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Corresponding Author: Prof. Jane E Harding, MB ChB DPhil

Corresponding Author's Institution: University of Auckland

First Author: Deborah L Harris, PhD

Order of Authors: Deborah L Harris, PhD; Jane M Alsweiler, PhD; Judith M Ansell, PhD; Greg D Gamble, MSc; Ben Thompson, PhD; Trecia A Wouldes, PhD; Tzu-Ying Yu, PhD; Jane E Harding, D Phil

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Study design: A follow-up study of 184 children who had been hypoglycemic (< 2.6mM) in the first 48 hours and randomized to either dextrose (90/118, 76%) or placebo gel (94/119, 79%). Assessments were undertaken at Kahikatea House, Hamilton, New Zealand, and included neurological function and general health (Pediatrician assessed); cognitive, language, behaviour and motor skills (Bayley-III); executive function (clinical assessment and BRIEF-P); and vision (clinical examination and global motion perception). Co-primary outcomes were neurosensory impairment (cognitive, language or motor score below -1 SD or cerebral palsy or blind or deaf) and processing problem (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 gestation 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 34 (38%) vs. placebo 32 (34%), RR 1.11, 95% CI 0.75-1.63). Processing difficulty was also similar between groups (dextrose 8 (10%) vs. placebo 16 (18%), RR 0.52, 95% CI 0.23-1.15).
Conclusions: Dextrose gel is safe for treatment of neonatal hypoglycemia, but neurosensory impairment is common amongst these children.

Outcome at two years after dextrose gel treatment for neonatal hypoglycemia; Follow up of a randomized trial

Deborah L Harris[a,b] PhD, Jane M Alsweiler[b] FRACP, PhD, Judith M Ansell[b] PhD, Greg D Gamble[b] MSc, Ben Thompson[c] PhD, Trecia A Wouldes[d] PhD, Tzu-Ying Yu[c] PhD, Jane E Harding[b] FRACP, D Phil on behalf of the CHYLD Study Team

Affiliations
[a]Newborn Intensive Care Unit Waikato District Health Board P.O. Box 934, Hamilton, New Zealand, 3200. [b]Liggins Institute, University of Auckland, [c]Department of Optometry and Vision Science, University of Auckland, [d]Department of Psychological Medicine, University of Auckland, New Zealand, 1142.

Address for correspondence
Distinguished Professor Jane E Harding, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand 1142. E-mail: j.harding@auckland.ac.nz, Telephone +64 9 373 7599 ext. 86439, Fax +64 9 373 7497

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Conflicts of Interest Statement
The authors declare that there are no potential, perceived or real conflicts of interests.
The study sponsor had no involvement in the study design, collection, analysis, or data interpretation, writing of the manuscript or the decision to submit for publication.

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Abstract

Objective: Dextrose gel increasingly is being used as first-line treatment for neonatal hypoglycemia, but longer-term effects are unknown. We determined neurodevelopmental outcome at two years' corrected age in children randomized to treatment with dextrose or placebo gel for hypoglycemia soon after birth (The Sugar Babies Study).

Study design: A follow-up study of 184 children who had been hypoglycemic (< 2.6mM) in the first 48 hours and randomized to either dextrose (90/118, 76%) or placebo gel (94/119, 79%). Assessments were undertaken at Kahikatea House, Hamilton, New Zealand, and included neurological function and general health (Pediatrician assessed); cognitive, language, behaviour and motor skills (Bayley-III); executive function (clinical assessment and BRIEF-P); and vision (clinical examination and global motion perception). Co-primary outcomes were neurosensory impairment (cognitive, language or motor score below -1 SD or cerebral palsy or blind or deaf) and processing problem (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 gestation 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 34 (38%) vs. placebo 32 (34%), RR 1.11, 95% CI 0.75-1.63). Processing difficulty was also similar between groups (dextrose 8 (10%) vs. placebo 16 (18%), RR 0.52, 95% CI 0.23-1.15).

Conclusions: Dextrose gel is safe for treatment of neonatal hypoglycemia, but neurosensory impairment is common amongst these children.

Introduction

Neonatal hypoglycemia is important because it is common and is associated with brain injury[1], neurodevelopmental delay[2, 3], visual impairment[4] and behavioural problems[5]. Between 5 and 15 % of otherwise healthy babies become hypoglycemic[6] and the prevalence is increasing due to the increasing incidence of preterm birth[7] and maternal diabetes[8]. Screening is recommended for babies with known risk factors, of whom half are likely to become hypoglycemic[9]

Treatment of hypoglycemic babies varies considerably[10]. We have 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 NICU for hypoglycemia, and less likely to be formula fed at two weeks of age. Importantly, dextrose gel was safe, and is inexpensive, simple to administer, and can be used in almost any setting.

Dextrose gel now increasingly is being used as first-line treatment for neonatal hypoglycemia[12, 13]. However, since 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 hypoglycemic babies with dextrose compared to placebo gel altered the rate of neurosensory impairment or processing difficulties at two years' corrected age.

Methods

Study design and participants

The Sugar Babies Study was a randomized, double-blind, placebo-controlled trial performed at a tertiary referral centre (Waikato Women's Hospital) in Hamilton, New Zealand 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 diabetic mothers, late preterm (35 or 36 weeks' gestation), small (< 10th centile or < 2500 g), large (> 90th centile or > 4500 g), or other). Babies who became hypoglycemic (blood glucose concentration < 2.6 mM) were randomized to receive either 40% dextrose gel or an identical appearing placebo gel 0.5ml/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 two treatment attempts. A total of 242 babies were randomized, of whom 237 actually met the eligibility criteria (five were randomized in error); 118 were randomized to dextrose and 119 to placebo gel. The trial was registered with Australian New Zealand Clinical Trials Registry, number ACTRN 12608000623392 (www.anzctr.org.au).

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, between July 21, 2010 and January 30, 2013. 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 four graded tasks, each scored out of six, to assess inhibitory control (Snack Delay, Shape Stroop), capacity for reverse categorization (Ducks and Buckets)[15] and attentional flexibility (Multi-search Multi-location 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 non-cycloplegic refractive error (Suresight Autorefractor 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 neurological 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, socio-economic status and medical history were obtained by parental questionnaire.

Analysis

The pre-specified co-primary 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 to 2 SD below the mean or mild developmental delay), moderate (moderate cerebral palsy or a Bayley-III motor composite score 2 to 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 to 2 SD below the mean), moderate (Bayley-III cognitive or language composite scores 2 to 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[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, no measurable stereopsis; 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 (i.e. in the bottom 7% of a cohort of 404 children born at risk of hypoglycemia, which included the children reported here).

Measurements of growth were converted to z-scores using WHO reference data (SAS igrowup.ref). Socioeconomic status was categorized using the NZDep2006 index[23].

Statistical tests were two sided and 5% significance level was maintained for the primary analysis by splitting the alpha value equally between the co-primary outcomes (i.e., $p < 0.025$ for either). For the primary outcomes, the proportion of children with neurosensory impairment and a processing difficulty were compared between those randomized to dextrose and those randomized to placebo using Chi-squared tests. For secondary and exploratory analyses groups were compared using generalized linear models (log-binomial for categorical variables, identify-normal for continuous variables), with adjustment for the reasons babies were identified as being at risk of hypoglycemia, socioeconomic status and sex, with no imputation for missing data.

Data were analysed using SAS version 9.3 (SAS Institute Inc. Cary NC) and are presented as unadjusted median (range), mean (SD), relative risk (RR) or median difference and 95% confidence intervals (CI).

Results

Of the 237 eligible babies, 184 (78%) were assessed at two years. (Figure). The characteristics of mothers of children who were and were not followed up were similar, except for higher parity in mothers of those who were followed up (Table 1). The characteristics of children who were and were not assessed at two years were also similar, as were those of assessed children who were randomized to dextrose gel and placebo (Table 1).

For the whole cohort of children followed up the mean Bayley-III cognitive and language composite scores were 0.25 to 0.5 SD below the standardized mean. Mean T-scores on the BRIEF-P were higher (worse), than the standardised mean of 50 for all indices (Table 2).

Sixty-six children (36%) were found to have neurosensory impairment, although most of this was mild (Table 2). Rates of impairment were similar in both treatment groups (dextrose 34 [38%] vs. placebo 32 [34%], RR 1.11, 95% CI 0.75 to 1.63, p = 0.60). The rate of processing difficulty was also similar in both treatment groups (dextrose 8 [10%] vs. placebo 16 [18%] RR 0.52, 95%CI 0.23 to 1.15, p = 0.10) (Table 2).

Sixty one children (33%) were found to be developmentally delayed (severe 1, moderate 6, mild 54), with similar rates in both treatment groups (dextrose 31 [34%] vs. placebo 30 [(32%], RR 1.07 95% CI 0.71 to 1.61, p =0.75). Two children had mild cerebral palsy. No children were blind or deaf. Forty-nine of 183 children tested (27%) had vision problems and 8/100 (8%) had a refractive error, with no difference between groups. Nine children had experienced seizures, with six of these reported to have had febrile seizures (four in the dextrose and two in the placebo group), (Table 2).

There were no differences between groups in any of the growth measurements (Table 2).

Adjustment for the reasons babies were identified as being at risk of hypoglycemia, socioeconomic status and sex did not change any of the findings.

Discussion

Dextrose gel is attractive as a primary treatment for neonatal hypoglycemia because it is simple, inexpensive, and with no adverse effects detected in the neonatal period.[11] This follow-up study provides the first evidence that treatment with dextrose gel is also not associated with adverse effects at two years' corrected age. These findings are consistent across assessment of a broad range of functions including neurodevelopment, executive function, vision and growth.

The major reason for treating neonatal hypoglycemia is to prevent hypoglycemia-induced brain injury. Since dextrose gel was effective in reversing hypoglycemia[11], we might have expected that this may be reflected in improved outcomes at two years. However, we found no evidence of improved outcome in babies treated with dextrose gel. This may be because all babies enrolled in the study were treated when a blood glucose concentration of < 2.6mM was detected. Hypoglycaemic babies were treated with either dextrose or placebo gel and fed, and the blood glucose concentration was measured again 30 minutes later. Treatment could be repeated once, and if the baby remained hypoglycaemic after the second dose of gel, the baby was admitted to NICU for further treatment. Thus babies randomized to the placebo gel group would have had additional treatment delayed by approximately one hour, and the proportion of time babies were hypoglycaemic in the first 48 hours was not significantly prolonged (placebo 6.1%, 95% CI 0.0 to 37.9% vs. dextrose 3.0%, 95% CI 0.0 to 31.8%, p = 0.13).[11] The duration and severity of hypoglycemia required to cause brain injury in any individual baby is not known.[6] However, in the context of the relatively low risk group of babies that we studied, and routine monitoring and treatment of blood glucose concentrations of < 2.6mM, there was no apparent benefit of more prompt treatment of hypoglycemia using dextrose gel on developmental outcomes at two years of age.

An alternative explanation for the lack of apparent benefit of treatment with dextrose gel may have been inadequate power to detect differences in outcome between groups. Our study had 92% power to detect a 5-point difference between groups in any of the Bayley-III composite scores, and the mean scores were almost identical between groups. Thus, it is unlikely that we would have failed to detect a clinically significant difference in developmental delay between groups. On the other hand, in the group randomized to dextrose gel, the number of children with a processing difficulty was half that of the group randomized to placebo, and the confidence intervals around the relative risk were wider (RR 0.52; 95% CI 0.23 to 1.15, p = 0.10), suggesting that we may not have had sufficient power to exclude a type 2 error for this outcome.

We are not aware of other reports regarding neurodevelopmental outcome from a cohort at risk of hypoglycemia similar to this. However, the rate of mild neurosensory impairment in our cohort appears higher than expected from the Bayley-III test standardization. Increased risk of neurodevelopmental impairment has been reported in late-preterm[24], small for gestational age[25] and infants of diabetic mothers[5] related to the abnormal intrauterine environment, or shortened gestation. Neonatal hypoglycemia is reported to be a important predictor of developmental delay in late preterm babies, and lower treatment thresholds may be associated with poorer neurodevelopmental outcomes[2]. Further, it was recently reported in a regional birth cohort that transient neonatal hypoglycemia was related to school performance at 10 years of age, with a graded relationship between severity of the hypoglycaemia and the odds of achieving proficiency in literacy and numeracy[26]. Nevertheless, it is not possible to determine whether these observed associations are causal, or whether neonatal hypoglycemia is a marker of impaired metabolic adaptation in infants who are already at risk for adverse later outcomes. Randomized trials comparing treatments at different thresholds will be required to address this question[27].

It is possible that the higher-than-expected rate of mild impairment in this cohort may be an underestimate, as the Bayley-III assessment has been reported to underestimate poor neurodevelopmental outcomes in at-risk British and Australian children[28, 29]. It is therefore important that our cohort is followed up at older ages. Our cohort will be re-assessed at 4.5 years' corrected, when neurosensory and processing difficulty outcomes can be more completely assessed.

A strength of our prospective study is the robust assessment of both visual global motion perception and executive function into a single measure that we called processing difficulty, since both assessments target cortical networks that may be susceptible to neonatal hypoglycemia. Magnetic resonance imaging of the brain, in both animal and human studies [30, 31] suggest that the occipital lobe may be particularly vulnerable to the injury caused by neonatal hypoglycemia, and a link between hypoglycemia and visual impairment has previously been reported[4, 30]. In this context, visual global motion perception was of particular interest as it involves extrastriate visual areas within the dorsal visual cortical processing stream, which emanates from the occipital lobe[32-34]. The combination of vision screening using standard clinical tests and a psychophysical measure of processing within the extrastriate visual cortex (global motion perception) is novel in 2-year olds and was intended to detect to any differences in visual development between the dextrose gel and placebo groups.

Recommendations for the follow-up of high-risk babies now also include the assessment of subtle neurocognitive and executive function[35]. Executive function is a collective term for the skills required to learn and interact with the environment, including working memory, reasoning,

task flexibility and problem solving. Findings from neuroimaging data show that these skills involve a network of areas within the brain[36]. Since there are no standardized tests for executive function in two-year-old children, we adapted tests that previously had been shown to be predictive of emerging executive function at 24 months[37]. Scores from these tests were converted to z-scores for comparing outcomes between groups.

Despite considerable effort, we succeeded in assessing only 78% of the children randomized. However, the similarity in baseline characteristics between those who were and were not assessed suggests that a systematic bias is unlikely. Since this is the first report of outcomes after a randomized trial of dextrose gel for treatment of hypoglycemia, it provides important reassurance for those who are beginning to treat neonatal hypoglycemia with dextrose gel that later adverse outcomes due to dextrose gel are unlikely in term and late preterm babies treated to maintain a blood glucose concentration >2.6mmol/L in the first 48 hours. These findings cannot be extrapolated to other groups of neonates such as more preterm babies or those with congenital hypoglycemic disorders.

We previously have shown dextrose gel is effective in reversing neonatal hypoglycemia, and has no adverse effects in the newborn period. This study shows that treatment with dextrose gel is not associated with additional risks or benefits at two years of age. Clinicians and families can be reassured that the advantages of treatment with dextrose gel soon after birth are not counterbalanced by increased risk of poor neurodevelopmental outcome at two years' corrected age.

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Clinical trial registration Australian New Zealand Clinical Trials Registry, number ACTRN 12608000623392 (www.anzctr.org.au).

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Table 1

Table 1 Characteristics of mothers and babies who were and were not followed up, and those randomized to dextrose and placebo gel

	Not followed up	Followed up		
		Total	Randomized to Dextrose Gel	Randomized to Placebo Gel
Mothers	**51**	**176**[$]	**88**	**91**
Age (y)	29.4 (7.4)	29.8 (6.0)	29.6 (5.6)	30.1 (6.3)
Parity	0 (0 - 6)	1 (0 - 10)*	1 (0 - 7)	1 (0 - 10)
BMI at booking (kg/m^2)	25.4 (18.8 - 43.6)	26.7 (15.6 - 55.9)	26.8 (15.6 - 55.9)	26.6 (18.6 - 52.9)
Diabetic	20 (39)	72 (41)	37 (42)	35 (38)
Ethnicity				
New Zealand European	27 (53)	117 (66)	61 (69)	58 (64)
Maori	18 (35)	44 (25)	19 (22)	26 (29)
Pacifica	0	6 (3.4)	3 (3.4)	3 (3.3)
Asian	6 (12%)	7 (4.0)	4 (4.6)	3 (3.3)
Not Reported	0	2 (1.1)	1 (1.1)	1 (1.1)
Highest Education Level				
Secondary	N/A	53 (32)	26 (32)	27 (32)
Tertiary	N/A	112 (67)	55 (67)	57 (68)

Deprived families#	27 (53)	65 (38)	29 (33)	36 (40)
Babies	**53**	**184**	**90 (49)**	**94 (51)**
Male	29 (55)	84 (46)	36 (40)	48 (51)
Singleton	46 (87)	153 (83)	75 (83)	78 (83)
Ethnicity	N/A			
New Zealand European		88 (50)	46 (52)	42 (47)
Maori		66 (37)	29 (33)	37 (42)
Other		23 (13)	13 (15)	10 (11)
Vaginal birth	34 (64)	113 (61)	57 (63)	56 (60)
Gestation	37.6 (1.6)	37.7 (1.6)	37.7 (1.6)	37.7 (1.6)
Birthweight (g)	2951 (799)	3093 (802)	3139 (804)	3049 (803)
Birthweight z-score	-0.19 (1.57)	0.14 (1.61)	0.26 (1.64)	0.02 (1.59)
Primary risk factor				
Maternal diabetes	20 (38)	72 (39)	37 (41)	35 (37)
Late preterm	20 (38)	61 (33)	27 (30)	34 (36)
Small	6 (11)	29 (16)	16 (18)	13 (14)

Large	4 (8)	15 (8)	7 (8)	8 (9)
Other	3 (6)	7(4)	3 (3)	4 (4)
Blood glucose concentrations (mM)				
Mean	3.3 (0.3)	3.2 (0.4)	3.2 (0.4)	3.2 (0.4)
Minimum	2.1 (0.3)	2.1 (0.4)	2.1 (0.3)	2.1 (0.4)
Admitted to NICU				
Total	22 (42)	75 (41)	33 (37)	42(45)
For hypoglycemia	8 (36)	39 (52)	13 (39)	26 (62)

[$] Three mothers had babies who were randomised to both groups. * $p < 0.05$ for comparison between those who were and were not followed up. # Deprived = NZDeprivation Index deciles 8 – 10. N/A = data not available Data are mean (SD), median (range), or number (%).