The Sugar Babies Study
Clinical Protocol

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Background

Neonatal hypoglycaemia (low blood sugar level) is a common problem and the only known common preventable cause of brain damage in the newborn period.[1, 2] Hypoglycaemia is most common in the first twenty four hours after birth, and is a common reason for admission to the Newborn Intensive Care Unit. The exact incidence is difficult to establish due to the varying criteria used to screen for and define hypoglycaemia.[3] There are groups of babies who are at greater risk of neonatal hypoglycaemia, including infants of diabetic mothers, growth restricted, small for gestational age (< 2500 g) and large for gestational age babies (> 4500 g).[4-6]

After a baby is born the blood glucose levels fluctuate as the baby adapts from continuous intravenous glucose supply from the placenta to the intermittent, fat-based enteral nutrient supply after birth. In clinical practice, blood glucose levels are measured in at-risk babies intermittently, commonly 3-4 hourly. However these intermittent blood tests may easily miss significant periods of low blood glucose levels, for example before feeds. Thus, it is possible that some infants with hypoglycaemia that may threaten brain function are not identified, or, alternatively, that some babies with only an occasional brief fall in blood glucose levels are at no risk of impaired brain function but are inappropriately and invasively treated. In diabetic patients, continuous monitoring of blood glucose levels can lead to improved metabolic control. [7] Continuous glucose monitoring has been shown to be safe in preterm babies [8] but its role in the management of neonatal hypoglycaemia has not yet been determined. The vast majority of neonatal hypoglycaemia is transient and is the result of delayed metabolic adaption following birth.

There has been controversy regarding the blood glucose level at which treatment should be provided to a baby. One of the reasons for the controversy is that it remains unclear how low the blood glucose level or for how long the blood glucose level needs to be below a certain value, before neurological damage occurs. Blood glucose levels below 2.6 mmol/l are generally accepted as requiring treatment. [3] Blood glucose levels below 2.6 mmol/l may increase the likelihood of neurological damage.[9, 10] However, once diagnosed, the best treatment for hypoglycaemia also remains unclear.

Current treatment choices vary depending on the baby's birthweight, gestational age, and associated risk factors. If the baby is able to feed, then initial treatment focuses on encouraging feeding. However, if the blood glucose level does not increase or the baby has difficulty with feeding then admission to the newborn intensive care unit is usually indicated. Standard clinical practice in the newborn intensive care unit can include breast feeds, additional feeding with infant formula, intravenous dextrose, or specific medications such as glucagon. However, ideal treatment would keep the mother and baby together wherever possible, optimise the establishment of breast feeding and support the metabolic transition.

There have been few studies investigating the best treatment for neonatal hypoglycaemia. Two studies performed in India aimed to prevent neonatal hypoglycaemia in both small- and large-for-gestation babies. All the babies were bottle fed and randomised to either receive standard formula or standard formula plus added powdered sugar (1.5 g added to each 30 ml formula). Both studies showed that with the additional carbohydrate the incidence of neonatal hypoglycaemia was significantly reduced.[11, 12] However, formula feeding is not the most common or the preferred method of feeding babies in New Zealand.

If additional feeding does not reverse hypoglycaemia, intravenous dextrose is a common next standard treatment. A recommended regimen includes a bolus of 200 mg/kg of glucose (2 ml/kg of dextrose 10%) followed by an infusion of 8 mg/kg.min. [13] This treatment has been shown to improve the blood glucose level without unnecessary hyperglycaemia. [13]

Another less commonly used treatment is 40% dextrose gel. Oral carbohydrate is first line treatment for low blood sugar levels in the conscious diabetic child or adult. [14] However the Waikato Newborn Intensive Care Unit is the only unit in Australasia to use dextrose gel for the management of hypoglycaemia. The dextrose is absorbed across the buccal membranes and is reported to increase the blood glucose level and reduce the need for intravenous glucose infusion. [15] The dose used (0.5 ml/kg or 200 mg/kg) is the same as that recommended for an intravenous bolus of dextrose.

Two studies regarding the use of dextrose gel have been reported in conference proceedings, although neither has been published in full. The first study was observational and reported using a dose of 0.5 ml/kg in 14 babies. There was a mean increase in blood glucose levels of 1.8 mmol/l twenty minutes after administration. [16] The second study randomised 75 babies ≥ 36 weeks gestation who had blood glucose levels <2.5 mmol/l to either feeding or feeding plus 40% dextrose gel 1 ml/kg. The authors reported no differences in blood glucose levels in either group at 15 or 30 minutes after treatment. However, in bottle feed babies, the volume of the subsequent feed was significantly reduced after dextrose gel. [17] Therefore, the role of dextrose gel in the management of hypoglycaemia remains unclear.

We therefore propose a randomised double blind placebo controlled trial to investigate the effectiveness of 40% dextrose gel as a treatment for hypoglycaemia in term and near term newborn infants.

Aim

To determine whether treatment with 40% dextrose gel is more effective than feeding alone in reversing neonatal hypoglycaemia in term and near term babies in the first 48 hours after birth.

Hypothesis

1. That 40% dextrose gel is more effective than feeding alone in reversing neonatal hypoglycaemia.

2. That intermittent blood glucose monitoring does not detect all episodes of hypoglycaemia.

Primary Outcome

Treatment failure, defined as a blood glucose level < 2.6 mmol/l 30 minutes after the second of two treatment attempts.

Secondary Outcomes

- The time taken to achieve an interstitial glucose level above 2.6 mmol/l for >1 hour.
- Incidence of recurrent hypoglycaemia (blood or interstitial glucose concentration <2.6 mmol/l) after initial successful treatment (defined as blood or interstitial glucose concentration > 2.6 mmol/l for >1 hour after initial treatment).
- Total duration of interstitial glucose levels < 2.6 mmol/l.
- Incidence of admission to the neonatal intensive care unit
- Frequency and total volume of formula administered in the first 48 hours
- Frequency and total volume of expressed breast milk administered in the first 48 hours
- Total dose of dextrose gel administered
- Incidence and total dose of intravenous dextrose administered in the first 48 hours
- Rate of full breast feeding at two weeks of age
- Mothers' experience of having a baby in the Sugar Babies Study

Study Design

Randomised, placebo controlled, double-blinded study in hypoglycaemic near-term and term babies, comparing the incidence of treatment failure in babies randomised to receive either 40% dextrose gel (BioMed New Zealand Limited), or a placebo vehicle gel (Carboxymethyl cellulose 2%).

Inclusion Criteria

- 35 weeks gestation or greater
- Age < 48 hours after birth
- Parental written informed consent

Exclusion Criteria

- Serious congenital malformations
- Terminal conditions
- Abnormalities of the skin or lesions which prevent application of the continuous glucose sensor monitor
- Prior administration of dextrose gel or medications for the management of neonatal hypoglycaemia
- Administration of intravenous dextrose or other treatments likely to affect blood glucose levels

Recruitment

Wherever possible at risk babies will be identified before birth and their parents invited to take part:

- Small for gestational age (estimated fetal weight <10th centile)
- Large for gestational age (estimated fetal weight > 90th centile)
- Estimated fetal weight < 2.5 kg or greater than > 4.5 kg
- Diabetic mothers

Additional at risk babies will be identified after birth including:

- Small for gestational age (birth weight <10th centile)
- Large for gestational age (birth weight > 90th centile)
- Birth weight < 2.5 kg or greater than > 4.5 kg
- Baby of diabetic mother
- Any baby thought to be at risk of hypoglycaemia for clinical reasons (eg not feeding well, possible symptoms)

Informed Consent

All parents identified before birth as expecting a baby at risk of hypoglycaemia will be provided with an information pamphlet in antenatal areas or delivery suite. After discussion with a member of the research team, written informed consent will be gained before birth whenever possible. When babies are identified after birth, a member of the research team will explain the study to the parents. After the parents have had time to consider the study, they will be asked for written informed consent. Parents may consent to take part in the study without giving consent for the continuous glucose sensor.

Methods

A continuous glucose sensor (CGMS® System Gold ™, Medtronic, Minimed®, Northridge, USA) will be inserted as soon as feasible after consent is obtained. Where consent is obtained before birth, the sensor will be inserted in delivery suite immediately after birth. The sensor will be secured with a Tegaderm™ transparent dressing.

The mother and baby will be encouraged to have skin to skin contact and breast feed on demand, consistent with the current Waikato guidelines for the management of a baby following birth. If a baby is not interested in breast feeding the mother will be encouraged to express breast milk which will be given via syringe to the baby. Babies who are to be formula fed will be offered a feed (60 ml/kg.day).on day one of life, increasing to 90ml/kg on day two. Where possible the volume of the fed taken will be recorded.

It is routine clinical practice for babies identified as at risk of neonatal hypoglycaemia to have blood taken by heel prick at one hour of age for measurement of blood glucose levels.[18]

Babies who become hypoglycaemic, defined as a blood glucose level < 2.6 mmol/l, measured on a blood gas analyser or laboratory autoanalyser at more than one hour after birth, will be fed, and in addition will be randomised to receive 40% dextrose gel or an identical appearing placebo gel.

The randomisation will be done by computer randomisation using a balanced block design with a variable block size, and stratified by risk factors (infant of a diabetic mother, small for gestational age or < 2.5 kg, large for gestational age or > 4500 g, other).

The researcher will access the randomisation number from a Sugar Babies Study computer programme. The number will correspond with previously prepared numbered pack containing six identical syringes of gel. The researcher will administer 0.5ml/kg of gel from one syringe. The syringe and any remaining gel will be returned to the pharmacy at the completion of the study.

Babies will have the inside of the mouth dried with gauze square. The gel (0.5 ml/kg) will then be massaged into the buccal (inside of cheek) membrane. The baby will then be fed (breast or formula, according to the parents' choice).

The blood glucose will be measured again 30 minutes after treatment.

If the blood glucose level is > 2.6mmol/l then blood glucose level monitoring will continue according to the current clinical protocol (three pre-feed blood glucose levels in 24 h).

If the blood glucose level remains < 2.6 mmol/l the treatment will be repeated using another syringe from the allocated treatment pack, and the blood glucose level measured again 30 minutes later. If hypoglycaemia persists,

this will be considered a treatment failure, and the baby will be reviewed by either the Neonatal Nurse Practitioner or Doctor on call for the Newborn Unit. Frequently the baby will require admission to the Newborn Intensive Care Unit for ongoing management. Babies in the study who require admission to the newborn intensive care unit for management of hypoglycaemia will have additional 0.8 ml of blood taken at this time and stored for later measurement of alternative cerebral fuels. This blood sample will be taken prior to any treatment for the management of hypoglycaemia in the nursery. All babies admitted to the Newborn Intensive Care Unit will receive the standard clinical care for the management of hypoglycaemia. This will mean that some babies may receive dextrose gel 40% as part of the clinical care.

If the blood glucose level rises to >2.6mmol after the initial one or two doses of gel, then later falls below 2.6mmol/l again, the treatment will be repeated as described above, using a further one or two syringes from the allocated treatment pack. Not more than six doses of gel may be administered in 48 hours.

The continuous glucose monitor will remain in place for 48 hours or until the baby is no longer being treated for hypoglycaemia if this is more than 48 hours. The baby will be able to leave the hospital with the continuous glucose monitor *in-situ*. Both the parents and lead maternity care provider will be taught how to monitor the continuous glucose monitor insertion site, and how to enter data into the continuous glucose monitor.

At the completion of the study the continuous glucose sensor will be removed from the baby's thigh using a Cavilon™ wand to reduce the discomfort associated with the removal of the dressing. Any remaining gel and syringes will be returned to the Pharmacist.

Clinical concern
If there is clinical concern about the baby, the baby will be admitted to the Newborn Intensive Care Unit for on-going treatment.

Withdrawal from the study
A baby will be withdrawn from the study if a member of the research team or medical specialist considers it medically necessary, or if the parents wish to withdraw the baby from the study. In the event of this happening the reason for withdrawal will be recorded.

Power calculation
A pilot study identified 91 babies at risk of neonatal hypoglycaemia born at Waikato Hospital between 1st January, 2006 and 30th April, 2006. Of these babies 51 (56%) became hypoglycaemic, and 9 (20%) of these babies remained hypoglycaemic following two doses of dextrose gel. It is predicted that the failure rate with placebo gel will be higher and clinically important if it is greater than 35%. Using a one tailed design with alpha at 0.05 and beta at 0.2, the sample size required is 109 babies in each group. Allowing for a five

percent withdrawal rate the sample size is required to be 115 babies in each group.

Analysis
Data will be analysed on an intention-to-treat basis. Prespecified subgroup analyses will be according to reason for risk of hypoglycaemia (SGA, LGA, baby of diabetic mother, other) and intended primary mode of feeding (breast or formula). Additional adjustment will be made for pre-randomisation perinatal risk factors that are not balanced between groups.

Study time table
The Sugar Babies Study commenced November 13th 2008. We expect the study to run for three years in order to achieve the numbers required.

Significance
Hypoglycaemia is very common in the newborn period. It is the most common cause of preventable brain damage in the newborn period. The diagnosis and management remain controversial. The majority of babies are admitted to the Newborn Intensive Care Unit for treatment. We hope to determine the effectiveness of an oral carbohydrate treatment regimen that will reverse hypoglycaemia and allow the mother and baby to remain together. This may result in improving the rate of breast feeding and decrease hospital costs

Sugar Babies Study Personnel

Steering Committee

The purpose of the steering committee is to manage every aspect of the Sugar Babies Study.

Members of the Steering Committee

- Professor Jane Harding: Professor of Neonatology, Liggins Institute, University of Auckland,
- Dr Phil Weston: Neonatologist, Waikato District Health Board
- Dr Malcolm Battin: Neonatologist, Newborn Services, Auckland City Hospital
- Deborah Harris: Neonatal Nurse Practitioner, Waikato District Health Board, and PhD student, Liggins Institute, University of Auckland,

Data Monitoring Committee

Terms of Reference

The purpose of the Data Monitoring Committee is to review the accumulating data and determine whether the Sugar Babies Study should continue or be discontinued. The reasons for stopping the trial earlier than planned may include evidence of benefit, evidence of harm and/or evidence of futility.

Members of the Data Monitoring Committee:

- Professor Caroline Crowther (Chair) Professor of Obstetrics and Gynaecology, University of Adelaide
- Associate Professor Frank Bloomfield: Associate Professor Neonatology, Liggins Institute, University of Auckland, and Neonatalogist, Newborn Services, Auckland City Hospital
- Dr David Graham: Paediatrician, Waikato District Health Board

The Data Monitoring Committee members are not study investigators nor have intellectual conflict of interests, which could impair his/her performance as part of the committee.

Meeting Schedule and Format

The Data Monitoring Committee will meet once, after 100 babies have been randomised.

Stopping Rules for Benefit

The standard stopping rules of O'Brien-Fleming will be used[19, 20] i.e. if the difference between the treatment and control group for the primary outcome shows a one-sided difference at $p < 0.005$.

Stopping Rules for Harm

The standard stopping rules of Fixed Nominal (Pocock)[20, 21] will be used i.e. if the difference between the treatment and control group for the primary outcome shows a one-sided difference at $p < 0.029$.

These stopping rules are provided as a guide for the Data Monitoring Committee. If the pre-determined statistical stopping boundary is crossed, the Data Monitoring Committee is required to make a wise judgement regarding whether to recommend stopping the Sugar Babies Study. This will be done after evaluation of the total evidence available and full assessment of the implications of stopping the study early.

The format of the meetings will be:

- Either by email correspondence, phone or face-to-face, as considered appropriate by the committee
- Confidential, between the Data Monitoring Committee members.

Extra open sessions can be arranged if the Data Monitoring Committee members require further information from the Steering Committee.
At these meetings, interim data analysis must remain confidential to the Data Monitoring Committee.

Interim Analysis

The pharmacist will be the only person who has access to the randomisation code. Therefore the pharmacist will prepare a report summarising the interim data of relevance to the Data Monitoring Committee. The report will identify the data only by groups A and B.

The researcher will inform the pharmacist of the primary outcome and any adverse events for each baby using the study number. The pharmacist will develop the Data Monitoring Committee report from these data (see attached draft report).
If the Data Monitoring Committee is considering recommending changes or early termination of the study, further data may be requested.

Safety Monitoring Committee

Terms of Reference

The purpose of the Safety Monitoring Committee is to review adverse events that occur during the study and determine whether such events may be associated with the Sugar Babies Study.

Members of the Safety Monitoring Committee:

- Associate Professor Frank Bloomfield: Associate Professor of Neonatology, Liggins Institute, University of Auckland, and Neonatologist, Newborn Services, Auckland City Hospital
- Dr David Graham: Paediatrician, Waikato District Health Board

Serious adverse events will be notified to the Safety Monitoring Committee by investigators within 48 hours of the event. The Safety Monitoring Committee will receive copies of all related documentation from the Investigators. The Safety Monitoring Committee is able to request further information as necessary.
Adverse events are to be reported to the Data Monitoring Committee.

Adverse events are:

Serious adverse events

- Death
- Seizures

Adverse events

- Severe hypoglycaemia (blood glucose level < 1 mmol/l)
- Hyperglycaemia (two consecutive blood glucose level > 8.0 mmol/l)
- Serious sepsis (proven by culture)
- Inflammation or swelling at insertion site of the continuous glucose sensor

The Safety Committee will report adverse events as

- Possibly related to the Sugar Babies Study
- Unrelated
- Not clear

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