

A Sweet Addition for the Treatment of Neonatal Hypoglycemia

[Laura D. Brown](#), [Paul J. Rozance](#),

Perinatal Research Center, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado

In this issue of The Journal, Harris et al¹ report the neurodevelopmental outcomes at 2 years corrected age in children randomized to treatment with dextrose gel or placebo for asymptomatic neonatal hypoglycemia (the Sugar Babies Study). All infants enrolled in this single-center trial were between 35 and 42 weeks gestational age and at risk for neonatal hypoglycemia due to late prematurity, maternal diabetes, or small or large birthweight for gestational age. Some were also included for poor feeding, which could be considered a symptom of hypoglycemia.² Screening for hypoglycemia (blood glucose concentration <2.6 mM or 47 mg/dL) was rigorous with glucose concentrations measured 1 hour after birth, every 3-4 hours before feeds for the first 24 hours, and every 6-8 hours for the next 24 hours. Using this protocol, 46% of the enrolled patients were identified as hypoglycemic and randomized to receive dextrose gel or placebo in conjunction with encouragement to breast feed. If feeding was poor, the infant was given expressed breast milk or formula by syringe. Neurodevelopmental outcomes at 2 years of age are available for 78% of the original hypoglycemic cohort. Rates of neurosensory impairment, processing difficulties, and multiple secondary growth and developmental outcomes were equivalent between the dextrose gel and placebo groups.

Even though this is a “negative” study, the results are important for practitioners. Short-term outcomes for these at-risk patients showed significant benefit to dextrose gel as a treatment for asymptomatic neonatal hypoglycemia. As originally reported,³ infants randomized to dextrose gel had significantly less treatment failure, defined as a glucose <47 mg/dL after 2 treatment attempts with dextrose gel or placebo. Treatment with dextrose gel also lowered rates of neonatal intensive care unit (NICU) admission for hypoglycemia, with a number needed to treat of 8. In addition, fewer infants were formula feeding in the dextrose gel group than in the placebo group at 2 weeks of age, perhaps because of the decreased rates of admission to the NICU for hypoglycemia. Treatment with dextrose gel was well tolerated and no harm was identified in the initial report.³

There was a theoretical concern that the dextrose gel treatment might have delayed definitive treatment with intravenous dextrose and adversely impacted long-term neurodevelopmental outcomes. However, rebound hypoglycemia (within 6 hours) and recurrent hypoglycemia (within 48 hours of birth) were similar between groups.³ The combined use of dextrose gel and feeds could also worsen outcomes by producing rapid correction of neonatal hypoglycemia, increased variability in glucose concentrations, or hyperglycemia.⁴ Continuous glucose monitoring sensor data from a subset of patients in the study allayed some of these concerns. The median time to restore glucose concentrations was equivalent between treatment groups, and increased rates of hyperglycemia were not reported.³ Despite the reassuring continuous glucose monitoring sensor data, safety remained a concern until appropriate follow-up was

completed. With the 2-year follow-up data, practitioners can be more confident that the early benefits seen with dextrose gel do not come at a cost of worse neurodevelopmental outcomes at 2 years of age.

The authors are to be commended for undertaking such a rigorous study with short-term, 2-year, and planned 4.5-year neurodevelopmental follow-up. Still, limitations in the study might affect the immediate generalizability of the results. First, this was a single center trial conducted in a tertiary referral center with an easily accessible Level 3 NICU. Ethnic diversity was limited, as the patient population was mostly either New Zealand European or Maori. A larger, multi-center trial would help broaden the applicability of the results, and could also include hospitals without the capability of providing intravenous dextrose to determine whether dextrose gel decreases need to transfer patients to hospitals with a higher level of care. Second, compared with the 2011 guidelines proposed by the American Academy of Pediatrics, the Sugar Babies protocol screened for hypoglycemia more frequently, for a longer duration, and used a higher glucose treatment threshold.⁵ This protocol more closely resembles the recent guidelines published by the Pediatric Endocrine Society.^{5, 6} Third, dextrose gel treatment was targeted to infants at-risk for hypoglycemia who were otherwise well-appearing and asymptomatic. Therefore, the results do not apply to infants with symptomatic, severe, prolonged, or recurrent hypoglycemia that is difficult to manage (ie, the infant with severe hyperinsulinism). Finally, 12% of infants treated with dextrose gel had at least 1 rebound episode of hypoglycemia, and 24% had at least 1 recurrent episode of hypoglycemia. Thus, although the gel decreased the need for dextrose from other sources, it did not completely eliminate the need for intravenous dextrose. However, dextrose gel appears to be safe and effective at decreasing rates of NICU admissions for hypoglycemia. Therefore, depending on the capacity of their local hospitals and health care system, some clinicians may choose to adopt this therapy as part of an overall strategy for the treatment of asymptomatic neonatal hypoglycemia.

The debate over the significance of asymptomatic hypoglycemia and the best strategy for screening and treating neonatal hypoglycemia continues, and the results of the Sugar Babies Study will probably not change opinions regarding the glucose threshold at which treatment should be initiated to avoid neurologic injury. Of particular concern is the high rate of neurosensory impairment at 2 years of age reported for all participants, which approached 35%. However, most of the neurosensory impairment was mild, and in an overlapping cohort of patients, hypoglycemia treated to glucose concentrations of ≥ 47 mg/dL was not associated with increased risk for neurodevelopmental impairment compared with at-risk patients without hypoglycemia.⁴ The blood glucose concentration defining hypoglycemia in both studies was arbitrary and did not take into account evolution of blood glucose concentrations in the first week of life. A blood glucose concentration of < 47 mg/dL is likely to be more clinically relevant after the first 3 days of age, when blood glucose concentrations should approach those of a normal adult (> 70 mg/dL).⁶

The Sugar Babies study was not designed to determine the optimal screening and treatment strategy. However, some may look at the high rates of adverse outcomes in treated and untreated at-risk infants and call for even more aggressive screening and treatment strategies. There are not yet convincing data to show that raising glucose concentrations in asymptomatic and otherwise healthy infants with low glucose concentrations improves outcomes. There are risks to more aggressive screening and treatment, which include increased frequency of blood sampling, separation of the infant from the mother, admission to the

NICU, complications of peripheral and central intravenous catheters, and side effects of medications used to achieve higher glucose concentrations. These concerns must be balanced against the uncertain risk of harm due to asymptomatic hypoglycemia, progression to symptomatic hypoglycemia, and delayed diagnosis and treatment of serious metabolic disorders such as congenital hyperinsulinism. A randomized trial was proposed in 2006 by Boluyt et al,⁷ and executing this type of study remains a goal to resolve the struggle with how to approach asymptomatic neonatal hypoglycemia.

In summary, dextrose gel is safe, and has the potential to decrease health care costs and other risks related to the treatment of hypoglycemia, including decreased breastfeeding. Although this study does not inform optimal screening frequency and treatment thresholds, it does introduce another modality for the management of asymptomatic neonatal hypoglycemia.

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