Dextrose Gel for Treating Neonatal Hypoglycemia:

A Randomized Placebo-Controlled Trial (The Sugar Babies Study)

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Background

Neonatal hypoglycemia is common and a preventable cause of brain damage. Dextrose gel is used to reverse hypoglycemia in diabetics. However, there is little evidence for its use in babies.

Method

We enrolled 514 babies 35 to 42 weeks' gestation, < 48 hours, and at risk of hypoglycemia, to a randomized, double-blind placebo controlled trial to determine whether 40% dextrose gel massaged into the buccal mucosa is more effective than feeding alone in reversing hypoglycemia. Hypoglycemic babies were randomized to 40% dextrose gel 200 mg/kg (n= 118) or placebo (n= 119) and encouraged to feed. Primary outcome was treatment failure (blood glucose concentration <2·6 mmol/L) after two treatment attempts.

Findings

Dextrose gel reduced the frequency of treatment failure (16/118 (14%) in dextrose vs. 29/119 (24%) in placebo group, RR 0·57; 95% CI 0·33 to 0·98; p=0·04). Babies receiving dextrose gel were less likely to be admitted to intensive care for hypoglycemia, (16/118 (14%) vs. 30/119 (25%); RR 0.54 (0.31, 0.93); P=0.03), to receive formula feeds (median 7 vs. 10 feeds; median difference 2; 95% CI 0 to 4; p=0·04) and to be formula fed at two weeks (5/118 (4%) vs.15/119 (13%), RR 0·34; 95% CI 0·13 to 0·90; p=0·03).

Interpretation

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

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Introduction

Neonatal hypoglycemia is important because it is common, and linked with brain injury and poor neurodevelopmental outcome.[1-3] The definition of neonatal hypoglycemia remains controversial.[4] However, thresholds for treatment have been established[5] and are used in clinical practice.[6] Neonatal hypoglycemia is reported to affect as many as 5 to 15% of otherwise healthy babies[5,7] and is also common in resource- poor countries.[8,9] Furthermore, the prevalence is increasing due to the increasing incidence of both preterm birth,[10] and maternal factors known to predispose babies to hypoglycemia including diabetes,[11] and obesity.[12] There is a paucity of evidence to guide treatment and there have been repeated calls to develop evidence based guidelines for the treatment of neonatal hypoglycemia.[5,7,13,14]

Current treatment choices vary depending on the baby's birth weight and gestational age. In late preterm and term babies, initial management focuses on feeding and increased monitoring, requiring repeated and painful blood tests. If the blood glucose concentration remains low, admission to the Newborn Intensive Care Unit (NICU) for intravenous glucose is usually indicated.[15] NICU admission usually means that mother and baby are separated, which may delay the establishment of breast feeding.

Another less commonly used treatment is 40% dextrose gel. Potential advantages include keeping the mother and baby together while treatment is provided, ease of administration of the gel, and low cost. Oral carbohydrate is first-line treatment for low blood glucose concentrations in the conscious diabetic child or adult,[16] and

sublingual glucose has been shown to be as effective as intravenous glucose for the treatment of hypoglycemic children with malaria.[17] Two small observational studies in babies between 28 to 42 weeks' gestation have reported improvement in blood glucose concentrations following massaging dextrose gel 200 mg/kg into the buccal mucosa.[18,19] However, a randomized trial reported only in abstract, in which 75 hypoglycemic babies on the first day after birth were randomized to a feed or feed plus dextrose gel 400 mg/kg, showed no differences in blood glucose concentrations 15 and 30 minutes after treatment. Further, formula fed babies randomized to the dextrose gel group suckled a smaller volume during the subsequent feed.[20] Therefore, the role of dextrose gel in the management of neonatal hypoglycemia remains unclear.

We sought to determine whether treatment with 40% dextrose gel is more effective than feeding alone in reversing neonatal hypoglycemia in at-risk late preterm and term babies in the first 48 hours after birth.

Methods

Participants

Eligible babies were born at Waikato Women's Hospital, a tertiary referral centre, ≥35 weeks' gestation, ≤48 hours old and identified as being at risk of neonatal hypoglycemia. Risk factors included being the infant of a diabetic mother (gestational, type I or type II diabetes); preterm (35 or 36 completed weeks' gestation); small (birthweight <10th centile or <2,500 g) or large (birthweight > 90th centile or > 4,500 g); or other reasons such as poor feeding. Exclusion criteria included any prior treatment for neonatal hypoglycemia, serious congenital

malformation, terminal conditions or skin abnormalities which would prevent use of the continuous glucose monitor.

Women identified as likely to give birth to an eligible baby were approached by a researcher prior to birth; those not recruited before birth were approached as soon as possible after the birth. The study was approved by the Northern Y Ethics Committee, and written informed consent was obtained from the mothers. The full study protocol is available at http://hdl.handle.net/2292/20460.

Procedures

Blood glucose concentrations were measured according to current clinical guidelines in our hospital[21] on samples obtained by heel lances at one hour after birth, then three to four hourly before feeds for the first 24 hours, then six to eight hourly for the subsequent 24 hours. All blood glucose concentrations were measured using the glucose oxidase method (Radiometer, ABL800Flex, Copenhagen, Denmark, reading range 0·0 to 60 mmol/L, coefficient of variation 2·1%).

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 hours or up to seven days until there was no longer clinical concern about hypoglycemia. These monitors have been shown to be 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 influenced by the results.

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

Randomization and masking

Babies who became hypoglycemic were randomized to either the dextrose or placebo gel treatment group by computer-generated random-number allocation using a balanced block design with variable block sizes and stratified by maternal diabetes (yes or no) and birth weight (small, appropriate, or large). Twins were randomized independently. The researcher entered demographic data into a computer that provided a randomization number corresponding to a numbered treatment pack containing six labeled syringes, each containing three ml of the same gel: either 40% dextrose gel or identical appearing 2% carboxymethyl cellulose placebo gel. Study packs were prepared by the hospital pharmacist, who was the only person holding the randomization schedule. Clinicians, families and researchers all remained unaware of the treatment group allocation until the data analysis was complete.

The researcher or midwife dried the baby's mouth with gauze, 0·5 ml/kg (200 mg/kg) gel was massaged into the buccal mucosa, and the baby was encouraged to feed. If feeding was poor, expressed breast milk or formula was given via syringe, according to maternal wishes. The blood glucose concentration was measured 30 minutes after

gel administration and if the baby remained hypoglycemic, or hypoglycemia recurred later, treatment was repeated using another syringe from the allocated pack. Up to six doses of gel could be administered over 48 hours.

Outcomes and Analysis

The primary outcome was treatment failure, defined as a blood glucose concentration <2·6 mmol/L 30 minutes after the second of two doses of gel. Secondary outcomes were admission to NICU; frequency of breast feeding, total volume and frequency of expressed breast milk and infant formula; intravenous dextrose; and dextrose gel in the first 48 hours; method of feeding two weeks after birth; incidence of rebound and recurrent hypoglycemia after successful treatment; time taken to achieve interstitial glucose ≥2·6 mmol/L following treatment; and total duration of interstitial glucose <2·6 mmol/L up to 48 hours after birth.

Hypoglycemia was defined as a blood or interstitial glucose concentration <2·6 mmol/L, which was the current accepted clinical threshold for treatment [6] and the threshold for treatment used in our hospital. Episodes of hypoglycemia were defined as one or more consecutive blood glucose concentrations <2·6 mmol/L or two or more consecutive interstitial glucose concentrations <2·6 mmol/L. Rebound hypoglycemia was defined as an episode of hypoglycemia within six hours following successful treatment (blood or interstitial glucose ≥2·6 mmol/L for ≥1 hour following treatment). Recurrent hypoglycemia was defined as a further episode of hypoglycemia following successful treatment, within 48 hours after birth.

Babies who failed treatment and remained hypoglycemic were admitted to the NICU and treated with open labeled dextrose gel, infant formula and or intravenous dextrose according to clinical guidelines and clinician preference.

Power calculation

A retrospective review of 91 babies at risk of neonatal hypoglycemia born at our hospital in 2006 found that 51 (56%) became hypoglycaemic, and of these nine (20%) remained hypoglycemic after two doses of dextrose gel. The study was planned as a superiority trial with a one-tailed design (alpha = 0·05, beta = 0·2), and allowing for 5% withdrawals, a sample size of 230 (115 in each group) was anticipated to detect a reduction in the rate of treatment failure from 35% in the placebo group to 20% in the dextrose gel group.

Data monitoring

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

Statistical analysis

Data from the interstitial glucose monitors were downloaded using CGMS® system solutions™ software version 3·0C, (CGMS® system gold™ Medtronic, MiniMed, Northridge, CA, USA) and recalibrated using a previously reported algorithm [24] to

optimise accuracy at low blood glucose concentrations using Matlab™ Version 7.14 2012a (The Mathworks; Natick, MA).

During the preparation of the data analysis plan, and prior to unblinded analysis it was recommended that a standard two-sided analysis be performed . Statistical analyses were on an intention to treat basis, and babies for whom primary outcome data were not available were allocated the conservative outcome of treatment failure. Data were analysed using SAS Enterprise Guide® Version 4·3 2010 (SAS Institute Inc©,Cary, NC) and are presented as median (range), mean (SD), relative risk (RR) or median difference and 95% confidence intervals (CI). Normally distributed continuous variables were analysed with t-tests; otherwise a Wilcoxon two sample test was used. Feeding at two weeks of age was analysed using an unordered generalised logistic regression with breast milk as the reference group. Rates of rebound and recurrent hypoglycemia were compared between groups using rate ratios, calculated using OpenEpi Version 2.3.1.[25] Primary outcome was adjusted for the reasons the baby was anticipated to be at risk of hypoglycaemia (maternal diabetes (yes or no) and birth weight (small, appropriate, or large)) since randomization was balanced across these risk categories. No other outcomes were adjusted.

Role of the funding source

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

Results

Between December 2008 and November 2010, we approached 1002 women, of whom 588 (59%) gave consent for their baby's participation. Seventy-four of their babies were not enrolled for reasons including not meeting study eligibility criteria after birth, consent withdrawal, not born at our hospital, or researchers not notified in time (Figure 1). Of the 514 babies enrolled, 242 (47%) became hypoglycemic and were randomized. Five babies were randomized in error (four treated prior to randomization and one randomized at 50 hours of age), leaving 237 babies; 118 allocated to dextrose, and 119 allocated to placebo gel.

Demographic variables were similar in babies and their mothers who were enrolled but not randomized because they did not become hypoglycemic (data not shown), and in those randomized to dextrose and placebo gel groups, although more boys were randomized to the placebo group (55 vs. 41%)(Table 1). Risk factors for hypoglycemia were also similar in both groups. Similar proportions of mothers in both groups did not know which treatment their baby received (85/112, 76% in dextrose vs 87/114, 76% in placebo gel group) or thought their baby received dextrose gel (25/112, 22% in dextrose vs 26/114, 23% in placebo gel group), showing that masking was successful.

Table 1 Characteristics of mothers and babies at trial entry

Maternal characteristics *	Dextrose gel	Placebo gel
	n =115 (50)	N = 115 (50)
Maternal age (y)	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/m^2)	27 (16 - 56)	26 (19 - 66)
Weight change during pregnancy (kg)	12.2 (8.0)	11.7 (6.8)
Diabetic women	46 (40)	46 (40)
Intended method of feeding		
Breast	114 (99)	109 (95)
Infant formula	1 (1)	2 (2)
Combination	0 (0)	4 (3)
Expressed breast milk prior to birth	24 (21)	23 (20)
Baby characteristics (n)	118	119
Male	48 (41)	65 (55)
Birth weight (g)	3091 (824)	3031 (782)
Gestation (wk)	37·4 (1·6)	37·2 (1·6)
Singleton	100 (85)	99 (83)
Vaginal birth	73 (62)	74 (62)
Apgar score at five min < 5	0	0
Blood glucose concentration at time of randomization (mmol/L)	2·2 (1·1 - 2·5)	2·2 (0·9 - 2·5)
Ethnicity		
New Zealand European	63 (53)	64 (54)
Maori	34 (29)	37 (31)
Other	21 (18)	18 (15)
Identified Risk factors for neonatal hypoglycemia †		
Infant of diabetic mother	46 (39)	46 (39)
Late preterm (35 or 36 weeks)	41 (35)	49 (41)
Birth weight < 2500 g	30 (25)	32 (27)
Birth weight > 4500 g	12 (10)	10 (8)
Birth weight < 10th centile	13 (11)	19 (16)
Birth weight > 90th centile	26 (22)	27 (23)
Other	6 (5)	4 (3)

* 3 mothers appear in both columns because one twin was randomized to each treatment group, n= 227 mothers

† many babies had more than one risk factor for hypoglycemia

Values are number (%), mean (SD) or median (range)

There were 432 doses of study gel administered, 215 in the dextrose and 217 in the placebo gel group. In both groups babies received a median of two doses of study gel of similar volume, resulting in those randomized to dextrose gel receiving a median of 0·3 (0·2 to 1·0) g/kg dextrose (Table 2).

Primary and Secondary Outcomes

Primary outcome data were available for 116/118 babies (98%) in the dextrose and 118/119 (99%) in the placebo gel group. Fewer babies in the dextrose group than in the placebo group met the criteria for treatment failure; (16/118 (14%) in the dextrose and 29/119 (24%) in the placebo group RR 0·57; 95% CI 0·33 to 0·98; p=0·04) (Table 2).

Overall 100/237 babies (42%) were admitted to NICU, 46/100 of these (46%) for treatment of hypoglycemia. NICU admission rates were similar in both treatment groups, but babies who received dextrose gel were less likely to be admitted for hypoglycemia (16/118 (14%) vs. 30/119 (25%), RR 0.54; CI 0.31 to 0.93; p=0.03).

Forty babies (17%) required additional treatment with dextrose. Babies randomized to dextrose gel were less likely to receive additional dextrose (12/118 (10%) vs. 28/119 (24%), RR 0·43; CI 0·23 to 0·81; p=0·01), but those who did receive intravenous dextrose received similar amounts (Table 2).

Table 2: Primary and Secondary Outcomes in babies randomized to dextrose or placebo gel

	Dextrose gel	Placebo gel	Relative risk or median difference	95% Confidence intervals	p value
Babies (n)	118 (50)	119 (50)			
Volume of study gel	0·84	0·97	0·005	-0·01 - 0·02	0·45
(ml/kg)	(0·43 - 2·44)	(0·47 - 2·49)			
Treatment failure	16 (14)	29 (24)	0·57	0·33 - 0·98	0·04
Dextrose administered as					
Study gel					
Babies (n)	118	119			
(g/kg)	0.3	0			
	(0·2 - 1·0)				
*Open label gel**					
Babies (n)	6 (5)	13 (11)	0·47	0·18 - 1·18	0·15
(g/kg)	0·2	0·4	0·14	0·00 - 0·20	0·10
	(0·1 - 0·4)	(0·2 - 0·6)			
Intravenous bolus					
Babies (n)	7 (6)	13 (11)	0.54	0·23 - 1·31	0·24
(g/kg)	0·2	0·2	0·0001	-0·004 - 0·20	0·96
	(0·2 - 0·2)	(0·1 - 1·0)			
Intravenous infusion					
Babies (n)	8 (7)	17 (14)	0·47	0·21 - 1.06	0·09
(g/kg)	6·7	7·7	2·12	-0·42 - 5·58	0·10
	(2·0 - 10·6)	(3·7 - 14·6)			
Total Intravenous	7·1	8·3	2·55	0·50 - 5·84	0·09
dextrose (g/kg)	(2·5 - 10·8)	(4·2 - 16·2)			
Total dextrose from sources other than study gel[†]					
Babies (n)	12 (10)	28 (24)	0·43	0·23 - 0·81	0·01
(g/kg)	4·5	6·6	0·20	-2·1 - 5·5	0·51
	(0·2 - 10·8)	(0·2 - 16·2)			
Total dextrose from all sources					
Babies (n)	118 (100)	119 (100)			
(g/kg)	0·3	0·0	0·20	0·19 - 0·23	<·0001
	(0·2 - 11·4)	(0·0 - 16·2)			
Feeding					

Breast feeding	112 (95)	113 (95)	1·00	0·94 - 1·06	0·99
Babies (n)					
Feeds per baby	13	11	-1·00	-3·00 - 0·00	0·16
	(1 - 29)	(1 - 24)			
Expressed breast milk	100 (85)	97 (82)	1·04	0·93 - 1·17	0·60
Babies (n)					
Feeds per baby	4	6	1·00	0·00 - 2·00	0·02
	(1 - 15)	(1 - 16)			
Volume (ml/kg)	2·4	4·7	1·07	0·14 - 2·37	0·03
	(0·1 - 96·1)	(0·0 - 43·6)			
Infant formula	68 (58)	72 (60)	0.95	0·77 - 1·18	0·69
Babies (n)					
Feeds per baby	7	10	2·00	0·00 - 4·00	0·04
	(1 - 21)	(1 - 24)			
Volume (ml/kg)	41	58	11·06	-3·01 - 26·89	0·14
	(1 - 162)	(2 - 208)			
Admitted to NICU					
Babies (n)	45 (38)	55 (46)	0·83	0·61 - 1·11	0·24
For hypoglycemia (n)	16 (14)	30 (25)	0·54	0·31 - 0·93	0·03

Values are number (%), median (range), relative risk or median difference and 95% confidence intervals

* 40% dextrose gel given according to usual clinical guidelines after the baby had failed treatment.

† Includes open label gel and intravenous dextrose.

Most mothers (98%) intended to breast feed, and 95% of babies were breast fed. Babies in the dextrose gel group received expressed breast milk less frequently than babies in the placebo group (median 4 vs. 6 feeds, median difference 1; 95% CI 0 to 2 feeds; p=0·02) and received a smaller volume of expressed breast milk (median 2·4 vs. 4·7 ml/kg; median difference 1·1; 95% CI 0·1 to 2·4 ml/kg; p=0·03). One hundred-forty babies (59%) received formula feeds, with babies in the dextrose gel group receiving fewer formula feeds (median 7 vs. 10 feeds; median difference 2; 95% CI 0 to 4 feeds; p=0·04) but there were no differences between groups in the volume of formula feeds. At two weeks of age fewer babies in the dextrose gel group were formula feeding (5/118 (4%) vs. 15/119 (13%), RR 0.34; 95% CI 0·13 to 0·90; p=0·03).

There were 175/237 (74%) babies with continuous glucose monitoring, 88/118 (75%) in the dextrose and 87/119 (73%) in the placebo gel group. However, there were only 76 gel treatments (38 in each group) that could be analysed for the secondary outcomes involving continuous glucose monitoring.

Episodes of rebound hypoglycemia were uncommon, and occurred with similar frequency in both groups (Table 3). Episodes of recurrent hypoglycemia were less common in babies randomized to dextrose gel than those randomized to placebo when measured by interstitial but not blood glucose concentrations (11 vs. 30 episodes, rate ratio 0·44, 95% CI 0·21-0·86; p=0·01). The time taken for interstitial glucose concentration to be restored was similar in both treatment groups (20·3 (0·2 to 215·4) min in the dextrose vs. 22·8 (1·9 to 165·2) min in the placebo group, median difference 4·9 min; 95% CI -4·4 to 19·4 min; p=0·13). The total duration of

low interstitial glucose concentrations was not significantly reduced by dextrose gel (Table 3).

Table 3

Rebound and recurrent hypoglycemia for babies randomized to dextrose or placebo gel

	Dextrose gel	Placebo gel	Rate ratio or median difference	95% Confidence Interval	p value
Blood glucose					
Babies (n)	118 (100)	119 (100)			
Rebound episodes					
Episodes per baby			1·46	0·67 - 3·26	0·33
nil	104 (88)	109 (92)			
one	12 (10)	9 (7)			
two	2 (2)	1 (1)			
Recurrent episodes					
Episodes per baby			0·89	0·55 - 1·44	0·66
nil	90 (76)	91 (76)			
one	23 (20)	22 (19)			
two	5 (4)	4 (3)			
≥ three	0 (0)	2 (2)			
Interstitial glucose					
Babies (n)	25 (21)	30 (25)			
Rebound episodes					
Episodes per baby			1·20	0·40 - 3·57	0·73
nil	20 (80)	25 (83)			
one	3 (12)	3 (10)			
two	2 (2)	2 (7)			
Recurrent episodes					
Episodes per baby			0·44	0·21 - 0·86	0·01
nil	16 (64)	18 (60)			
one	8 (32)	4 (13)			
two	0 (0)	3 (10)			
≥ three	1 (4)	5 (17)			
Duration of low interstitial glucose concentrations*					
Babies (n)	32 (27)	36 (30)			
Duration (min/baby)	81 (0-840)	164 (0-1064)	48	-7 - 124	0·23
Proportion of time (%)	3.0 (0·0 -31·8)	6·1 (0·0-37·9)	1·8	-0·2 - 4·6	0·13

*Over first 48 h after birth for babies with at least 40 h of satisfactory continuous glucose monitoring

Values are number (%) or median and 95% confidence intervals

The gel treatment was well tolerated, with similar numbers of doses reported as tolerated in both groups (213/215 (99%) dextrose and 211/217 (97%) placebo gel doses). Parents also reported the gel treatment was an acceptable and easy treatment for their babies (113/116 (97%) dextrose and 113/118 (96%) placebo gel group).

There were no serious adverse events. Three babies, all in the placebo group, each had one blood glucose concentration of 0·9 mmol/L. There were no other adverse events.

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

Discussion

We have shown that treatment with 40% dextrose gel is more effective than feeding alone in reversing neonatal hypoglycemia in at-risk late preterm and term babies in the first 48 hours after birth. Further, babies who received dextrose gel were less likely to be admitted to NICU for management of hypoglycemia, to receive additional dextrose, receive formula feeds, and to be formula fed at two weeks of age.

Dextrose gel did not increase the risk of rebound or recurrent hypoglycemia, was well tolerated and was not associated with adverse effects.

Dextrose gel has been recommended for the management of neonatal hypoglycemia[26] and there are anecdotal reports of improvement in blood glucose concentration following dextrose gel via the buccal mucosa.[18,19] However, the only randomized trial reported that in babies admitted to neonatal intensive care, treatment with dextrose gel 400 mg/kg did not increase blood glucose concentrations.[20] Our study is the first report in babies showing that buccal dextrose gel is a safe effective treatment for the management of hypoglycemia (Panel).

One early concern was the possibility that dextrose gel may adversely affect breast feeding, since receipt of any supplements in the neonatal period is reported both to delay the establishment of and decrease the duration of breast feeding.[27,28] However, our data show that babies in the dextrose gel group required fewer formula feeds and less expressed breast milk. If the mother's intention was to breast feed and the baby was hypoglycemic, mothers were encouraged either to feed the baby or express breast milk. Some women may have felt pressured to provide breast milk, which may have negatively affected the establishment of breast feeding. Furthermore, fewer babies in the dextrose gel group received additional dextrose, either intravenously or as open label gel following treatment failure. 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 may have contributed to our finding that at two weeks of age formula feeding was less common in babies randomized to receive dextrose gel. We speculate that providing a

treatment which allows the mother and baby to remain together while supporting metabolic transition to extra-uterine life may reduce maternal anxiety and support breast feeding establishment in the early post-natal period.

Perhaps surprisingly, continuous glucose monitoring data showed that the time taken for the interstitial glucose concentration to recover following 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 of the treatment episodes were available for analysis. There were two reasons for this. Firstly, although the continuous glucose monitor was placed as soon after birth as possible, it takes one hour to initialise. This meant that in 152 cases the first gel treatment was given before continuous glucose data were available. Secondly, there were 24 episodes of hypoglycemia when, although the blood and interstitial glucose concentrations were <2.6 mmol/L at the time of diagnosis of the hypoglycemic episode, the interstitial glucose concentration was ≥2.6 mmol/L at the time of gel administration and therefore the secondary outcomes could not be determined.

One potential risk of administering dextrose gel is the possibility of causing rebound hypoglycemia secondary to stimulation of insulin secretion. Lilen and colleagues reported that a mini-bolus of 200 mg/kg intravenous dextrose improved blood glucose concentrations without hyperglycemia.[15] We chose the same dose for buccal glucose administration, and also found that rebound hypoglycemia was uncommon and occurred with similar frequency in both groups. However, consistent with the overall findings that dextrose gel reduced treatment failure, recurrent hypoglycemia was less common in babies who received dextrose gel when measured by

continuous interstitial glucose monitoring, despite these babies receiving less frequent feeds. Furthermore, babies who received dextrose gel appeared to spend less time hypoglycemic overall than babies who received placebo gel, although this finding did not reach statistical significance.

Babies enrolled in this trial were similar to the majority of babies who are at risk of hypoglycemia in the immediate neonatal period. Although dextrose gel did not decrease admission to NICU in this study, most likely because babies were admitted for a variety of reasons other than hypoglycemia, it did reduce admission for hypoglycemia. This suggests that, in babies at risk of hypoglycemia but without other co-morbidities, dextrose gel treatment may potentially avert the need for NICU admission, reducing costs and keeping mother and baby together. We cannot extrapolate from our data whether dextrose gel may be effective treatment in babies of other gestational or postnatal ages. Neither can we determine if the dose we have used is the ideal dose. Further randomized studies are needed to clarify these issues.

Dextrose gel treatment has a number of 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 approximately US $70/100 ml or $2 per baby, can easily be made in the hospital pharmacy, and is stable at room temperature. Therefore, dextrose gel may also be useful in resource-poor settings where hypoglycemia is common and under diagnosed.[8,9,29]

We have shown that dextrose gel is an effective, well tolerated and acceptable treatment for neonatal hypoglycemia. Dextrose gel should be considered for first line management of late preterm and term hypoglycemic babies in the first 48 hours after birth.

Research in context panel.

Systematic Review

We searched Pubmed and CNAHL plus using keywords infant/newborn, hypoglycemia, glucose, buccal, sublingual, treatment, Hypostop to 1 May 2013. Our search did not reveal any systematic reviews of this treatment. The only randomized trial, available only in abstract, reported that treatment of babies admitted to neonatal intensive care with dextrose gel 400 mg/kg did not increase blood glucose concentrations, although with 75 babies randomized there was limited power to detect relevant clinical outcomes[20].

Interpretation

Treatment with 40% dextrose gel 200mg/kg is more effective than feeding alone in reversing neonatal hypoglycemia in at-risk late preterm and term babies in the first 48 hours after birth. This treatment may help avoid admission to NICU in babies not requiring admission for other reasons, and appears to support breast feeding, in part by reducing the use of formula in the neonatal period. Dextrose gel did not increase the risk of rebound or recurrent hypoglycemia, was well tolerated and was not associated with adverse effects. Since this treatment is also inexpensive and simple to administer, it should be considered for first line management of late preterm and term hypoglycemic babies in the first 48 hours after birth.

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Conflicts of interests

The authors have no conflicts of interest to declare.

Authors' contributions

Deborah Harris contributed to the literature search, study design, data collection, analysis and interpretation. Deborah wrote the first draft of the manuscript and contributed to the subsequent revisions.

Philip Weston contributed to the study design, data collection, analysis and interpretation and the final manuscript.

Matthew Signal contributed to the data analysis and interpretation of the continuous glucose monitoring data, and the final manuscript.

Geoffery Chase contributed to the data analysis and interpretation of the continuous glucose monitoring data, and the final manuscript.

Jane Harding contributed to the study design, data analysis and interpretation, contributed to writing all versions of the manuscript and held overall responsibility for the Sugar Babies Study.

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