Prophylactic Dextrose Gel Does Not Prevent Neonatal Hypoglycemia: A Quasi-Experimental Pilot Study

Sarah M. Coors, DO[1], Joshua J. Cousin, MD[1], Joseph L. Hagan, ScD[1], and Jeffrey R. Kaiser, MD, MA[1,2]

Objective To test the hypothesis that prophylactic dextrose gel administered to newborn infants at risk for hypoglycemia will increase the initial blood glucose concentration after the first feeding and decrease neonatal intensive care unit (NICU) admissions for treatment of asymptomatic neonatal hypoglycemia compared with feedings alone.

Study design This quasi-experimental study allocated asymptomatic at-risk newborn infants (late preterm, birth weight <2500 or >4000 g, and infants of mothers with diabetes) to receive prophylactic dextrose gel (Insta-Glucose; Valeant Pharmaceuticals North America LLC, Bridgewater, New Jersey); other at-risk infants formed the control group. After the initial feeding, the prophylactic group received dextrose gel (0.5 mL/kg) rubbed into the buccal mucosa. The blood glucose concentration was checked 30 minutes later. Initial glucose concentrations and rate of NICU admissions were compared between the prophylactic group and controls using bivariate analyses. A multivariable linear regression compared first glucose concentrations between groups, adjusting for at-risk categories and age at first glucose concentration.

Results There were 236 subjects (72 prophylactic, 164 controls). The first glucose concentration was not different between the prophylactic and control groups in bivariate analysis (52.1 ± 17.1 vs 50.5 ± 15.3 mg/dL, $P = .69$) and after adjusting for covariates ($P = .18$). Rates of NICU admission for treatment of transient neonatal hypoglycemia were 9.7% and 14.6%, respectively ($P = .40$).

Conclusions Prophylactic dextrose gel did not reduce transient neonatal hypoglycemia or NICU admissions for hypoglycemia. The carbohydrate concentration of Insta-Glucose (77%) may have caused a hyperinsulinemic response, or alternatively, exogenous enteral dextrose influences glucose homeostasis minimally during the first few hours when counter-regulatory mechanisms are especially active. *(J Pediatr 2018;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT02523222.

See related article, p •••

Transient neonatal hypoglycemia affects up to 15% of healthy newborn infants[1-4] and >50% of neonates in certain at-risk populations.[5] Those at risk include late preterm infants, small for gestational age (SGA) or large for gestational age (LGA) infants, and infants of mothers with diabetes (IMD). The definition and long-term neurodevelopmental significance of transient neonatal hypoglycemia is controversial; many recent studies have focused on its potentially adverse effects and reported conflicting results.[6-9] Recently, the Pediatric Endocrine Society[10] recommended more conservative glucose treatment targets compared with those of the American Academy of Pediatrics.[11]

Transient neonatal hypoglycemia is thought to be a hypoketotic hypoglycemia because of immature counter-regulatory pathways resembling hyperinsulinemia during the first 48-72 hours. It is associated with a lowered glucose threshold for suppression of insulin secretion and inappropriate preservation of liver glucose stores.[12] It is unclear if transient hypoglycemia is a normal neonatal physiologic response mediated by counter-regulatory mechanisms or if it may be associated with long-term harm if severe or prolonged. This is important because the newborn brain predominantly uses glucose for energy when other energy substrates are

BW	Birth weight
HHBTH	Harris Health Ben Taub Hospital
IMD	Infant of a mother with diabetes
IV	Intravenous
LGA	Large for gestational age
NICU	Neonatal intensive care unit
NICU2	Intermediate NICU
SGA	Small for gestational age

From the [1]Department of Pediatrics, Section of Neonatology; and [2]Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX

Supported by a Thrasher Research Fund Early Career Award, Salt Lake City, UT (12990); the Texas Pediatric Society Foundation, Austin, TX; and the Baylor College of Medicine Evangelina "Evie" Whitlock Fellowship Award in Neonatology, Houston, TX (to S.C.). Those providing support were not involved in the study design, methods, data collection, analysis, results, manuscript preparation, or the decision to submit the paper for publication. J.H. received salary support from the Texas Pediatric Society Foundation. The authors declare no conflicts of interest.

Portions of this study were presented as an abstract at the Southern Society for Pediatric Research annual meeting, New Orleans, LA, February 12, 2017, and the Pediatric Academic Societies annual meeting, San Francisco, CA, May 6-9, 2017.

https://doi.org10.1016/j.jpeds.2018.02.025

suppressed, and newborn infants are particularly vulnerable to glucose deprivation. The tolerance of the newborn brain to lower glucose concentrations is unclear.[10,12]

Dextrose gel (40%) applied to the buccal mucosa as treatment for transient neonatal hypoglycemia has been shown in both randomized and nonrandomized studies to safely reduce neonatal intensive care unit (NICU) admissions for hypoglycemia by one-half.[13-17] Given its ease, safety, and success for treating established transient neonatal hypoglycemia, the aim of this study was to assess if prophylactic dextrose gel provided to at-risk newborns after the first milk feeding would decrease the incidence of hypoglycemia and reduce NICU admissions for intravenous (IV) dextrose treatment.

Methods

This study used a quasi-experimental approach. When researchers were available, informed consent was obtained antenatally from English- or Spanish-speaking parents of infants presumed to be late preterm, have estimated fetal weight of <2500 or >4000 g, and IMDs; these infants received prophylactic dextrose gel. The control group consisted of at-risk infants born during the same period when researchers were unavailable. The study was approved by the Baylor College of Medicine Institutional Review Board and the Research and Sponsored Programs at Harris Health Ben Taub Hospital (HHBTH), an affiliate hospital of Baylor College of Medicine. The trial was registered in ClinicalTrials.gov (NCT02523222).

At-risk infants, including late preterm infants ($35^{0/7}$–$36^{6/7}$ weeks of gestation), infants with birth weights (BWs) <2500 or >4000 g, and IMDs born at HHBTH were eligible, per the hospital's hypoglycemia protocol. Infants who were SGA or LGA but did not meet BW criteria were not eligible. HHBTH is a Baby Friendly Hospital.[18] Infants were excluded after birth if they were symptomatic, did not meet gestational age or BW criteria, and had no other risk factors such as prematurity or maternal diabetes. Infants were also excluded if they had chromosomal abnormalities, congenital anomalies, hyperinsulinemic disorders, received hypoglycemia treatment after 72 hours, were transferred to the NICU before the first feeding, received early IV fluids without feedings, or feeding times were not documented. Infants who met criteria, yet were transferred to the intermediate NICU (NICU2) for antibiotics or prematurity were not excluded. At HHBTH, all infants ≤$35^{6/7}$ weeks gestational age and/or BW <2250 g are admitted to NICU2 for continuous monitoring.

HHBTH Hypoglycemia Protocol

The 2013 Protocol was adapted from the American Academy of Pediatrics' guidelines[11] and standardized using BW cut-offs rather than cut-offs based on weight for gestational age if the infant was not preterm or an IMD.

The protocol dictated that feeding was initiated as soon after birth as possible, and a blood glucose concentration was obtained 30 minutes after completion of the feeding. During the first 4 hours, the goal glucose concentration was >40 mg/dL; thereafter it was >45 mg/dL. Asymptomatic at-risk newborns also had glucose screening at 2 hours and 6 hours; late preterm infants had 2 additional screens at 12 and 18 hours.

If the initial glucose concentration was <25 mg/dL, the nurse obtained a serum glucose concentration, ensured that the infant was fed by breast or bottle, and repeated the glucose concentration 30 minutes later. If the glucose concentration remained <25 mg/dL, the infant was transferred to NICU2 for IV dextrose.

If the initial screen was between 25 and 40 mg/dL, the mother fed the infant again, and a glucose concentration was rechecked 30 minutes later. If the glucose concentration was <25 mg/dL on the second screen, the infant was transferred to NICU2 for IV dextrose. After 4 hours, if the glucose concentration was <35 mg/dL, the infant was transferred to NICU2 for IV dextrose. A bedside glucometer (Abbott Precision XceedPro, Alameda, California) was used for the initial glucose screens. Glucose specimens were obtained by heel stick, performed by bedside nurses in Labor and Delivery, the postpartum floor, and in NICU2.

Dextrose Gel Experimental Procedure

For infants with parental consent for prophylactic dextrose gel, after weighing, the nurse obtained an order for dextrose gel. The ordering provider verified the consent and that the infant met the criteria for dextrose gel. Insta-Glucose (Valeant Pharmaceuticals North America LLC, Bridgewater, New Jersey) 0.5 mL/kg was rubbed into the buccal mucosa after finishing the first feeding. Insta-Glucose is an oral dextrose gel used for rapid treatment of adult hypoglycemia and is on the hospital formulary.

Data abstracted from the newborn record and laboratory database included name, birth date and time, BW and percentile,[19,20] estimated gestational age, size for gestational age, sex, Apgar scores, singleton or multiple status, delivery mode, feeding data (type [breast/formula], volume [formula], duration [breastfeeding], dates, and times), glucose concentrations (dates and times), date and time of gel administration, feeding type on discharge, and whether or not the infant was transferred to the NICU for IV dextrose. Data abstracted from the mother's record included name, age, pregnancy-associated and obstetrical conditions, diabetes type, and type of treatment (diet, oral antidiabetics, or insulin). Data were stored using Research Electronic Data Capture (Baylor College of Medicine, Houston, Texas).[21]

The primary outcome was glucose concentration 30 minutes after the first milk feeding (controls) or dextrose gel administration (prophylactic subjects). The secondary outcome was the rate of NICU admission for IV dextrose.

Statistical Analyses

For bivariate analyses between groups, the Fisher exact test and Wilcoxon rank sum test were used for categorical and quantitative variables, respectively. Multiple linear regression was used to compare the groups' first glucose concentrations after controlling for risk factors and age at first glucose specimen. To determine if the relationship between dextrose gel prophylaxis and the first glucose concentration differed across risk

FLA 5.5.0 DTD ■ YMPD9809_proof ■ March 28, 2018