	1.2	
Day of life - Hypoglycemia	Cholestasis	12	63.3	26.2	0.07
	Control	3	31.0	16.1	
Hypoglycemia after days on full feeds	Cholestasis	10	16.8	13.1	0.81
	Control	3	14.7	15.0	

There were no differences in the incidence of hypoglycemic episodes between cases and controls while on exclusive parenteral nutrition. However, cholestatic infants had an average of nine documented episodes (range 1-23) of hypoglycemia when on full enteral feeds. Twenty five percent of these infants (3/12) needed significant intervention to alleviate hypoglycemia.

Range of low blood glucose levels in cholestatic infants ranged from 13-48mg/dl vs 35-47mg/dl in controls. Only one infant in the control group needed intervention. In contrast, only one control infant had two episodes of hypoglycemia, and the remaining two infants had only one.

The duration of hypoglycemia was 1-7 days in cholestatic infants vs 1-2 days in control infants. Interventions included transient reintroduction of parenteral glucose and or alteration of feeding regimens from bolus to continuous feeds. There was no significant difference in the prevalence of small for gestational age infants between the groups. Post conceptional age at the onset of hypoglycemia in cholestatic infants ranged from 31-43 weeks in cholestatic infants vs 31-32 weeks in control infants. Cholestasis and hypoglycemia resolved in all infants. The extended metabolic newborn screen results, which screens for more than 50 metabolic disorders were normal in both cases, and control infants.

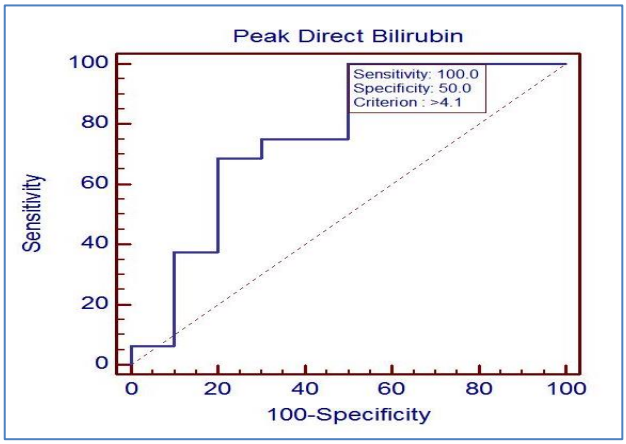

Figure 1: Receiver operating characteristic curve (ROC).

Receiver operating characteristic curve analysis showed a peak direct bilirubin of >4.1mg/dl (before full enteral feeds) could predict hypoglycemia while on full enteral feeds, with a sensitivity of 100%, specificity of 50%, and negative predictive value of 100% (Figure 1). Area under the curve for receiver operating characteristic predicted hypoglycemia was 75% (95% CI 0.53-.97, P value= 0.029).

DISCUSSION

The study was prompted as we serendipitously noted lower blood glucose levels in exclusively enterally fed VLBW infants who had cholestasis. This is the first report to document perturbations in blood glucose levels in premature infants who had parenteral nutrition associated cholestasis. We have demonstrated that hypoglycemia occurs with much lower frequency (4.5%) in VLBW infants without cholestatic jaundice, who are receiving full enteral nutrition. It is important to underscore that the observed changes in blood glucose levels were noted while infants were on full enteral feeds, and the hypoglycemic events were not accompanied by clinical symptoms. Resolution of asymptomatic hypoglycemia in all our patients was accomplished by transient introduction of parenteral glucose and or changes in the feeding regimen. The extended metabolic newborn screen results, which screens for more than 50 metabolic disorders were normal in both cases, and control infants. Thus other metabolic causes for hypoglycemia were very unlikely. Though severity of sickness is not evaluated, an awareness of this biochemical abnormality in patients with recent or remote history of cholestasis is of critical importance to ensure implementation of ongoing monitoring of blood glucose and restoration of euglycemia in the subset of premature infants with cholestasis.

The etiopathogenesis of hypoglycemia in premature infants with history of cholestasis while receiving complete enteral nutrition is not clear. There is no published literature describing the association of hypoglycemia with a history of cholestasis or hepatic dysfunction in preterm infants. It is also important to note that both cases and controls received parenteral nutrition before transitioning to full enteral nutrition. The incidence of hypoglycemia prior to full enteral feeds and while on exclusive parenteral nutrition was also not different between the groups. Recent in-vitro evidence implicates FXR (Farnesoid X Receptor, a nuclear receptor super family) gene in parenteral nutrition associated cholestasis. FXR induces Fibroblast growth factor 19 (FGF 19), which in turn suppresses CYP7A1 (cholesterol 7α-hydroxylase) thus suppressing synthesis or excretion of bile acids.[12] When TPN (total parenteral nutrition) is administered, FGF19 (fibroblast growth factor 19) secretion in the intestines is decreased. Diminished FGF19 concentrations with TPN could increase CYP7A1 expression in the liver, resulting in persistent activation of bile acid synthesis and cholestasis.[13] Bile acids in turn modulate gluconeogenesis by regulating the expression of the key rate-controlling phosphoenol pyruvate carboxykinase (PEPCK), fructose 1,6 bisphosphatase (FBP1) and glucose-6-phosphatase (G6Pase).[14] Repression of the preceding gluconeogenic enzymes has been shown, both in-vitro and in-vivo, to be mediated by short heterodimer partner (SHP) and hepatic nuclear factor 4α (HNF4α).[15,16]Additionally, bile acids have been shown to rapidly activate G-protein coupled receptor(s), which activate the AKT insulin-signaling pathway. Japanese investigators demonstrated that bile acids, by stimulating the bile acid membrane receptor TGR5 (Takeda G-protein coupled receptor clone 5) release Glucagon like Peptide 1 (GLP1) from enterocytes lead to insulin secretion and glycogen synthesis.[12,13] A higher concentration of bile acids in patients with prior gastric bypass suggests their regulatory role in glucose and lipid metabolism.[17] The first evidence of the role of bile acids in the glucose metabolism came from a study that showed that concomitant use of cholestyramine reduced plasma glucose by 13% with a trend to lower glycosylated Hb.[18] There was no difference in use of cholestyramine in cholestatic infants with and without hypoglycemia.

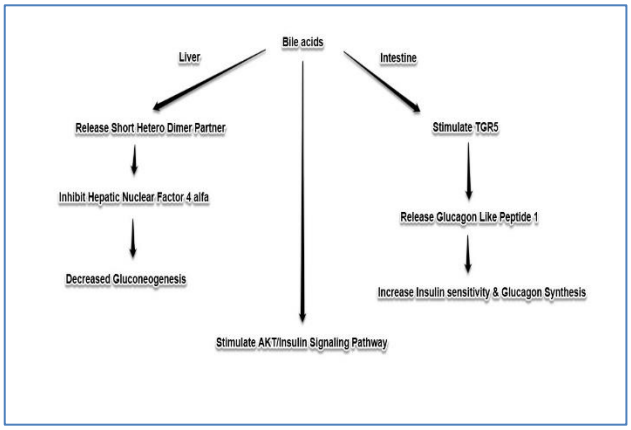

Figure 2: Proposed mechanism for cholestasis causing hypoglycemia.

Based on both in-vitro and in-vivo evidence, it seems biologically plausible that bile acids stimulate the insulin signaling pathway, promote glycogen synthesis and suppress gluconeogenesis in the liver.[19] At the same time, once full enteral feedings are established, bile acids may stimulate TGR5 in the enterocytes releasing GLP-1, which in turn improves insulin sensitivity, and thus increase the risk for hypoglycemia (Figure 2). It will be interesting to study if this phenomenon is responsible for the hypoglycemia observed in our VLBW infants with cholestasis. As present study is retrospective, we are unable to establish a causal relationship between cholestasis and hypoglycemia.

Further studies are needed to correlate bile acid levels in cholestatic infants with hypoglycemia, and to further characterize the timing of onset and resolution of

hypoglycemia in this population. Present study emphasizes the importance of implementing blood glucose screening protocols in the subset of patients with cholestasis to identify and treat occult hypoglycemia. Recurrent occult hypoglycemia in VLBW infants with a history of cholestasis, if present, may have significant implications for neurodevelopmental outcomes.

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