Outcome at 2 Years after Dextrose Gel Treatment for Neonatal Hypoglycemia: Follow-Up of a Randomized Trial

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Objective To determine neurodevelopmental outcome at 2 years' corrected age in children randomized to treatment with dextrose gel or placebo for hypoglycemia soon after birth (The Sugar Babies Study).

Study design This was a follow-up study of 184 children with hypoglycemia (<2.6 mM [47 mg/dL]) in the first 48 hours and randomized to either dextrose (90/118, 76%) or placebo gel (94/119, 79%). Assessments were performed at Kahikatea House, Hamilton, New Zealand, and included neurologic function and general health (pediatrician assessed), cognitive, language, behavior, and motor skills (Bayley Scales of Infant and Toddler Development, Third Edition), executive function (clinical assessment and Behaviour Rating Inventory of Executive Function-Preschool Edition), and vision (clinical examination and global motion perception). Coprimary outcomes were neurosensory impairment (cognitive, language or motor score below −1 SD or cerebral palsy or blind or deaf) and processing difficulty (executive function or global motion perception worse than 1.5 SD from the mean). Statistical tests were two sided with 5% significance level.

Results Mean (±SD) birth weight was 3093 ± 803 g and mean gestation was 37.7 ± 1.6 weeks. Sixty-six children (36%) had neurosensory impairment (1 severe, 6 moderate, 59 mild) with similar rates in both groups (dextrose 38% vs placebo 34%, relative risk 1.11, 95% CI 0.75-1.63). Processing difficulty also was similar between groups (dextrose 10% vs placebo 18%, relative risk 0.52, 95% CI 0.23-1.15).

Conclusions Dextrose gel is safe for the treatment of neonatal hypoglycemia, but neurosensory impairment is common among these children. *(J Pediatr 2016;170:54-9)*.

Trial registration Australian New Zealand Clinical Trials Registry: ACTRN 12608000623392.

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Neonatal hypoglycemia is a common finding that can be associated with brain injury,[1] neurodevelopmental delay,[2,3] visual impairment,[4] and behavioral problems.[5] Between 5% and 15% of otherwise-healthy infants have hypoglycemia,[6] and the prevalence is increasing as a result of the increasing incidence of preterm birth[7] and maternal diabetes.[8] Screening is recommended for babies with known risk factors, of whom one-half are likely to have hypoglycemia.[9]

Treatment of infants with hypoglycemia varies considerably.[10] We previously reported a randomized trial of dextrose gel massaged into the buccal mucosa for treatment of neonatal hypoglycemia (The Sugar Babies Study).[11] Babies who received dextrose gel were less likely than those who received placebo to remain hypoglycemic, less likely to be admitted to the neonatal intensive care unit for hypoglycemia, and less likely to be formula fed at 2 weeks of age. Importantly, dextrose gel is safe, inexpensive, simple to administer, and can be used in almost any setting.

Dextrose gel is now being used in some settings as first-line treatment for neonatal hypoglycemia[12,13]; however, because the primary objective of treatment of neonatal hypoglycemia is to prevent brain injury, it is important to determine whether treatment with dextrose gel is associated with any beneficial or adverse effects on later development. Therefore, children who had participated in the Sugar Babies Study were invited to participate in this follow-up study. Our primary aim was to determine whether treatment of infants with hypoglycemia with dextrose compared with placebo gel altered the rate of neurosensory impairment or processing difficulties at 2 years' corrected age.

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
BRIEF-P	Behaviour Rating Inventory of Executive Function-Preschool Edition
RR	Relative risk

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Methods

The Sugar Babies Study was a randomized, double-blind, placebo-controlled trial performed at a tertiary referral center (Waikato Women's Hospital) in Hamilton, New Zealand (Australian New Zealand Clinical Trials Registry: ACTRN 12608000623392) between December 1, 2008, and November 26, 2010, and has been reported previously.[11] In brief, eligible babies were ≥35 weeks' gestation, <48 hours old, and at risk for neonatal hypoglycemia (infant of mothers with diabetes, late preterm [35 or 36 weeks' gestation], small [<10th percentile or <2500 g], large [>90th percentile or >4500 g], or other). Babies who developed hypoglycemia (blood glucose concentration <2.6 mM/L [47 mg/dL]) were randomized to receive either 40% dextrose gel or an identical appearing placebo gel 0.5 mL/kg massaged into the buccal mucosa and were encouraged to feed. The primary outcome was treatment failure, defined as a blood glucose concentration <2.6 mM after 2 treatment attempts. A total of 242 babies were randomized, of whom 237 met the eligibility criteria (5 were randomized in error); 118 were randomized to dextrose and 119 to placebo gel.

All parents or caregivers of babies enrolled in the Sugar Babies Study were invited to participate in this follow-up study and provided written informed consent. Children were assessed at 24 months' corrected age at Kahikatea Research House, Hamilton, New Zealand, in suitable local clinics or in the child's own home. Families and all assessors were unaware of the neonatal treatment group allocation. The Sugar Babies study (NTY/08/03/025) and this follow-up study (NTY/10/03/021) were approved by the Northern Y Ethics Committee.

Development was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III).[14] Executive function tests comprised 4 graded tasks, each scored out of 6, to assess inhibitory control (Snack Delay, Shape Stroop), capacity for reverse categorization (Ducks and Buckets),[15] and attentional flexibility (Multisearch Multilocation Task).[16] Scores were summed to give an Executive Function Score of up to 24 points. In addition parents were asked to complete the Behaviour Rating Inventory of Executive Function (BRIEF-P) questionnaire.[17]

Visual assessment included measures of visual acuity (Cardiff Acuity Cards), stereopsis (Frisby stereotest and Lang stereotest), ocular health, alignment and motility, and noncycloplegic refractive error (SureSight Autorefractor [Welch Allyn Inc, Skaneateles Falls, New York] and retinoscopy). Dorsal visual pathway function was measured from optokinetic reflex responses to random dot kinematograms of varying coherence, as previously reported.[18] A motion coherence threshold corresponding to 63% correct was determined from a Weibull fit to the proportion of correct responses at different coherence levels.

Children also underwent neurologic examination and standard growth measurements.[19] All children had newborn hearing screening at birth; an audiologist assessed any who failed neonatal screening. Details of family environment, socioeconomic status, and medical history were obtained by parental questionnaire.

The prespecified coprimary outcomes were neurosensory impairment (any impairment) and processing difficulty. Secondary outcomes were developmental delay, cerebral palsy, executive function composite score, BRIEF-P score, motion coherence threshold, vision problem, refractive error, deafness, growth, and history of seizures.

Neurosensory impairment was defined as mild (mild cerebral palsy or Bayley-III motor composite score 1-2 SD below the mean or mild developmental delay), moderate (moderate cerebral palsy or a Bayley-III motor composite score 2-3 SD below the mean or moderate developmental delay or deaf), or severe (severe cerebral palsy [the child is not ambulant at 2 years and likely to remain so] or Bayley-III motor composite score more than 3 SD below the mean or severe developmental delay or blind).[20]

Developmental delay was defined as mild (Bayley-III cognitive or language composite scores 1-2 SD below the mean), moderate (Bayley-III cognitive or language composite scores 2-3 SD below the mean), or severe (Bayley-III cognitive or language composite scores more than 3 SD below the mean). Children unable to complete the cognitive, language, or motor scales because of severe delay were assigned scores of 49. The Gross Motor Function Classification System was used to categorize cerebral palsy, according to Palisano et al.[21]

Children were considered to have a vision problem if they had any one of the following: internal ocular health problem, external ocular health problem, strabismus, abnormal ocular motility, or no measurable stereopsis or binocular visual acuity >0.5 LogMAR or unmeasurable. Blindness was defined as visual acuity ≥1.4 LogMAR in both eyes. Children were considered to have a refractive error if any of the following thresholds were reached[22]: retinoscopy measurements; hyperopia ≥2.75D, myopia ≥2.75D, astigmatism ≥1.25D, anisometropia ≥1.50D, autorefractor measurements; hyperopia ≥4.00D, myopia ≥1.00D, astigmatism ≥1.50D, anisometropia ≥3.00D. Because these parameters were highly correlated between right and left, eyes were selected at random for inclusion in the data analysis.

Processing difficulty was defined as either an Executive Function Score or a motion coherence threshold more than 1.5 SD from the mean (ie, in the bottom 7% of a cohort of 404 children born at risk of hypoglycemia, which included the children reported here).

Statistical Analyses

Measurements of growth were converted to z-scores using World Health Organization reference data.[23] Socioeconomic status was categorized using the NZDep2006 index.[24] Statistical tests were 2-sided and 5% significance level was maintained for the primary analysis by splitting the alpha value equally between the coprimary outcomes (ie, $P < .025$ for either). For the primary outcomes, the proportion of children with neurosensory impairment and a processing difficulty were compared between those randomized to