Dextrose gel for treating neonatal hypoglycaemia: A randomised placebo-controlled trial (The Sugar Babies Study)

Article *in* The Lancet · September 2013

DOI: 10.1016/S0140-6736(13)61645-1 · Source: PubMed

5 authors, including:

Deborah Harris
Victoria University of Wellington
52 PUBLICATIONS **1,824** CITATIONS

SEE PROFILE

Philip J Weston
Waikato District Health Board
35 PUBLICATIONS **1,224** CITATIONS

SEE PROFILE

James Geoffrey Chase
University of Canterbury
1,017 PUBLICATIONS **11,195** CITATIONS

SEE PROFILE

Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial

Deborah L Harris, Philip J Weston, Matthew Signal, J Geoffrey Chase, Jane E Harding

Summary

Background Neonatal hypoglycaemia is common, and a preventable cause of brain damage. Dextrose gel is used to reverse hypoglycaemia in individuals with diabetes; however, little evidence exists for its use in babies. We aimed to assess whether treatment with dextrose gel was more effective than feeding alone for reversal of neonatal hypoglycaemia in at-risk babies.

Methods We undertook a randomised, double-blind, placebo-controlled trial at a tertiary centre in New Zealand between Dec 1, 2008, and Nov 31, 2010. Babies aged 35–42 weeks' gestation, younger than 48-h-old, and at risk of hypoglycaemia were randomly assigned (1:1), via computer-generated blocked randomisation, to 40% dextrose gel 200 mg/kg or placebo gel. Randomisation was stratified by maternal diabetes and birthweight. Group allocation was concealed from clinicians, families, and all study investigators. The primary outcome was treatment failure, defined as a blood glucose concentration of less than 2·6 mmol/L after two treatment attempts. Analysis was by intention to treat. The trial is registered with Australian New Zealand Clinical Trials Registry, number ACTRN12608000623392.

Findings Of 514 enrolled babies, 242 (47%) became hypoglycaemic and were randomised. Five babies were randomised in error, leaving 237 for analysis: 118 (50%) in the dextrose group and 119 (50%) in the placebo group. Dextrose gel reduced the frequency of treatment failure compared with placebo (16 [14%] *vs* 29 [24%]; relative risk 0·57, 95% CI 0·33–0·98; p=0·04). We noted no serious adverse events. Three (3%) babies in the placebo group each had one blood glucose concentration of 0·9 mmol/L. No other adverse events took place.

Interpretation Treatment with dextrose gel is inexpensive and simple to administer. Dextrose gel should be considered for first-line treatment to manage hypoglycaemia in late preterm and term babies in the first 48 h after birth.

Funding Waikato Medical Research Foundation, the Auckland Medical Research Foundation, the Maurice and Phyllis Paykel Trust, the Health Research Council of New Zealand, and the Rebecca Roberts Scholarship.

Published **Online** September 25, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61645-1

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(13)61755-9

Newborn Intensive Care Unit, Waikato District Health Board, Hamilton, New Zealand (D L Harris PhD, P J Weston MBChB)**; Liggins Institute, University of Auckland, Auckland, New Zealand** (D L Harris, Prof J E Harding FRACP)**; and Mechanical Engineering Department, University of Canterbury, Christchurch, New Zealand** (M Signal BE [Hons], Prof J G Chase PhD)

Correspondence to: Prof Jane E Harding, Liggins Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand **j.harding@auckland.ac.nz**

Introduction

Neonatal hypoglycaemia is important because it is a common disorder, which is associated with brain injury and poor neurodevelopmental outcome.[1–3] Although the definition of neonatal hypoglycaemia is controversial,[4] thresholds for treatment have been established[5] and are used in clinical practice.[6] Neonatal hypoglycaemia affects as many as 5–15% of otherwise healthy babies[5,7] and is widespread in resource-poor countries.[8,9] Furthermore, prevalence of the disorder is increasing because of the increasing incidence of preterm birth[10] and maternal factors, such as diabetes[11] and obesity,[12] which can predispose babies to hypoglycaemia. Little evidence exists to guide treatment and repeated calls have been made to develop evidence-based guidelines for the treatment of neonatal hypoglycaemia.[5,7,13,14]

Treatment choices vary dependent on the baby's birthweight and gestational age. In late preterm and term babies, initial management focuses on feeding and increased monitoring, requiring repeated and painful blood tests. If blood glucose concentration remains low, admission to the newborn intensive-care unit for intravenous glucose is usually indicated.[15] Such admission usually means that mother and baby are separated, which can delay the establishment of breastfeeding.

In addition to intravenous glucose, 40% dextrose gel is another less commonly used treatment. Potential advantages of dextrose gel are that it keeps mother and baby together while treatment is provided, is easy to administer, and is low cost. Oral carbohydrate is first-line treatment for low blood glucose concentrations in the conscious diabetic child or adult,[16] and sublingual glucose is as effective as intravenous glucose for treatment of hypoglycaemic children with malaria.[17] Two small observational studies[18,19] in babies aged between 28 weeks' and 42 weeks' gestation have reported improvement in blood glucose concentrations after massaging of 200 mg/kg dextrose gel into the buccal mucosa. However, a randomised trial,[20] in which 75 babies with hypoglycaemia were randomly assigned to a feed or feed plus 400 mg/kg dextrose gel on the first day after birth, showed no differences in blood glucose concentrations at 15 min and 30 min after treatment. Furthermore, formula-fed babies assigned to the dextrose-gel group suckled a smaller volume during the subsequent feed than did those in the feed-alone group.[20] Therefore, the role of dextrose gel in the management of neonatal hypoglycaemia remains unclear.

We assessed whether treatment with 40% dextrose gel was more effective than feeding alone for reversal of

neonatal hypoglycaemia in at-risk late preterm and term babies.

Methods

Study design and participants

We undertook this randomised, double-blind, placebo-controlled study at a tertiary referral centre (Waikato Women's Hospital) in Hamilton, New Zealand, between Dec 1, 2008, and Nov 31, 2010. Eligible babies were born at 35 weeks' gestation or older, aged 48 h or younger, and at risk of neonatal hypoglycaemia. Risk factors were being the infant of a diabetic mother (gestational, type 1, or type 2 diabetes), being preterm (35 or 36 weeks' gestation), being small (birthweight <10th centile or <2500 g) or large (birthweight >90th centile or >4500 g), or other reasons such as poor feeding. Exclusion criteria were any previous treatment for neonatal hypoglycaemia, serious congenital malformation, terminal disorders, or skin abnormalities that would prevent use of the continuous glucose monitor. A researcher contacted women identified as likely to give birth to an eligible baby before birth; those not recruited before birth were contacted as soon as possible after the birth.

The study was approved by the Northern Y Ethics Committee and all mothers provided written informed consent. The study protocol is available online.

For **study protocol** see http://hdl.handle.net/2292/20460

Randomisation and masking

We used computer-generated blocked randomisation, with variable block sizes, to assign babies (1:1) who became hypoglycaemic to either 40% dextrose gel or placebo gel. Randomisation was stratified by maternal diabetes (yes or no) and birthweight (small, appropriate, or large). We assigned twins independently. The researcher entered demographic data into a computer that provided a randomisation number corresponding to a numbered treatment pack containing six labelled syringes, each containing 3 mL of the same gel: either 40% dextrose gel or 2% carboxymethyl cellulose placebo gel, which was identical in appearance. Study packs were prepared by the hospital pharmacist, who had no other involvement in the study. Clinicians, families, and all study investigators were all masked to group allocation until data analysis was complete.

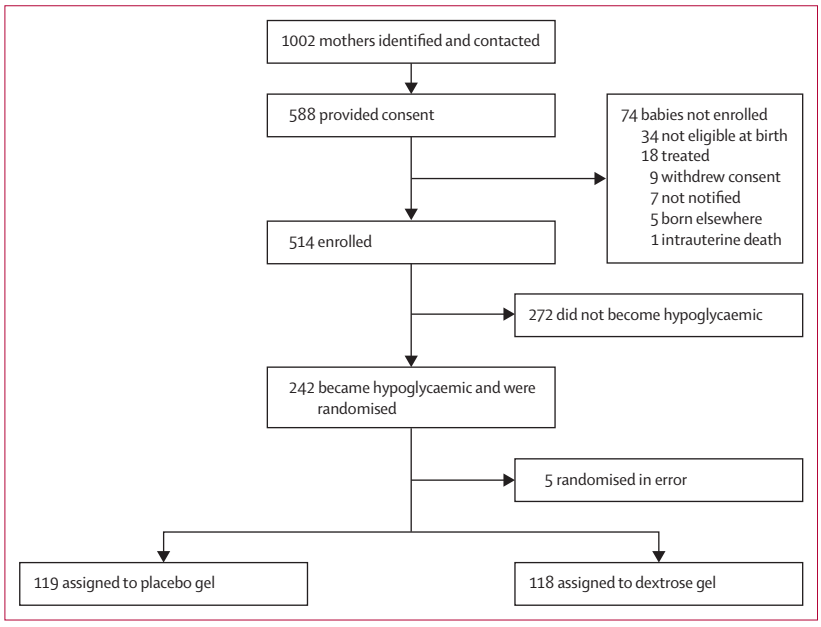

Figure: **Trial profile**

Procedures

The researcher or midwife dried the baby's mouth with gauze, massaged 200 mg/kg (0·5 mL/kg) gel into the buccal mucosa, and the baby was encouraged to feed. If feeding was poor, the baby was given expressed breastmilk or formula by syringe, according to maternal wishes. The blood glucose concentration was measured 30 min after gel administration and, if the baby remained hypoglycaemic or hypoglycaemia recurred later, treatment was repeated with another syringe from the allocated pack. Up to six doses of gel could be given over 48 h.

We measured blood glucose concentrations according to clinical guidelines in our hospital[21] on samples obtained by heel lances 1 h after birth, then every 3–4 h before feeds for the first 24 h, then every 6–8 h for the subsequent 24 h. All blood glucose concentrations were measured by the glucose oxidase method (Radiometer, ABL800 FLEX, Copenhagen, Denmark). A continuous glucose monitor (CGMS System Gold, Medtronic, MiniMed, Northridge, CA, USA) was placed subcutaneously in the lateral thigh as soon as possible after birth, or after recruitment if this was after birth.[22] The monitor remained in place for at least 48 h or for up to 7 days until hypoglycaemia was no longer a clinical concern. These monitors are safe and reliable in newborn babies, including at low glucose concentrations.[22,23] Interstitial glucose concentrations cannot be viewed in real time, ensuring clinical practice was not affected by the results.

Mothers were encouraged to provide skin-to-skin contact and feed the baby within the first hour after birth. Before birth many mothers expressed and stored breastmilk, and when possible, babies who did not breastfeed adequately were given expressed breastmilk by syringe. Babies who were to be formula fed were offered up to 60 mL/kg per day on day one, and 90 mL/kg per day on day two.

The primary outcome was treatment failure, defined as a blood glucose concentration of less than 2·6 mmol/L 30 min after the second of two doses of gel. Secondary outcomes were admission to the neonatal intensive-care unit; frequency of breastfeeding; total volume and frequency of expressed breastmilk and infant formula, intravenous dextrose, and dextrose gel in the first 48 h; method of feeding 2 weeks after birth; incidence of

rebound and recurrent hypoglycaemia after successful treatment; time taken to achieve interstitial glucose concentrations of 2·6 mmol/L or more after treatment; and total duration of interstitial glucose concentrations of less than 2·6 mmol/L up to 48 h after birth.

Hypoglycaemia was defined as a blood or interstitial glucose concentration of less than 2·6 mmol/L, which was the accepted clinical threshold for treatment[6] and the threshold for treatment used in our hospital. Episodes of hypoglycaemia were defined as one or more consecutive blood glucose concentrations of less than 2·6 mmol/L or two or more consecutive interstitial glucose concentrations of less than 2·6 mmol/L. Rebound hypoglycaemia was defined as an episode of hypoglycaemia within 6 h after successful treatment (blood or interstitial glucose ≥2·6 mmol/L for ≥1 h after treatment). Recurrent hypoglycaemia was defined as a further episode of hypoglycaemia after successful treatment, within 48 h after birth. Babies who met the criteria for treatment failure and remained hypoglycaemic were admitted to the neonatal intensive-care unit and treated with open-label dextrose gel, infant formula, or intravenous dextrose, according to clinical guidelines and clinician preference.

An independent data monitoring committee reviewed results after 100 babies had been randomised and recommended the study continue. The safety monitoring committee received reports of serious adverse events (death and seizures), and of other adverse events of severe hypoglycaemia (blood glucose concentration <1 mmol/L), hyperglycaemia (two consecutive blood glucose concentrations >8·0 mmol/L), culture proven sepsis, and inflammation or swelling at the insertion site of the continuous glucose monitor.

Statistical analysis

A retrospective review of 91 babies at risk of neonatal hypoglycaemia born at our hospital in 2006 showed that 51 (56%) became hypoglycaemic, of whom nine (20%) remained hypoglycaemic after two doses of dextrose gel. We planned the study as a superiority trial with a one-tailed design (α 0·05, β 0·2) and, with an allowance of 5% withdrawal, a sample size of 230 (115 per group) would be needed to detect a reduction in the rate of treatment failure from 35% in the placebo group to 20% in the dextrose gel group.

Data from the interstitial glucose monitors were downloaded with CGMS Solutions software (version 3.0C) and recalibrated with a previously reported algorithm[24] to optimise accuracy at low concentrations of blood glucose with use of Matlab (version 7.14 2012a). During preparation of the data analysis plan, and before unblinded analysis, we decided to use a standard two-sided analysis. Statistical analyses were on an intention-to-treat basis, and we allocated babies for whom primary outcome data were not available to the conservative outcome of treatment failure. Data were analysed with SAS Enterprise Guide (version 4·3) and are presented as median (range), mean (SD), relative risk (RR), or median difference and 95% CIs. We analysed normally distributed continuous variables with *t* tests; otherwise we used a Wilcoxon two-sample test. We analysed feeding at 2 weeks of age with unordered generalised logistic regression with breastmilk as the reference group. We compared rates of rebound and recurrent hypoglycaemia between groups with rate ratios that were calculated with OpenEpi (version 2.3.1).[25] We adjusted the primary outcome for reasons why the baby was anticipated to be at risk of hypoglycaemia (maternal diabetes and birthweight) because randomisation was balanced across these categories. No other

	Dextrose gel	Placebo gel
Mothers		
Number*	115	115
Maternal age (years)	29·2 (6·0)	30·2 (6·5)
Gravidity	2 (1–11)	2 (1–12)
Parity	1 (0–7)	1 (0–10)
BMI at booking (kg/m²)	27 (16–56)	26 (19–66)
Weight change during pregnancy (kg)	12·2 (8·0)	11·7 (6·8)
Diabetic	46 (40%)	46 (40%)
Intended method of feeding		
Breast	114 (99%)	109 (95%)
Infant formula	1 (1%)	2 (2%)
Combination	0	4 (3%)
Expressed breast milk before birth	24 (21%)	23 (20%)
Babies		
Number	118	119
Boys	48 (41%)	65 (55%)
Birthweight (g)	3091 (824)	3031 (782)
Gestation (week)	37·4 (1·6)	37·2 (1·6)
Singleton birth	100 (85%)	99 (83%)
Vaginal birth	73 (62%)	74 (62%)
Apgar score of <5 at 5 min	0	0
Blood glucose concentration at time of randomisation (mmol/L)	2·2 (1·1–2·5)	2·2 (0·9–2·5)
Ethnic origin		
New Zealand European	63 (53%)	64 (54%)
Maori	34 (29%)	37 (31%)
Other	21 (18%)	18 (15%)
Risk factors for neonatal hypoglycaemia†		
Infant of diabetic mother	46 (39%)	46 (39%)
Late preterm (35 weeks or 36 weeks)	41 (35%)	49 (41%)
Birthweight		
<2500 g	30 (25%)	32 (27%)
>4500 g	12 (10%)	10 (8%)
<10th centile	13 (11%)	19 (16%)
>90th centile	26 (22%)	27 (23%)
Other	6 (5%)	4 (3%)

Data are mean (SD), median (range), and n (%), unless otherwise indicated. BMI=body-mass index.*Three mothers are in both columns because one twin was assigned to each treatment group (ie, n=227 mothers). †Many babies had more than one risk factor for hypoglycaemia.

Table 1: **Baseline characteristcs**

outcomes were adjusted. The trial is registered with Australian New Zealand Clinical Trials Registry, number ACTRN12608000623392.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, nor decision to submit the manuscript for publication.

Results

The figure shows the trial profile. Of 514 babies enrolled, 242 (47%) became hypoglycaemic and were randomised. Five babies were randomised in error, leaving 237 for analysis: 118 (50%) in the dextrose group and 119 (50%) in the placebo group. Demographic and baseline characteristics were similar between groups, although more boys were allocated to the placebo group (table 1). Characteristics were also similar in babies and their mothers who were enrolled but not randomised because they did not become hypoglycaemic (data not shown). Risk factors for hypoglycaemia were similar in both groups (table 1). Similar proportions of mothers in both groups did not know what treatment their baby had received (85 [76%] of 112 in the dextrose group *vs* 87 [76%] of 114 in the placebo group) or thought their baby had received dextrose gel (25 [22%] *vs* 26 [23%]), showing that masking was successful.

	Dextrose gel (n=118)	Placebo gel (n=119)	Relative risk or median difference (95% CI)	p value
Volume of study gel (mL/kg)	0·84 (0·43–2·44)	0·97 (0·47–2·49)	0·005 (–0·01 to 0·02)	0·45
Treatment failure	16 (14%)	29 (24%)	0·57 (0·33 to 0·98)	0·04
Dextrose administered as:				
Study gel				
Babies	118 (100%)	119 (100%)	..	..
Dose (g/kg)	0·3 (0·2–1·0)	0	..	..
Open-label gel*				
Babies	6 (5%)	13 (11%)	0·47 (0·18 to 1·18)	0·15
Dose (g/kg)	0·2 (0·1–0·4)	0·4 (0·2–0·6)	0·14 (0·00 to 0·20)	0·10
Intravenous bolus				
Babies	7 (6%)	13 (11%)	0·54 (0·23 to 1·31)	0·24
Dose (g/kg)	0·2 (0·2–0·2)	0·2 (0·1–1·0)	0·0001 (–0·004 to 0·20)	0·96
Intravenous infusion				
Babies	8 (7%)	17 (14%)	0·47 (0·21 to 1·06)	0·09
Dose (g/kg)	6·7 (2·0–10·6)	7·7 (3·7–14·6)	2·12 (–0·42 to 5·58)	0·10
Total Intravenous dextrose (g/kg)	7·1 (2·5–10·8)	8·3 (4·2–16·2)	2·55 (0·50 to 5·84)	0·09
Total dextrose from sources other than study gel†				
Babies	12 (10%)	28 (24%)	0·43 (0·23 to 0·81)	0·01
Dose (g/kg)	4·5 (0·2–10·8)	6·6 (0·2–16·2)	0·20 (–2·1 to 5·5)	0·51
Total dextrose from all sources				
Babies	118 (100%)	119 (100%)	..	..
Dose (g/kg)	0·3 (0·2–11·4)	0·0 (0·0–16·2)	0·20 (0·19 to 0·23)	<0·0001
Feeding				
Breastfed babies	112 (95%)	113 (95%)	1·00 (0·94 to 1·06)	0·99
Feeds per baby	13 (1–29)	11 (1–24)	–1·00 (–3·00 to 0·00)	0·16
Babies receiving expressed breastmilk	100 (85%)	97 (82%)	1·04 (0·93 to 1·17)	0·60
Feeds per baby	4 (1–15)	6 (1–16)	1·00 (0·00 to 2·00)	0·02
Volume (mL/kg)	2·4 (0·1–96·1)	4·7 (0·0–43·6)	1·07 (0·14 to 2·37)	0·03
Babies receiving Infant formula	68 (58%)	72 (60%)	0·95 (0·77 to 1·18)	0·69
Feeds per baby	7 (1–21)	10 (1–24)	2·00 (0·00 to 4·00)	0·04
Volume (mL/kg)	41 (1–162)	58 (2–208)	11·06 (–3·01 to 26·89)	0·14
Admitted to NICU				
Babies (n)	45 (38%)	55 (46%)	0·83 (0·61 to 1·11)	0·24
For hypoglycaemia (n)	16 (14%)	30 (25%)	0·54 (0·31 to 0·93)	0·03

Data are n (%) or median (range), unless otherwise indicated. NICU=neonatal intensive-care unit. *40% dextrose given according to usual clinical guidelines after the baby had failed treatment. †Includes open-label and intravenous dextrose.

***Table 2*: Primary and secondary outcomes**

432 doses of study gel were administered—215 in the dextrose group and 217 in the placebo gel group. In both groups babies received a median of two doses (range 1–5) of study gel of similar volume, resulting in those randomised to dextrose receiving a median of 0·3 g/kg (95% CI 0·2–1·0) dextrose (table 2). Primary outcome data were available for 116 (98%) babies in the dextrose group, and 118 (99%) in the placebo group. For the remaining three babies, blood glucose concentration was not measured at the appropriate time so the primary outcome could not be measured (table 2). Fewer babies in the dextrose group than in the placebo group met the criteria for treatment failure (table 2). Overall 100 (42%) of 237 babies were admitted to the neonatal intensive-care unit, of whom roughly half were admitted for treatment of hypoglycaemia (table 2). Admission rates were similar in both treatment groups, but babies who received dextrose gel were less likely to be admitted for hypoglycaemia (table 2). 40 (17%) babies needed additional treatment with dextrose. Babies in the dextrose group were less likely to receive additional dextrose than were those in the placebo group, but those who did receive intravenous dextrose had similar amounts (table 2).

98% (n=220) of mothers intended to breastfeed, and almost all babies were breastfed (table 2). Babies in the dextrose group received expressed breastmilk less frequently and in smaller volumes than did those in the placebo group (table 2). Babies in the dextrose gel group received fewer formula feeds than those in the placebo group, but the volume of formula feeds did not differ significantly between groups (table 2). At 2 weeks of age, fewer babies were formula feeding in the dextrose gel group than in the placebo group (5 [4%] *vs* 15 [13%]; RR 0·34. 95% CI 0·13–0·90; p=0·03).

175 (74%) of babies had continuous glucose monitoring: 88 (75%) in the dextrose group and 87 (73%) in the placebo group. However, only 76 gel treatments (38 in each group) could be analysed for the secondary outcomes that involved continuous glucose monitoring. Episodes of rebound hypoglycaemia were uncommon and similar in frequency in both groups (table 3). Episodes of recurrent hypoglycaemia were less common in babies in the dextrose gel group than in those randomised to placebo when measured by interstitial, but not blood, glucose concentrations (table 3). The median time taken for interstitial glucose concentration to be restored was similar in both treatment groups, at 20·3 min (95% CI 0·2–215·4) in the dextrose group and 22·8 min (1·9–165·2) in the placebo group (median difference 4·9 min, 95% CI 4·4–19·4; p=0·13). The total duration of low interstitial glucose concentrations was not significantly reduced by dextrose gel (table 3).

Treatment with dextrose gel was well tolerated, with similar numbers of doses reported as tolerated in both groups (213 [99%] of 215 given dextrose and 211 [97%] of 217 given placebo). Furthermore, 113 mothers in each of the dextrose (97%) and placebo (96%) groups reported that gel treatment was an acceptable and easy treatment for their babies. We noted no serious adverse events. Three (3%) babies in the placebo group each had one blood glucose concentration of 0·9 mmol/L. No other adverse events were reported.

Prespecified subgroup analysis showed no differences in response between babies with different risk factors (data not shown). If the three babies for whom primary outcome was not available were excluded, findings for treatment failure remained unchanged (14 [12%] of 116 babies in the dextrose gel and 28 [24%] of 118 in the placebo group; RR 0·51, 95% CI 0·28–0·92; p=0·03).

	Dextrose gel (n=118)	Placebo gel (n=119)	Rate ratio or median difference	95% CI	p value
Blood glucose					
Rebound episodes					
Episodes per baby	..	..	1·46	0·67 to 3·26	0·33
0	104 (88%)	109 (92%)	..	..	..
1	12 (10%)	9 (7%)	..	..	..
2	2 (2%)	1 (1%)	..	..	..
Recurrent episodes					
Episodes per baby	..	..	0·89	0·55 to 1·44	0·66
0	90 (76%)	91 (76%)	..	..	..
1	23 (20%)	22 (19%)	..	..	..
2	5 (4%)	4 (3%)	..	..	..
≥3	0	2 (2%)	..	..	..
Interstitial glucose					
Babies (n)	25 (21%)	30 (25%)	..	..	..
Rebound episodes					
Episodes per baby	..	..	1·20	0·40 to 3·57	0·73
0	20 (80%)	25 (83%)	..	..	..
1	3 (12%)	3 (10%)	..	..	..
2	2 (2%)	2 (7%)	..	..	..
Recurrent episodes					
Episodes per baby	..	..	0·44	0·21 to 0·86	0·01
0	16 (64%)	18 (60%)	..	..	..
1	8 (32%)	4 (13%)	..	..	..
2	0	3 (10%)	..	..	..
≥3	1 (4%)	5 (17%)	..	..	..
Duration of low interstitial glucose concentrations*					
Babies (n)	32 (27%)	36 (30%)	..	..	..
Duration (min per baby)	81 (0 to 840)	164 (0 to 1064)	48	−7·0 to 124	0·23
Proportion of time (%)	3·0% (0·0 to 31·8)	6·1% (0·0 to 37·9)	1·8	−0·2 to 4·6	0·13

Data are n (%) or median (95% CI). *During the first 48 h after birth for babies with at least 40 h of satisfactory continuous glucose monitoring.

***Table 3*: Rebound and recurrent hypoglycaemia in babies assigned to dextrose or placebo gel**

Discussion

Our findings show that treatment with 40% dextrose gel is more effective than feeding alone for reversal of neonatal hypoglycaemia in at-risk late preterm and term babies in the first 48 h after birth. Furthermore, babies who received

***Panel*: Research in context**

Systematic review

We searched PubMed and Cumulative Index to Nursing and Allied Health Literature to May 1, 2013, with keywords infant/newborn, hypoglycaemia, glucose, buccal, sublingual, treatment, and Hypostop. Our search did not reveal any systematic reviews of this treatment. The only randomised trial, available only in abstract, reported that treatment of babies admitted to neonatal intensive care with 400 mg/kg dextrose gel did not increase blood glucose concentrations, although for 75 randomly assigned babies, power to detect relevant clinical outcomes was restricted.[20]

Interpretation

Treatment with 40% dextrose gel 200 mg/kg was more effective than feeding alone for reversal of neonatal hypoglycaemia in at-risk late preterm and term babies in the first 48 h after birth. This treatment could help to avoid admission to neonatal intensive-care units in babies not needing admission for other reasons, and seems to support breastfeeding, partly by reducing the use of formula in the neonatal period. Dextrose gel did not increase the risk of rebound or recurrent hypoglycaemia, was well tolerated, and was not associated with adverse effects. Because this treatment is inexpensive and simple to administer, it should be considered for first-line management of late preterm and term hypoglycaemic babies in the first 48 h after birth.

dextrose gel were less likely to be admitted to neonatal intensive-care units for management of hypoglycaemia, to receive additional dextrose or formula feeds, or to be formula fed at 2 weeks of age. Dextrose gel did not increase the risk of rebound or recurrent hypoglycaemia, was well tolerated, and was not associated with adverse effects.

Dextrose gel has been recommended for the management of neonatal hypoglycaemia[26] and there are anecdotal reports of improvement in blood glucose concentration after dextrose gel absorption via the buccal mucosa.[18,19] However, the only randomised trial of dextrose gel for neonatal hypoglycaemia reported that babies admitted to neonatal intensive care had no increases in blood glucose concentrations with 400 mg/kg gel.[20] Our study is the first report in babies showing that buccal dextrose gel is a safe effective treatment for management of hypoglycaemia (panel).

One early concern was the possibility that dextrose gel might adversely affect breastfeeding, because receipt of any supplements in the neonatal period is reported to delay the establishment of, and decrease the duration of, breastfeeding.[27,28] However, our data show that babies in the dextrose gel group needed fewer formula feeds and less expressed breastmilk than did those in the feeding only group. If the mother's intention was to breastfeed and the baby was hypoglycaemic, mothers were encouraged to either feed the baby or express breastmilk. Some women could have felt pressured to provide breastmilk, which might have negatively affected the establishment of breastfeeding. Furthermore, fewer babies in the dextrose gel group received additional dextrose, either intravenously or as open-label gel after treatment failure, than did those in the placebo group; thus, babies in the dextrose gel group received less additional clinical intervention, and therefore spent less time separated from their parents. All of these factors might have contributed to our finding that at 2 weeks of age, formula feeding was less common in babies receiving dextrose gel than in those receiving placebo. We postulate that provision of a treatment that allows the mother and baby to remain together while supporting metabolic transition to extrauterine life could reduce maternal anxiety and support establishment of breastfeeding in the early postnatal period.

Perhaps surprisingly, continuous glucose monitoring showed that time taken for the interstitial glucose concentration to recover after gel treatment was similar in both groups. However, these findings are from a subset of babies who had continuous glucose monitoring, and of these, fewer than half the treatment episodes were available for analysis. There were two reasons for this restricted availability: (1) although the continuous glucose monitor was placed as soon after birth as possible, it takes 1 h to initialise, meaning that in 152 cases the first gel treatment was given before continuous glucose data were available; (2) we noted 24 episodes of hypoglycaemia when, although the blood and interstitial glucose concentrations were less than 2·6 mmol/L at the time of diagnosis of the hypoglycaemic episode, the interstitial glucose concentration was 2·6 mmol/L or more at the time of gel administration, and therefore the secondary outcomes could not be established.

One potential risk of administration of dextrose gel is the possibility of the occurrence of rebound hypoglycaemia secondary to stimulation of insulin secretion. Lilien and colleagues[15] reported that a minibolus of 200 mg/kg intravenous dextrose improved blood glucose concentrations without hyperglycaemia. We chose the same dose for administration of buccal glucose, and also noted that rebound hypoglycaemia was uncommon and occurred with similar frequency in both groups. However, consistent with the overall findings that dextrose gel reduced treatment failure, recurrent hypoglycaemia was less common in babies who received dextrose gel when measured by continuous interstitial glucose monitoring, despite these babies receiving less frequent feeds than those in the placebo gel group. Furthermore, babies who received dextrose gel seemed to spend less time overall in a hypoglycaemic state than did babies who received placebo gel, although this finding was not statistically significant.

Babies in this trial were similar to most of those who are at risk of hypoglycaemia in the immediate neonatal period. Although dextrose gel did not decrease admission to the neonatal intensive-care unit in this study, most likely because babies were admitted for various reasons other than hypoglycaemia, it did reduce admission for hypoglycaemia. This finding suggests that, in babies at risk of hypoglycaemia but without other comorbidities, treatment with dextrose gel could avert the need for admission to intensive care, thus reducing costs and

keeping mother and baby together. We cannot extrapolate from our data whether dextrose gel is effective treatment in babies of other gestational or postnatal ages. Neither can we establish whether the dose we have used is ideal.

Dextrose gel treatment has various advantages including ease of administration and low cost. Babies tolerated both the administration of the gel and the gel itself. Both parents and staff reported gel treatment to be acceptable and simple to administer. Dextrose gel is inexpensive and can be purchased commercially for roughly US$70 per 100 mL or $2 per baby, can easily be made in the hospital pharmacy, and is stable at room temperature. Therefore, the gel could also be useful in resource-poor settings where hypoglycaemia is common and underdiagnosed.[8,9,29]

Dextrose gel should be considered for first-line management of late preterm and term hypoglycaemic babies in the first 48 h after birth.

Contributors

DLH and PJW contributed to the literature search, study design, data collection, analysis, and interpretation. DLH wrote the first draft of the manuscript; and contributed to subsequent revisions. MS and JGC contributed to the data analysis and interpretation of the continuous glucose monitoring data and the final manuscript. JEH contributed to the study design, data analysis and interpretation, and to writing all versions of the manuscript, and had overall responsibility for the study.

Conflicts of interests

We declare that we have no conflicts of interest.

Acknowledgments

This trial was funded by the Waikato Medical Research Foundation, the Auckland Medical Research Foundation, the Maurice and Phyllis Paykel Trust, the Health Research Council of New Zealand, and the Rebecca Roberts Scholarship. We thank all the Sugar Babies and their families for being part of the study, and the staff at Waikato Women's Hospital, particularly research nurses Catherine McBride and Paula Middlemiss; the Independent Data and Safety Monitoring Committee: Caroline Crowther, Frank Bloomfield, and David Graham; and members of the CHYLD data team who assisted with data entry and the analyses: Greg Gamble, Janine Paynter, Pei Wen Chen, Tineke Crawford, Yann Henry, Grace Knight, and Rebecca Young.

References

1 Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF. Neonatal morbidities and developmental delay in moderately preterm-born children. *Pediatrics* 2012; **130:** 265–72.

2 Koh TH, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycaemia. *Arch Dis Child* 1988; **63:** 1353–58.

3 Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988; **297:** 1304–08.

4 Rozance PJ, Hay WW. Describing hypoglycaemia—definition or operational threshold? *Early Hum Dev* 2010; **86:** 275–80.

5 Cornblath MD, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycaemia: suggested operational thresholds. *Pediatrics* 2000; **105:** 1141–45.

6 Harris DL, Weston PJ, Battin MR, Harding JE. A survey of the management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network. *J Paediatr Child Health* 2009; **26:** 1–8.

7 Hay WW, Raju T, Higgins R, Kalhan S, Devaskar S. Knowledge gaps and research needs for understanding and treating neonatal hypoglycaemia. *J Pediatr* 2009; **155:** 612–17.

8 Anderson S, Shakya KN, Shrestha LN, Costello AM. Hypoglycaemia: a common problem among uncomplicated newborn infants in Nepal. *J Trop Pediatr* 1993; **39:** 273–77.

9 Osier FHA, Berkley AR, Sanderson F, Mohammed S, Newton CRJC. Abnormal blood glucose concentrations on admission to a rural Kenyan district hospital: prevalence and outcome. *Arch Dis Child* 2003; **88:** 621–25.

10 Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012; **379:** 2162–72.

11 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes. *Diabetes Care* 2004; **27:** 1047–53.

12 Doherty DA, Magann EF, Francis J, Morrison JC, Newnham JP. Pre-pregnancy body mass index and pregnancy outcomes. *Int J Gynaecol Obstet* 2006; **95:** 242–47.

13 Achoki R, Opiyo N, English M. Mini-review: management of hypoglycaemia in children aged 0–59 months. *J Trop Pediatr* 2010; **56:** 227–34.

14 Williams AF. Hypoglycaemia of the newborn. *Bull World Health Organ* 1997; **75:** 261–90.

15 Lilien LD, Pildes RS, Srinivasan G, Voora S, Yeh T. Treatment of neonatal hypoglycaemia with minibolus and intravenous glucose infusion. *J Pediatr* 1980; **97:** 295–98.

16 Clarke W, Jones T, Rewers A, Dunger D, Klingensmith G. Assessment and management of hypoglycaemia in children and adolescents with diabetes: ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. *Paediatr Diabetes* 2009; **10** (suppl 12)**:** 134–45.

17 Barennes H, Valea I, Nagot N, Van de Peree P, Pussard E. Sublingual sugar administration as an alternative to intravenous dextrose administration to correct hypoglycaemia among children in the tropics. *Pediatrics* 2005; **116:** e648–53.

18 Ang I, Koh THHG, Halloren M, Berry A. New treatment of neonatal hypoglycaemia. Perth: Congress of the Federation of Asian Oceania Perinatal Society, 1990.

19 Bourchier D, Weston P, Heron P. Hypostop for neonatal hypoglycaemia. *N Z Med J* 1992; **105:** 22.

20 Troughton KEV, Corrigan NP, Tait RME. Hypostop gel in the treatment of neonatal hypoglycaemia: a randomised controlled trial. *Arch Dis Child* 2000; **82** (suppl 1)**:** A30.

21 Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycaemia in babies identified as at risk. *J Pediatr* 2012; **161:** 787–91.

22 Harris DL, Weston PJ, Battin MR, Harding JE. Continuous glucose monitoring in newborn babies at risk of neonatal hypoglycaemia. *J Pediatr* 2010; **157:** 198–202.

23 Beardsall K, Ogilvy-Stuart AL, Ahluwalia J, Thompson M, Dunger DB. The continuous glucose monitoring sensor in neonatal intensive care. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F307–10.

24 Signal M, Le Compte A, Harris DL, et al. Impact of retrospective calibration algorithms on hypoglycaemia detection in newborn infants using continuous glucose monitoring. *Diabetes Technol Ther* 2012; **14:** 883–90.

25 Dean AG, Sullivan KM, Soe MM. OpenEpi: open source epidemiologic statistics for public health. http://www.OpenEpi.com (accessed Oct 15, 2012).

26 Ogilvy-Stuart A, Midgley P. Hypoglycaemia. In: Ogilvy-Stuart A, Midgley P, eds. Practical neonatal endocrinology. Cambridge: Cambridge University Press, 2006: 7–16.

27 Blomquist HK, Jonsbo F, Serenius F, Persson LA. Supplementary feeding in the maternity ward shortens the duration of breast feeding. *Acta Paediatr Scand* 1994; **83:** 1122–26.

28 Dewey KG, Nommsen-Rivers LA, Heinig MJ, Cohen RJ. Risk factors for suboptimal infant breastfeeding behavior, delayed onset of lactation, and excess neonatal weight loss. *Pediatrics* 2003; **112:** 607–19.

29 Allen CW, Jeffery H. Implementation and evaluation of a neonatal educational program in rural Nepal. *J Trop Pediatr* 2006; **52:** 218–22.