What Happens to Blood Glucose Concentrations After Oral Treatment for Neonatal Hypoglycemia?

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Objective To determine the change in blood glucose concentration after oral treatment of infants with hypoglycemia in the first 48 hours after birth.

Study design We analyzed data from 227 infants with hypoglycemia (blood glucose <46.8 mg/dL, 2.6 mmol/L) born at a tertiary hospital who experienced 295 episodes of hypoglycemia. Blood glucose concentrations were measured (glucose oxidase) within 90 minutes after randomization to dextrose or placebo gel plus feeding with formula, expressed breast milk, or breast feeding.

Results The overall mean increase in blood glucose concentration was 11.7 mg/dL (95% CI 10.4-12.8). The increase was greater after buccal dextrose gel than after placebo gel (+3.0 mg/dL; 95% CI 0.7-5.3; $P = .01$) and greater after infant formula than after other feedings (+3.8 mg/dL; 95% CI 0.8-6.7; $P = .01$). The increase in blood glucose concentration was not affected by breast feeding (+2.0 mg/dL; 95% CI −0.3 to 44.2; $P = .09$) or expressed breast milk (−1.4 mg/dL; 95% CI −3.7 to 0.9; $P = .25$). However, breast feeding was associated with reduced requirement for repeat gel treatment (OR = 0.52; 95% CI 0.28-0.94; $P = .03$).

Conclusions Treatment of infants with hypoglycemia with dextrose gel or formula is associated with increased blood glucose concentration and breast feeding with reduced need for further treatment. Dextrose gel and breast feeding should be considered for first-line oral treatment of infants with hypoglycemia. *(J Pediatr 2017;■■:■■-■■).*

See editorial, p •••

Neonatal hypoglycemia is common and can be associated with brain injury and developmental delay.[1-3] Treatments for neonatal hypoglycemia are intended to increase the blood glucose concentration and thus provide fuel for the newborn infant's brain. Initial treatment often includes feeding with or without buccal dextrose gel.[4,5] If oral treatment is unsuccessful, then intravenous dextrose is usually required. However, there is little evidence about the magnitude of the change in blood glucose concentration after different treatments for neonatal hypoglycemia.

Feeding remains the most common treatment for neonatal hypoglycemia,[5] and breast feeding is recognized as the best way to feed an infant.[6] However, hypoglycemia most commonly occurs in the first 48 hours after birth, when the supply of breast milk supply is limited.[7] Although mothers likely to give birth to an infant at risk of developing hypoglycemia may be encouraged to express breast milk before the birth, this practice is controversial,[8] and there is no evidence that giving expressed breast milk improves blood glucose concentration in infants with hypoglycemia.[9]

Dextrose gel has been shown to be useful for treating neonatal hypoglycemia without harming the establishment of breast feeding,[10,11] but there is little evidence about the magnitude of the resulting change in blood glucose concentration. Similarly, infant formula is a common treatment for neonatal hypoglycemia, but the magnitude of change in blood glucose concentration after formula feeding has not been reported.

In clinical practice, it would be useful to know the likely blood glucose response to different oral treatments in different at-risk infants, because this information may help clinicians to select the best treatment for an individual. We previously reported a trial in which infants who developed hypoglycemia in the first 48 hours after birth were randomized to receive 40% dextrose gel or a placebo gel followed by a feed.[10] In this study, data from that trial were used to determine the change in blood glucose concentration after different oral treatments for hypoglycemia, and whether these differed in infants with different sex, ethnicity, and risk factors for hypoglycemia.

Methods

The Sugar Babies Study was performed at a tertiary referral center (Waikato Women's Hospital) in Hamilton, New Zealand, between December 1, 2008, and November 26, 2010.[10] Eligible infants were ≤48 hours old and at risk for neonatal hypoglycemia including infants of mothers with diabetes, late preterm infants (35 or 36

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weeks of gestation), infants who were small (<10th percentile or <2500 g) or large (>90th percentile or >4500 g), or infants with other problems predisposing to hypoglycemia (poor feeding or hypothermia). All blood glucose concentrations were measured on a blood gas analyzer (Radiometer, ABL800Flex, Copenhagen, Denmark) using the glucose oxidase method (reading range 0.0-60 mmol/L, coefficient of variation 2.1%).

Infants who became hypoglycemic (blood glucose concentration of <46.8 mg/dL [2.6 mmol/L]) were randomized to receive either 40% dextrose gel or placebo gel 0.5 mL/kg massaged into the buccal mucosa, and were encouraged to feed. If the blood glucose concentration after treatment remained <46.8 mg/dL, the treatment could be repeated once using the same gel type. The type of feed was determined by maternal choice and could include expressed breast milk, breast feeding, infant formula, or a combination. Expressed breast milk and infant formula were given by syringe, cup, bottle, or gastric tube.

An episode of hypoglycemia was defined as ≥1 sequential blood glucose concentrations of <46.8 mg/dL. Episodes were included in this analysis if blood glucose concentration was measured again between 15 and 90 minutes after the treatment was given. Episodes of hypoglycemia requiring 2 treatments were included in that analysis if the blood glucose concentration was measured between 15 and 90 minutes after each treatment.

The Sugar Babies study was approved by the Northern Y ethics committee, and registered with Australian New Zealand Clinical Trials Registry, number ACTRN 12608000623392 (www.anzctr.org.au). Parents gave written informed consent.

Statistical Analysis

Data were analyzed using Stata version 14 (StataCorp 2015, College Station, Texas) and are presented as number (percent), mean (SD), median (minimum-maximum), or ORs (95% CIs). Volumes of breast milk expressed by mothers before and after birth were compared using robust CIs for Hedges Lehmann median difference.[12] Mixed model linear regression in both univariate and multivariable forms were used to investigate the change in blood glucose after different treatments, with a covariance structure that addressed the repeated measures at varying frequencies and times, and minimized the Aikaike information criterion. The multivariable model included all feeding and gel options being the subjects of specific interest, plus the blood glucose concentration at the beginning of the episode to account for any regression to the mean. Finally, any other variables with a change in blood glucose generating $P < .10$ on univariate analysis were included. Logistic regression models, adjusted for repeated measures, were used to compare episodes treated with 1 vs 2 doses of gel. All tests were 2 tailed. $P < .05$ was considered significant. No adjustment for multiplicity was performed.

Results

Of the 514 infants enrolled in the Sugar Babies Study,[10] 227 infants (44%) had 295 episodes of hypoglycemia that were included in this analysis (**Table I**).

Table I. Baseline characteristics of mother, babies, and hypoglycemic episodes

Mothers (n = 218)	
Age (years)	29.6 [6.2]
Parity	1 (0-10)
Body mass index at booking (kg/m^2)	28.6 [7.0]
Planned to exclusively breast feed	211 (97)
Expressed milk before birth	44 (20)
Babies (n = 227)	
Birthweight (g)	2890 [1590-5550]
Gestation (weeks)	37.6 (35.0-42.3)
Male	108 (48)
Vaginal birth	139 (61)
Singleton	190 (84)
Apgar score < 7 at 5 minutes	6 (3)
Ethnicity	
New Zealand European	115 (51)
Maori	64 (28)
Other	46 (21)
Risk factors for hypoglycemia*	
Infant of a mother with diabetes	88 (39)
Preterm	88 (39)
Small	67 (30)
Large	49 (22)
Other	10 (4)
Hypoglycemic episodes (n = 295)	
Number of babies who experienced	
1 episode	173 (76)
2 episodes	41 (18)
≥3 episodes	13 (6)

Data are mean [SD], median (minimum-maximum), or n (%).
*Some babies had >1 risk factor for hypoglycemia.

Most hypoglycemic episodes occurred within the first 12 hours after birth (209/295, 71%). The median postnatal age at the time of the hypoglycemic episode was 4.5 hours (range 0.4-47.2 hours). The mean time from treatment to repeat blood glucose measurement was 45 minutes (SD 15; range 17-88) and was similar for all feed types and risk factors (data not shown). One-quarter of the infants had >1 hypoglycemic episode (**Table I**). The median blood glucose concentration at the beginning of the hypoglycemic episode was 41.4 mg/dL (range 16.2-45.0).

The overall mean (SD) change in blood glucose concentration after treatment of an episode of hypoglycemia was 11.7 (10.3) mg/dL.

Treatment

Formula was given to treat 55 of 295 episodes of hypoglycemia (19%) in 49 of 227 infants (22%). The median volume of formula milk was 4.5 mL/kg (range 0.6-15.0). Expressed breast milk was given to treat 117 of 295 episodes of hypoglycemia (40%) in 105 of 227 infants (46%). The median volume of expressed breast milk was 0.5 mL/kg (range 0.0-7.3).

Of the 295 hypoglycemic episodes, 186 (63%) were treated with only breast milk. Of these 186 episodes, 78 (42%) were treated with breast feeding, 45 (24%) were treated with expressed breast milk, and 63 (34%) were treated with a combination of breast feeding and expressed breast milk.

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