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Complete List of Authors:	Laing, Don; The University of Auckland, Liggins Institute Walsh, Eamon; The University of Auckland, Liggins Institute Alsweiler, Jane; The University of Auckland, Paediatrics:Child and Youth Health; Starship Children's Health Hanning, Sara M; The University of Auckland, School of Pharmacy Meyer, Michael P.; The University of Auckland, Paediatrics: Child and Youth Health; Counties Manukau District Health Board, Kidz First Neonatal Care Ardern, Julena; Counties Manukau District Health Board, Kidz First Neonatal Care Cutfield, Wayne; The University of Auckland, Liggins Institute; Starship Children's Health Rogers, Jenny; The University of Auckland, Liggins Institute Gamble, Greg; The University of Auckland, Liggins Institute Chase, J; University of Canterbury, College of Engineering Harding, Jane; The University of Auckland, Liggins Institute McKinlay, Christopher; The University of Auckland, Liggins Institute; Counties Manukau District Health Board, Kidz First Neonatal Care
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Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) Study; a randomised controlled trial.

Authors:

Don Laing[1]*

Eamon Walsh[1]*

Jane M Alsweiler[2,3]

Sara M Hanning[4]

Michael P Meyer[2,5]

Julena Ardern[5]

Wayne S Cutfield[1]

Jenny Rogers[1]

Greg D Gamble[1]

Geoff J Chase[6]

Jane E Harding[1]

Christopher JD McKinlay[1,5]

*Joint first authors

1. Liggins Institute, University of Auckland, New Zealand
2. Department of Paediatrics: Child and Youth Health, University of Auckland, New Zealand
3. Starship Child Health, Auckland District Health Board, New Zealand
4. School of Pharmacy, University of Auckland, New Zealand
5. Kidz First Neonatal Care, Counties Manukau Health, Auckland, New Zealand
6. College of Engineering, University of Canterbury, Christchurch, New Zealand

Corresponding author: Christopher JD McKinlay +64274725099

c.mckinlay@auckland.ac.nz

Liggins Institute, University of Auckland, Private Bag 92019, Victoria Street West, Auckland 1142, New Zealand

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Article summary

Strengths and limitations of this study

- The NeoGluCO Study is investigating a new approach to the management of severe or recurrent transitional hypoglycaemia with early use of low-dose oral diazoxide.
- Strengths of the NeoGluCO Study are double blinding through use of a placebo, measurement of blood glucose concentrations by gas analyser, recruitment in the early newborn period and use of a bedside algorithm to titrate the intervention to maintain blood glucose concentrations within a normal range (2.6 to 5.4 mmol/L).
- A limitation of the study is that infants are only being recruited from neonatal units and the primary outcome is a short-term measure.
- Future trials will be needed to determine if early treatment of severe or recurrent transitional hypoglycaemia with diazoxide reduces neonatal admission and long-term neurodevelopmental impairment.

Abstract

Introduction: Infants with severe or recurrent transitional hypoglycaemia continue to have high rates of adverse neurological outcome and new treatment approaches are needed that target the underlying pathophysiology. Diazoxide is one such treatment that acts on the pancreatic β-cell in a dose-dependent manner to decrease insulin secretion.

Methods and analysis: Phase IIB, double-blind, two-arm, parallel, randomised trial of diazoxide versus placebo in neonates ≥35 weeks' gestation for treatment of severe (blood glucose concentration [BGC] <1.2 mmol/L or BGC 1.2 to <2.0 mmol/L despite two doses of buccal dextrose gel and feeding in a single episode) or recurrent (≥3 episodes <2.6 mmol/L in 48 hours) transitional hypoglycaemia. Infants are loaded with diazoxide 5 mg/kg orally and then commenced on a maintenance dose of 1.5 mg/kg every 12 hours, or equal volume of placebo. The intervention is titrated from the third maintenance dose by protocol to target BGC in the range 2.6 to 5.4 mmol/L. The primary outcome is time to resolution of hypoglycaemia, defined as the first point at which the following criteria are met concurrently for ≥24 hours: no intravenous fluids, enteral bolus feeding and normoglycaemia. Groups will be compared for the primary outcome using Cox's proportional hazard regression analysis, expressed as adjusted hazards ratio with a 95% confidence interval.

Ethics and dissemination: This trial has been approved by the Health and Disability Ethics Committees of New Zealand (19CEN189). Findings will be disseminated in peer-reviewed journals, to clinicians and researchers at local and international conferences, and to the public.

Registration: 11 February 2020, ANZCTR12620000129987.

Introduction

At least 30% of all newborn infants are at risk of transitional hypoglycaemia or low blood glucose concentration (BGC) due to being born small, large, preterm, or the infant of a women with diabetes.[1] They require regular testing of BGC in the first 24 to 48 hours after birth and approximately 50% develop hypoglycaemia and require further testing and intervention. Optimal management of transitional neonatal hypoglycaemia is important not only because of its impact on breastfeeding,[2,3] and the use of health care resources,[4,5] but also because of the potential for hypoglycaemia to cause permanent brain injury. We have shown that infants with asymptomatic hypoglycaemia have a two- to three-fold increased likelihood of later neurocognitive difficulties by 4 to 5 years of age, especially of executive function and visual-motor integration.[6] These functions are critical for learning, and even brief transitional neonatal hypoglycaemia has been associated with a two-fold increased likelihood of poor school achievement.[7] Moreover, in moderately preterm infants, transitional hypoglycaemia is the main modifiable risk factor for developmental delay at preschool age.[8]

If oral dextrose gel and additional feeding do not correct hypoglycaemia or if there are recurrent episodes, infants are typically admitted to the neonatal unit for frequent or continuous feeding by gastric tube or intravenous dextrose, to correct BGC to a normal range.[1] These infants often have prolonged neonatal admission, ongoing hypoglycaemia despite the provision of intravenous fluids, and can be difficult to establish on enteral feeds due to glucose instability.[9] Even with standard management, infants with severe or recurrent transitional hypoglycaemia continue to have higher rates (approximately four-fold) of adverse neurological outcome.[10]

An important cause of severe or recurrent transitional hypoglycaemia is dysregulated insulin secretion, especially the inability to suppress insulin secretion at low BGC.[11,12] If insulin secretion remains inappropriately high during the transition period after birth, hepatic glucose output is inadequate for metabolic requirements, and hypoglycaemia ensues. Increasing delivery of exogenous glucose, either with formula or intravenous dextrose, may stimulate additional insulin secretion and cause ongoing suppression of endogenous glucose production, further delaying normal metabolic transition. Thus, alternative management strategies are needed for infants with severe or recurrent transitional hypoglycaemia that address the underlying pathophysiology and promote metabolic transition.

Diazoxide is one such potential treatment that acts on the pancreatic β cell in a dose-dependent manner to decrease insulin secretion by interacting with the sulfonylurea receptor (SUR1).[13]

Advantages of diazoxide include rapid onset of action, oral formulation, and low cost. Diazoxide has been used for many decades as first-line treatment for certain forms of congenital (genetic) hyperinsulinism with a good efficacy and safety profile, although reversable congestive heart failure has been occasionally reported with prolonged high-dose treatment.[14]

Diazoxide has also been used selectively in babies with transient hyperinsulinism. Hoe *et al.* described 21 hyperinsulinaemic babies without known genetic defect, 20 (95%) of whom were responsive to diazoxide (5 to 15 mg/kg/day), when commenced at a median age of 13 days.[15] Additionally, in a randomised trial of 30 small-for-gestational age (SGA) neonates with transient hyperinsulinism in the first 5 days of age, diazoxide at 6 to 12 mg/kg/day reduced the median time to achieve hypoglycaemic control (40 vs. 72 hours, P=0.02), the total duration of intravenous fluids (114 vs. 164 hours, P=0.04) and time to achieve full feeds (74 vs. 124 hours, P=0.02).[16] There were no apparent adverse events, although episodes of hyperglycaemia were not reported. Together these data suggest that diazoxide may have a role in early management of severe neonatal hypoglycaemia to reduce the need for intravenous glucose, shorten neonatal unit admissions and facilitate earlier introduction of enteral feeds.

We are therefore undertaking the Neonatal Glucose Care Optimisation (NeoGluCO) Study to determine if early use of low-dose oral diazoxide is beneficial for treatment of severe or recurrent transitional neonatal hypoglycaemia. This trial was registered with the Australian New Zealand Clinical Trials Registry on 11 February 2020 (ANZCTR12620000129987).

Aim

To determine if early use of diazoxide in late preterm and term neonates with severe or recurrent transitional hypoglycaemia reduces time to resolution of hypoglycaemia, defined as achieving enteral bolus feeding and normal BGC without intravenous fluids.

Hypothesis

Diazoxide therapy will improve glycaemic stability, allowing earlier weaning of intravenous fluids and establishment of enteral feeds.

Methods and analysis

Study design

The NeoGluCO Study is a phase IIB, double-blind, two-arm, parallel randomised trial of diazoxide versus placebo for treatment of severe or recurrent transitional hypoglycaemia in late preterm and term neonates.

Participants

Infants are eligible for this study if they are born at ≥35 weeks' gestation, are admitted to the neonatal care unit in the first week after birth with recurrent or severe hypoglycaemia, and their parents have provided informed written consent. Severe hypoglycaemia is defined as any BGC <1.2 mmol/L or BGC 1.2 to <2.0 mmol/L despite two doses of buccal dextrose gel and feeding in a single episode; recurrent hypoglycaemia is defined as ≥3 episodes (one or more consecutive BGC <2.6 mmol/L) of hypoglycaemia in 48 hours. Infants must also be receiving ongoing management for hypoglycaemia at the time of randomisation, e.g., intravenous dextrose, carbohydrate supplements, continuous or frequent feeding (≤2 hourly intervals), or inability to wean off formula due to hypoglycaemia. Eligibility is based on BGC measured by gas analyser (portable or laboratory) or plasma glucose concentration measured on a laboratory chemical analyser.

Infants are excluded if they have a confirmed major congenital malformation or chromosomal disorder, suspected genetic syndrome associated with hypoglycaemia, gastrointestinal disorder likely to affect feed tolerance, confirmed sepsis (culture of pathogenic organism from blood, cerebrospinal fluid or urine) or hypoxic-ischaemic encephalopathy; are planned or likely to have neonatal surgery; there is a family history of congenital hyperinsulinism; are suspected of suffering from an inborn error of metabolism; or are a triplet.

Recruitment, randomisation and allocation concealment

Recruitment commenced on 14 May 2020. Infants are being recruited at Middlemore Hospital, Counties Manukau Health, South Auckland and Auckland City Hospital, Auckland District Health Board, Auckland, New Zealand. These hospitals provide all tertiary neonatal services for the wider Auckland region. Infants are recruited after birth by investigators, study personnel and clinical staff. Following written, informed parental consent and once all eligibility criteria are met, infants are allocated via an online randomisation system (Clinical Data Research Hub,

Liggins Institute, University of Auckland) to one of two masked interventions, diazoxide or placebo. The allocation ratio is 1:1. The allocation sequence was computer-generated with random permuted blocks of 4 and 6, stratified by centre and SGA status (<10th customised centile).[17] Twins are individually randomised.

The interventions are provided in opaque bottles labelled with a four-digit random number. At randomisation, the system assigns the appropriate bottle number according to the allocation sequence. Only the data manager and trial pharmacists have access to the allocation sequence and know the content of bottles; study personnel, clinical staff and parents are blinded to the allocation.

Interventions

The active intervention is prepared by hospital trial pharmacists by adding five 100 mg diazoxide capsules to 50 ml of Ora Blend sugar free paediatric compounding solution, giving a concentration of 10 mg/ml. Infants are loaded with 5 mg/kg (0.5 ml/kg) orally or by gastric tube and then commenced on a maintenance dose of 1.5 mg/kg (0.15 ml/kg) every 12 h. The intervention is prescribed on hospital medication charts as "NeoGluCO study drug" in ml along with the bottle allocation number and is administered by hospital nurses or midwives. The active intervention is physically and chemically stable for up to 35 days at room temperature (25°) and when refrigerated (2°C to 8°C).

The maintenance dose is at the lower end of the range recommended in the New Zealand Formulary for Children. Although infants with congenital hyperinsulinism usually receive higher maintenance doses of 5 to 10 mg/kg/day, our clinical experience has shown that this dose is often too high for infants with transitional hypoglycaemia and may cause hyperglycaemia, whereas lower doses appear to be similarly efficacious but avoid high BGC. Adverse effects, such as congestive heart failure, are also likely to be rare with low-dose treatment.

A bedside algorithm is used to titrate the study drug according to BGC, commencing immediately before the third maintenance dose (Table 1**Error! Reference source not found.**). Once the primary outcome is reached, one further dose of study drug is given and then the intervention is discontinued. The intervention may also be stopped before the primary outcome is reached as per the titration protocol. Weekly dose adjustment for weight is made if required, once the infant returns to birthweight.

The control intervention consists of an equal volume of Ora Blend (0.5 ml/kg load, 0.15 ml/kg maintenance), combined with a small amount of cornstarch (4 g per 50 mL) to ensure that the placebo is identical in appearance to the diazoxide solution. The glucose load from the cornstarch is trivial (0.03 g per maintenance dose) and will not affect BGC. Dosing, administration and discontinuation is as per diazoxide.

Blinding

Tetrad testing was used to validate the comparability of the control and active interventions in 42 neonatal staff volunteers (36 females; 27 nurses).[18] Four bottles of study drug, two diazoxide and two placebo, were presented to the staff who were asked to examine the bottles and draw up the study drug into a clear syringe. Staff were then asked to group the bottles into two groups of two based on perceived similarities, after which staff were asked to identify the diazoxide and control pairs, using a forced-choice procedure. Only nine participants (21%) correctly paired the study interventions, corresponding to a Thurstonian effect size (95% CI) for sensory discrimination of 0.00 (0.00, 0.24).[19] This outcome indicates sensory equivalence of the interventions (an effect size ≤0.61 represents differences too small to be noticed).[20] Of those who identified the correct pairings, only two (22%) correctly identified the diazoxide pair, which is less than the percentage expected by chance alone of 50%.

Blood glucose target and monitoring

The target BGC range for infants in the NeoGluCO Study is 2.6 to 5.4 mmol/L, which represents the 10th and 90th centiles, respectively, over the first week in healthy breastfed infants.[21] Management decisions are based on BGC by gas analyser (portable or laboratory) or plasma glucose concentration by laboratory chemical analyser. Capillary, arterial, or venous blood samples are acceptable. Because gas analysers provide plasma-equivalent glucose concentration, whole-blood gas analyser and laboratory plasma measurements are used interchangeably without adjustment, and are referred to in this protocol as BGC.[22] BGC are measured at least every 6 hours (pre-feed if on enteral bolus feeding) until the primary outcome is reached. Once the primary outcome is achieved, BGC measurement frequency is at clinical discretion but is performed at least every 12 hours while the infant is receiving the intervention.

Episodes of hypoglycaemia after randomisation (BGC ≤2.5 mmol/L) are managed according to local practice, which could include buccal dextrose gel, increasing enteral feed volume or frequency, and starting or increasing intravenous dextrose fluids. If hypoglycaemia occurs after

the intervention titration algorithm has commenced (immediately before the third maintenance dose), the maintenance dose may be increased according to titration protocol (Table 1**Error! Reference source not found.**).

Wherever possible, episodes of elevated blood glucose (5.5 to 6.9 mmol/L) or hyperglycaemia (≥7 mmol/L)[23] will be avoided. If this occurs before commencing the intervention titration algorithm (immediately before the third maintenance dose) intravenous fluids are weaned by 50% or stopped, or if the infant is receiving formula while establishing breastfeeding, the supplementary feed volume is halved or stopped. Once the intervention titration algorithm has commenced, intravenous fluids and supplementary feeds are weaned as soon as possible.

Co-interventions

Management of fluids and feeding is as per local practice but with the aim of weaning intravenous fluids and introducing enteral feeds as soon as possible once BGC have stabilised.

Glucagon injections are to be used only in emergencies when intravenous access cannot be obtained and BGC persists <1.2 mmol/L. Glucagon infusions are not permitted. Glucocorticoids are not permitted for treatment of hypoglycaemia but may be used if deemed essential for management of other conditions, e.g., adrenal insufficiency.

Where possible, infants enrolled in the trial will have subcutaneous real-time continuous glucose monitoring (CGM) (Guardian Connect System, Enlite 3 sensor, Medtronic) to help identify the need for additional BGC testing (Supplement). The CGM is calibrated against BGC by gas analyser, four times in the first 24 hours, then every 12 hours while *in situ*.[24] Using Bluetooth transmission to a bedside tablet computer and remote cloud monitoring with text alerts, research staff will use pre-defined Trend Alarm criteria to inform the bedside nurse that a BGC measurement is indicated, i.e., sensor glucose concentration (SGC) is trending out of range (Table 3). Clinical management decisions are based solely on BGC. The CGM will remain in place for 24 hours after either discontinuation of the study drug or attainment of the primary outcome, whichever is longer, up to a maximum of 7 days. CGM alert and SGC data are recorded along with all BGC measurements for later agreement analysis.

All other neonatal care will occur according to local practice. Open label diazoxide may be considered in refractory cases once other management strategies have been maximised and after discussion with the attending neonatologist, site principal investigator and a paediatric endocrinologist. This requires unblinding of treatment allocation, which will generally not

occur before 2 weeks of age. If emergency unblinding occurs, the intervention will be revealed only to the senior medical staff caring for the infant. Study personnel collecting outcome data will remain blinded to intervention allocation.

Assessments

Demographic, obstetric and relevant family medical history are collected at study entry. Neonatal clinical data are obtained from the electronic health record and bedside charts. The study schedule is summarised in Table 2.

Blood is collected at baseline and sent to the hospital laboratories to measure plasma concentrations of insulin, beta-hydroxybutyrate, free fatty acids, creatinine, and blood gases. All infants will have a standard metabolic screen by Guthrie card at ≥48 hours. Additional heparinised blood is collected before the third study maintenance dose (36 hours after commencing the intervention) and plasma is stored for latter measurement of insulin, creatinine, and diazoxide concentrations.

To assess if low dose diazoxide has any effect on cardiac function, infants at the primary site (Middlemore Hospital) will undergo cardiac ultrasound at ≥72 hours after commencing the study intervention to assess a) ductal patency, flow and shunt; b) pulmonary arterial pressure; and c) cardiac function. Infants with suspected congestive heart failure will also undergo formal echocardiography.

Outcomes

The primary outcome is time to resolution of hypoglycaemia, defined as the first time point at which all of the following criteria are met concurrently:

- No intravenous fluids for ≥24 h (time recorded at the end of the 24-hour period).
- Enteral bolus feeding for ≥24 h defined as a) breastfeeding without supplements; or b) breastfeeding with supplements at >2 hourly intervals, or c) if not breastfeeding, gastric tube or bottle feeds at 3 to 4 hourly intervals (time recorded at the end of the 24-hour period).
- Normoglycaemia for ≥24 h, defined as a minimum of four pre-feed BGC in the target range of 2.6 to 5.4 mmol/L (last BGC measured within 4 hours of primary outcome

time point); four pre-feed BGC spanning >20 hours; no BGC out of range for ≥24 hours; time recorded at the end of the period).

The following secondary outcomes will be assessed from the time of randomisation:

- Time to achieve normoglycaemia (as per primary outcome)
- Time to establish enteral bolus feeding (as per primary outcome)
- Time to establish full sucking feeds defined as ≥five full breastfeeds (≥10 minutes) in 24 hours or ≥120 ml/kg/d of expressed breast milk or formula by bottle (up to discharge to home)
- Type of feeding at discharge from hospital and to home (breast milk, formula, mixed)
- Use of intravenous fluids and type
- Duration of intravenous fluids (up to discharge from hospital)
- Episodes of hypoglycaemia (BGC <2.6 mmol/L), elevated glucose concentration (BGC 5.5 to 6.9 mmol/L) and hyperglycaemia (BGC ≥7 mmol/L), including frequency, duration, timing and treatment before, during and after the episode (up to discharge from hospital)
- Number of blood glucose tests: during the study intervention and during hospital admission
- Duration of admission to first discharge home: neonatal care, postnatal ward, community birthing unit
- Duration of study intervention (up to discharge from hospital)
- Guthrie metabolic screen (≥48 hours from birth)
- Plasma insulin, creatinine and diazoxide concentrations at ≥36 hours after commencing the intervention
- Death (up to discharge from hospital)
- Seizures (total; presumed hypoglycaemic) (up to discharge from hospital)

- Discontinuation of study intervention due to elevated BGC or hyperglycaemia (up to discharge from hospital)
- Discontinuation of study intervention due to another adverse event (serious; non-serious) (up to discharge from hospital)
- Congestive heart failure (respiratory distress as evidenced by tachypnoea, recession, or use of oxygen or positive pressure support with consistent chest x-ray findings, including cardiomegaly, plethora, interstitial fluid or effusions) (up to discharge from hospital)
- Commencement of low flow oxygen or positive pressure respiratory support (up to discharge from hospital)
- Cardiac ultrasound (Middlemore Hospital) at (≥72 hours)
    - Ductus arteriosus: closed; trivial (<1.5 mm and a constricted pattern on Doppler); patent (≥1.5 mm, growing, pulsatile or bidirectional pattern on Doppler)
    - Pulmonary hypertension: pulmonary artery pressure ≥systemic as estimated by tricuspid regurgitant jet (RV-RA gradient +5 mmHg) or ductal shunt right to left (>20%) with characteristic pulmonary Doppler envelope (TPV/ RVET <20%)
    - Cardiac impairment: left ventricular internal diameter diastolic z-score >2 and reduced systolic function (fractional shortening <25% or myocardial performance index >0.41)

Data management

Web-based data management is provided by the Clinical Data Research Hub at the Liggins Institute, University of Auckland. This includes a bespoke online randomisation system, with intervention stock management, that is integrated with the REDCap system.[25] Study data are collected directly into electronic case record forms (eCRF). Range and logic checks are used to reduce data entry errors. CGM data are captured in a secure cloud account and subsequently uploaded to the REDCap system.

A data monitor checks all eCRF for completeness and logic errors, after which eCRFs are locked. If the data monitor identifies potential errors, an electronic query is raised and referred to the site for checking.

Statistical analysis

Data analysis will be performed in SAS 9.4 (SAS Institute). Customised birthweight centiles will be calculated using GROW software (Perinatal Institute, United Kingdom). Population z-scores for weight, length, and head circumference at birth will be calculated using UK-WHO centiles.[26]

Categorical data will be presented as number and percent, and continuous data as mean and standard deviation or median and inter-quartile range, as appropriate. Count data will be presented as median and inter-quartile range or grouped into ordinal categories. Denominators will be given for all outcomes.

In the primary analysis, intervention groups will be compared for the primary outcome using Cox's proportional hazard regression analysis, with treatment effect expressed as adjusted hazards ratio with a 95% confidence interval (CI). The analysis will be right censored at 4 weeks. Proportionality assumptions will be assessed by inspecting Kaplan-Meier curves and Schoenfeld residuals. Secondary outcomes will be compared between groups using generalised linear models (normal, binomial or Poisson) with treatment effect presented as adjusted odds ratio, count ratio, mean difference, or ratio of geometric means (positively skewed data), as appropriate, with 95% CI. Regression models will be adjusted for stratification variables (centre and customised birthweight centile, fixed effects), gestation length (fixed effect) and non-independence of multiples (random effect). If models fail to converge, the analysis algorithm will be optimised and the maximum number of iterations increased to get convergence with minimum Akaike Information Criteria (AIC). If this is unsuccessful, adjustment variables may be collapsed or excluded if necessary, for model convergence. For significance tests, the alpha level will be set at 0.05 (two-tailed). No adjustment will be made for multiple comparisons but results for secondary outcomes will be interpreted cautiously. All infants who meet eligibility will be included in the primary analysis (modified intention-to-treat analysis). Secondary exploratory analysis may include per protocol analysis of the primary outcome.

Sample size

A trial of 74 babies randomised in 1:1 ratio (37 per group) will give 80% power to detect a relative hazard of 2.0 (two-tailed alpha 0.05), assuming 90% of infants in each group have a primary outcome event within the study period (PASS Software 16). A hazard ratio of 2.0 indicates that the diazoxide group reaches the primary outcome at twice the rate (events per unit of time) of the control group. An adaptive sample size approach will be adopted where the number of randomised participants will be increased by the number of participants who withdraw or who are lost to follow-up.

Data and safety monitoring

An independent Data Monitoring and Safety Committee (DMSC) is monitoring recruitment, completeness of data acquisition and participant safety. The DMSC advises the Trial Steering Committee (TSC) on trial continuation or protocol modification. DMSC Terms of Reference were agreed before commencement of trial.

The following Serious Adverse Events (SAE) are reported to the DMSC for immediate review:

- Death
- Seizure
- Congestive heart failure
- Discontinuation of study intervention due to another serious adverse event, as judged by the site principal investigator or attending neonatologist (an adverse event is considered serious if it is immediately life-threatening, requires prolongation of hospitalisation or substantial escalation in care, or results in persistent or significant disability or incapacity)

SAE are reported until the time of primary hospital discharge. The TSC Chair notifies the DMSC Chair of all SAE within 72 hours of onset. The DMSC reviews SAE within 1 week of receiving the SAE report, to determine if participation in the trial is likely to be a causative factor and reports back to the TSC with the findings.

The DMSC will undertake an interim safety review when the primary outcome is known for 25% and 60% of participants, including rates of SAE and the following Adverse Events (AE) by masked treatment group:

- Hyperglycaemia (≥7 mmol/L)

- Discontinuation of study intervention due to elevated BGC (5.5 to 6.9 mmol/L) or hyperglycaemia
- Discontinuation of study intervention due to another adverse event (non-serious)
- Commencement of low flow oxygen or positive pressure respiratory support

There is no planned interim efficacy analysis.

Patient and public involvement

The NeoGluCO Study was presented and developed at an ON TRACK Network (https://ontrack.perinatalsociety.org.nz/) clinical trials workshop, Auckland, New Zealand in February 2020, which was attended by consumers, including parents of infants admitted to neonatal intensive care. Consumer input was received about study design and participant information.

Ethics and dissemination

Approval has been obtained from the Health and Disability Ethics Committees of New Zealand (reference 19CEN189) and by the local institutional research review committees at each centre.

The primary and secondary outcomes will be published in an international peer-reviewed journal and disseminated via presentations at local and international conferences to researchers and clinicians. A lay summary of the research findings will be made available to those parents who indicated a wish to receive these on their consent forms.

Data availability

For each main publication, the corresponding data set will be electronically archived with the Clinical Data Research Hub, Liggins Institute, University of Auckland. Anonymised data may be shared with external researchers upon request, according to the Data Sharing Protocol of Research Hub (https://wiki.auckland.ac.nz/display/ontrack/Data+Sharing).

Discussion

Despite current management, infants with severe or recurrent transitional hypoglycaemia continue to have higher rates (approximately four-fold) of adverse neurological outcome than at-risk infants without hypoglycaemia.[10] In addition, they often have prolonged neonatal admission, ongoing blood glucose instability despite the provision of intravenous fluids, and

can be difficult to establish on enteral feeds.[9] New treatment approaches are needed that target the underlying pathophysiology, especially dysregulated insulin secretion. A systematic review found low certainty evidence from one randomised trial that early use of diazoxide in SGA infants receiving intravenous dextrose for transitional neonatal hypoglycaemia decreased the duration of intravenous fluids and time to full enteral feeding by approximately 2 days.[27] The NeoGluCO Study will add to this evidence and determine if early use of low-dose oral diazoxide for severe or recurrent transitional hypoglycaemia in late preterm and term infants reduces time to resolution of hypoglycaemia.

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Author contributions

CJDM, DL conceived and developed the study design, drafted the original study protocol, approved the final study protocol and drafted and reviewed the article for publication. EW contributed to study design, approved the final study protocol and drafted and reviewed the article for publication. JMA, SMH, MPM, JA, WSC, JR, GJC and JEH contributed to the study design, approved the final version of the study protocol and reviewed the article for publication. GDG assisted with the sample size calculation and statistical analysis plan, contributed to study design, approved the final version of the study protocol and reviewed the article for publication.

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Competing interests

None

Patient consent for publication

Not required

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Table 1: Intervention bedside algorithm

BGC	Action
≤2.5 mmol/L	Increase maintenance dose to 0.25 ml/kg (diazoxide 2.5 mg/kg) every 12 h and adjust fluids and feeds as clinically appropriate. If hypoglycaemia persists after two doses of study drug at 0.25 ml/kg, increase maintenance dose to 0.5 ml/kg (diazoxide 5.0 mg/kg) every 12 h. If further hypoglycaemia occurs after 2 doses of study drug at 0.5 ml/kg, discuss with the site principal investigator and a paediatric endocrinologist. Consider congenital hyperinsulinism in refractory infants, in which case unblinding may be required.
2.6 to 5.4 mmol/L	Continue maintenance dose every 12 h while weaning intravenous fluids and grading up feeds. Give one more dose after the primary outcome point is reached.
5.5 to 6.9 mmol/L	If on intravenous dextrose, stop or wean fluids more rapidly. If on supplementary feeds (formula or EBM) and the mother is planning to breastfeed, stop or wean supplementary feeds. Withhold intervention dose. If glucose returns to the target range (2.6-5.4 mmol/L), recommence the next maintenance at 0.1 ml/kg (diazoxide 1 mg/kg) every 12 h. If glucose remains elevated for ≥12 h, discontinue the intervention.
≥7 mmol/L	Discontinue intervention; wean any intravenous dextrose

BGC, blood glucose concentration; EBM, expressed breast milk. The intervention algorithm commences before the third maintenance dose.

Table 2: Study schedule

TIMEPOINT	Pre-randomisation	Randomisation	*Week 1*	*Week 2-4*	*Discharge*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Baseline data	X				
Demographics and contacts	X				
Baseline metabolic bloods	X				
Allocation		X			
INTERVENTIONS:					
Study drug			X	±	
ASSESSMENTS:					
Continuous glucose monitor			X		
Primary outcome assessment			X	±	
Blood collection (≥36 hours)			X		
Echocardiogram (≥72 hours)			X		
Secondary outcome assessment			X	X	X

Table 3: Continuous glucose monitor trend alarms

Trend Alarm	Medtronic Guardian setting	Interpretation
Low	Low Alert SGC=3.1 mmol/L AND Fall Alert ≥1 for 10 min*	BGC expected to be 2.5 mmol/L
	Low Alert SGC=3.1 AND ≤2.5 mmol/L after 20 min**	BGC falling by 0.03 mmol/L/min
High	High Alert SGC=5.6 mmol/L AND Rise Alert ≥1 for 10 min*	BGC expected to be 6.2 mmol/L
	High Alert SGC=5.6 mmol/L AND ≥6.1 mmol/L after 20 min***	BGC rising by 0.03 mmol/L/min

SGC/BGC, sensor/blood glucose concentration. Medtronic Guardian provides an SGC reading ever 5 min. *Fall/Rise Alert 1 indicates SGC is changing by 0.06 mmol/L/min; Fall/Rise Alert 2 indicates SGC is changing by 0.11 mmol/L/min; Fall/Rise Alert 3 indicates SGC is changing by 0.17 mmol/L/min. **If the SGC is ≥2.6 after 20 min, no Trend Alert is signalled. Snooze time for device Low Alert set to 20 min. ***The BGC 97th percentile for healthy breastfed babies >72 h is 6.0 mmol/L.[21]

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Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) Study; a randomised controlled trial.

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Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) Study; a randomised controlled trial.

Authors:

Don Laing[1]*

Eamon Walsh[1]*

Jane M Alsweiler[2,3]

Sara M Hanning[4]

Michael P Meyer[2,5]

Julena Ardern[5]

Wayne S Cutfield[1]

Jenny Rogers[1]

Greg D Gamble[1]

J Geoff Chase[6]

Jane E Harding[1]

Christopher JD McKinlay[1,5]

*Joint first authors

1. Liggins Institute, University of Auckland, New Zealand
2. Department of Paediatrics: Child and Youth Health, University of Auckland, New Zealand
3. Starship Child Health, Auckland District Health Board, New Zealand
4. School of Pharmacy, University of Auckland, New Zealand
5. Kidz First Neonatal Care, Counties Manukau Health, Auckland, New Zealand
6. College of Engineering, University of Canterbury, Christchurch, New Zealand

Corresponding author: Christopher JD McKinlay +64274725099

c.mckinlay@auckland.ac.nz

Liggins Institute, University of Auckland, Private Bag 92019, Victoria Street West, Auckland 1142, New Zealand

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Abstract

Introduction: Infants with severe or recurrent transitional hypoglycaemia continue to have high rates of adverse neurological outcome and new treatment approaches are needed that target the underlying pathophysiology. Diazoxide is one such treatment that acts on the pancreatic β-cell in a dose-dependent manner to decrease insulin secretion.

Methods and analysis: Phase IIB, double-blind, two-arm, parallel, randomised trial of diazoxide versus placebo in neonates ≥35 weeks' gestation for treatment of severe (blood glucose concentration [BGC] <1.2 mmol/L or BGC 1.2 to <2.0 mmol/L despite two doses of buccal dextrose gel and feeding in a single episode) or recurrent (≥3 episodes <2.6 mmol/L in 48 hours) transitional hypoglycaemia. Infants are loaded with diazoxide 5 mg/kg orally and then commenced on a maintenance dose of 1.5 mg/kg every 12 hours, or equal volume of placebo. The intervention is titrated from the third maintenance dose by protocol to target BGC in the range 2.6 to 5.4 mmol/L. The primary outcome is time to resolution of hypoglycaemia, defined as the first point at which the following criteria are met concurrently for ≥24 hours: no intravenous fluids, enteral bolus feeding and normoglycaemia. Groups will be compared for the primary outcome using Cox's proportional hazard regression analysis, expressed as adjusted hazards ratio with a 95% confidence interval.

Ethics and dissemination: This trial has been approved by the Health and Disability Ethics Committees of New Zealand (19CEN189). Findings will be disseminated in peer-reviewed journals, to clinicians and researchers at local and international conferences, and to the public.

Registration: 11 February 2020, ACTRN12620000129987.

Strengths and limitations of study methods

- The main strength of the NeoGluCO Study is its two-arm, parallel, randomised, double-blind design, comparing low-dose diazoxide with placebo.
- The interventions have been shown to have sensory equivalence, thus enhancing blinding.
- Other strengths include measurement of all blood glucose concentrations by gas analyser and targeting of blood glucose concentrations within a normal range (2.6 to 5.4 mmol/L) rather than just a minimum threshold.

- The main limitation of the study is that the primary outcome is a short-term measure.
- Other limitations are that infants are only being recruited from neonatal units and the study will have inadequate power to assess rare side effects.

Introduction

At least 30% of all newborn infants are at risk of transitional hypoglycaemia or low blood glucose concentration (BGC) due to being born small, large, preterm, or the infant of a women with diabetes.[1,2] They require regular testing of BGC in the first 24 to 48 hours after birth and approximately 50% develop hypoglycaemia and require further testing and intervention. Optimal management of transitional neonatal hypoglycaemia is important not only because of its impact on breastfeeding,[3,4] and the use of health care resources,[5,6] but also because of the potential for hypoglycaemia to cause permanent brain injury. We have shown that infants with asymptomatic hypoglycaemia have a two- to three-fold increased likelihood of later neurocognitive difficulties by 4 to 5 years of age, especially of executive function and visual-motor integration.[7] These functions are critical for learning, and even brief transitional neonatal hypoglycaemia has been associated with a two-fold increased likelihood of poor school achievement.[8] Moreover, in moderately preterm infants, transitional hypoglycaemia is the main modifiable risk factor for developmental delay at preschool age.[9]

If oral dextrose gel and additional feeding do not correct hypoglycaemia or if there are recurrent episodes, infants are typically admitted to the neonatal unit for frequent or continuous feeding by gastric tube or intravenous dextrose, to correct BGC to a normal range.[1] These infants often have prolonged neonatal admission, ongoing hypoglycaemia despite the provision of intravenous fluids, and can be difficult to establish on enteral feeds due to glucose instability.[10] Even with standard management, infants with severe or recurrent transitional hypoglycaemia continue to have higher rates (approximately four-fold) of adverse neurological outcome.[11]

An important cause of severe or recurrent transitional hypoglycaemia is dysregulated insulin secretion, especially the inability to suppress insulin secretion at low BGC.[10,12,13] If insulin secretion remains inappropriately high during the transition period after birth, hepatic glucose output is inadequate for metabolic requirements, and hypoglycaemia ensues. Increasing delivery of exogenous glucose, either with formula or intravenous dextrose, may stimulate additional insulin secretion and cause ongoing suppression of endogenous glucose production, further delaying normal metabolic transition. Thus, alternative management strategies are needed for infants with severe or recurrent transitional hypoglycaemia that address the underlying pathophysiology and promote metabolic transition.

Diazoxide is one such potential treatment that acts on the pancreatic β cell in a dose-dependent manner to decrease insulin secretion by interacting with the sulfonylurea receptor (SUR1).[14]

Advantages of diazoxide include rapid onset of action, oral formulation, and low cost. Diazoxide has been used for many decades as first-line treatment for certain forms of congenital (genetic) hyperinsulinism with a good efficacy and safety profile, although reversable congestive heart failure has been occasionally reported with prolonged high-dose treatment.[15]

Diazoxide has also been used selectively in babies with transient hyperinsulinism. Hoe *et al.* described 21 hyperinsulinaemic babies without known genetic defect, 20 (95%) of whom were responsive to diazoxide (5 to 15 mg/kg/day), when commenced at a median age of 13 days.[16] Additionally, in a randomised trial of 30 small-for-gestational age (SGA) neonates with transient hyperinsulinism in the first 5 days of age, diazoxide at 6 to 12 mg/kg/day reduced the median time to achieve hypoglycaemic control (40 vs. 72 hours, P=0.02), the total duration of intravenous fluids (114 vs. 164 hours, P=0.04) and time to achieve full feeds (74 vs. 124 hours, P=0.02).[17] There were no apparent adverse events, although episodes of hyperglycaemia were not reported. Together these data suggest that diazoxide may have a role in early management of severe neonatal hypoglycaemia to reduce the need for intravenous glucose, shorten neonatal unit admissions and facilitate earlier introduction of enteral feeds.

We are therefore undertaking the Neonatal Glucose Care Optimisation (NeoGluCO) Study to determine if early use of low-dose oral diazoxide is beneficial for treatment of severe or recurrent transitional neonatal hypoglycaemia. This trial was registered with the Australian New Zealand Clinical Trials Registry on 11 February 2020 (ACTRN12620000129987).

Aim

To determine if early use of diazoxide in late preterm and term neonates with severe or recurrent transitional hypoglycaemia reduces time to resolution of hypoglycaemia, defined as achieving enteral bolus feeding and normal BGC without intravenous fluids.

Hypothesis

Diazoxide therapy will improve glycaemic stability, allowing earlier weaning of intravenous fluids and establishment of enteral feeds.

Methods and analysis

Study design

The NeoGluCO Study is a phase IIB, double-blind, two-arm, parallel randomised trial of diazoxide versus placebo for treatment of severe or recurrent transitional hypoglycaemia in late preterm and term neonates.

Participants

Infants are eligible for this study if they are born at ≥35 weeks' gestation, are admitted to the neonatal care unit in the first week after birth with recurrent or severe hypoglycaemia, and their parents have provided informed written consent. Severe hypoglycaemia is defined as any BGC <1.2 mmol/L or BGC 1.2 to <2.0 mmol/L despite two doses of buccal dextrose gel and feeding in a single episode; recurrent hypoglycaemia is defined as ≥3 episodes (one or more consecutive BGC <2.6 mmol/L) of hypoglycaemia in 48 hours. Infants must also be receiving ongoing management for hypoglycaemia at the time of randomisation, e.g., intravenous dextrose, carbohydrate supplements, continuous or frequent feeding (≤2 hourly intervals), or inability to wean off formula due to hypoglycaemia. Eligibility is based on BGC measured by gas analyser (portable or laboratory) or plasma glucose concentration measured on a laboratory chemical analyser.

Infants are excluded if they have a confirmed major congenital malformation or chromosomal disorder, suspected genetic syndrome associated with hypoglycaemia, gastrointestinal disorder likely to affect feed tolerance, confirmed sepsis (culture of pathogenic organism from blood, cerebrospinal fluid or urine) or hypoxic-ischaemic encephalopathy; are planned or likely to have neonatal surgery; there is a family history of congenital hyperinsulinism; are suspected of suffering from an inborn error of metabolism; or are a triplet.

Recruitment, randomisation and allocation concealment

Recruitment commenced on 14 May 2020. Infants are being recruited at Middlemore Hospital, Counties Manukau Health, South Auckland and Auckland City Hospital, Auckland District Health Board, Auckland, New Zealand. These hospitals provide all tertiary neonatal services for the wider Auckland region. At both sites, neonatal care focuses on supporting breastfeeding, skin-to-skin care, keeping mother and baby together where possible and use of dextrose buccal gel as first line management of neonatal hypoglycaemia.[18] Neonatal medical advice is sought

if an infant has severe or recurrent hypoglycaemia (as defined above), at which point the infant may be given artificial feed supplements or admitted to the neonatal care unit for intravenous dextrose, depending on caregiver preference and infant risk factors. BGC screening of at-risk infants is commenced between 1 and 2 hours of age using capillary whole-blood and a gas analyser (portable or laboratory).

Infants are recruited after birth by investigators, study personnel and clinical staff. Following written, informed parental consent and once all eligibility criteria are met, infants are allocated via an online randomisation system (Clinical Data Research Hub, Liggins Institute, University of Auckland) to one of two masked interventions, diazoxide or placebo. The allocation ratio is 1:1. The allocation sequence was computer-generated with random permuted blocks of 4 and 6, stratified by centre and SGA status (<10th customised centile).[19] Twins are individually randomised.

The interventions are provided in opaque bottles labelled with a four-digit random number. At randomisation, the web-based system assigns the appropriate bottle number according to the allocation sequence. Only the data manager and trial pharmacists have access to the allocation sequence and know the content of bottles; study personnel, clinical staff and parents are blinded to the allocation.

Interventions

The active intervention is prepared by hospital trial pharmacists by adding five 100 mg diazoxide capsules to 50 ml of Ora Blend sugar free paediatric compounding solution, giving a concentration of 10 mg/ml. Infants are loaded with 5 mg/kg (0.5 ml/kg) orally or by gastric tube and then commenced on a maintenance dose of 1.5 mg/kg (0.15 ml/kg) every 12 h. The intervention is prescribed on hospital medication charts as "NeoGluCO study drug" in ml along with the bottle allocation number and is administered by hospital nurses or midwives. The active intervention is physically and chemically stable for up to 35 days at room temperature (25°) and when refrigerated (2°C to 8°C).

The maintenance dose is at the lower end of the range recommended in the New Zealand Formulary for Children. Although infants with congenital hyperinsulinism usually receive higher maintenance doses of 5 to 10 mg/kg/day, our clinical experience has shown that this dose is often too high for infants with transitional hypoglycaemia and may cause hyperglycaemia, whereas lower doses appear to be similarly efficacious but avoid high BGC.

Adverse effects, such as congestive heart failure, are also likely to be rare with low-dose treatment.

A bedside algorithm is used to titrate the study drug according to BGC, commencing immediately before the third maintenance dose (Table 1**Error! Reference source not found.**). Once the primary outcome is reached, one further dose of study drug is given and then the intervention is discontinued. The intervention may also be stopped before the primary outcome is reached as per the titration protocol. Weekly dose adjustment for weight is made if required, once the infant returns to birthweight.

The control intervention consists of an equal volume of Ora Blend (0.5 ml/kg load, 0.15 ml/kg maintenance), combined with a small amount of cornstarch (4 g per 50 mL) to ensure that the placebo is identical in appearance to the diazoxide solution. The glucose load from the corn-starch is trivial (0.03 g per maintenance dose) and will not affect BGC. Dosing, administration and discontinuation is as per diazoxide.

Blinding

Tetrad testing was used to validate the comparability of the control and active interventions in 42 neonatal staff volunteers (36 females; 27 nurses).[20] Four bottles of study drug, two diazoxide and two placebo, were presented to the staff who were asked to examine the bottles and draw up the study drug into a clear syringe. Staff were then asked to group the bottles into two groups of two based on perceived similarities, after which staff were asked to identify the diazoxide and control pairs, using a forced-choice procedure. Only nine participants (21%) correctly paired the study interventions, corresponding to a Thurstonian effect size (95% CI) for sensory discrimination of 0.00 (0.00, 0.24).[21] This outcome indicates sensory equivalence of the interventions (an effect size ≤0.61 represents differences too small to be noticed).[22] Of those who identified the correct pairings, only two (22%) correctly identified the diazoxide pair, which is less than the percentage expected by chance alone of 50%.

Blood glucose target and monitoring

The target BGC range for infants in the NeoGluCO Study is 2.6 to 5.4 mmol/L, which represents the 10th and 90th centiles, respectively, over the first week in healthy breastfed infants.[23] Management decisions are based on BGC by gas analyser (portable or laboratory) or plasma glucose concentration by laboratory chemical analyser. Capillary, arterial, or venous blood samples are acceptable. Because gas analysers provide plasma-equivalent glucose

concentration, whole-blood gas analyser and laboratory plasma measurements are used interchangeably without adjustment, and are referred to in this protocol as BGC.[24] BGC are measured at least every 6 hours (pre-feed if on enteral bolus feeding) until the primary outcome is reached. Once the primary outcome is achieved, BGC measurement frequency is at clinical discretion but is performed at least every 12 hours while the infant is receiving the intervention.

Episodes of hypoglycaemia after randomisation (BGC ≤2.5 mmol/L) are managed according to local practice, which could include buccal dextrose gel, increasing enteral feed volume or frequency, and starting or increasing intravenous dextrose fluids. If hypoglycaemia occurs after the intervention titration algorithm has commenced (immediately before the third maintenance dose), the maintenance dose may be increased according to titration protocol (Table 1**Error! Reference source not found.**).

Wherever possible, episodes of elevated blood glucose (5.5 to 6.9 mmol/L) or hyperglycaemia (≥7 mmol/L)[25] will be avoided. If this occurs before commencing the intervention titration algorithm (immediately before the third maintenance dose) intravenous fluids are weaned by 50% or stopped, or if the infant is receiving formula while establishing breastfeeding, the supplementary feed volume is halved or stopped. Once the intervention titration algorithm has commenced, intravenous fluids and supplementary feeds are weaned as soon as possible.

Co-interventions

Management of fluids and feeding is as per local practice but with the aim of weaning intravenous fluids and introducing enteral feeds as soon as possible once BGC have stabilised.

Glucagon injections are to be used only in emergencies when intravenous access cannot be obtained and BGC persists <1.2 mmol/L. Glucagon infusions are not permitted. Glucocorticoids are not permitted for treatment of hypoglycaemia but may be used if deemed essential for management of other conditions, e.g., adrenal insufficiency.

Where possible, infants enrolled in the trial will have subcutaneous real-time continuous glucose monitoring (CGM) (Guardian Connect System, Enlite 3 sensor, Medtronic) to help identify the need for additional BGC testing (Supplement). The CGM is calibrated against BGC by gas analyser, four times in the first 24 hours, then every 12 hours while *in situ*.[26] Using Bluetooth transmission to a bedside tablet computer and remote cloud monitoring with text alerts, research staff will use pre-defined Trend Alarm criteria to inform the bedside nurse that a BGC measurement is indicated, i.e., sensor glucose concentration (SGC) is trending out of

range (Table 3). Clinical management decisions are based solely on BGC. The CGM will remain in place for 24 hours after either discontinuation of the study drug or attainment of the primary outcome, whichever is longer, up to a maximum of 7 days. CGM alert and SGC data are recorded along with all BGC measurements for later agreement analysis.

All other neonatal care will occur according to local practice. Open label diazoxide may be considered in refractory cases once other management strategies have been maximised and after discussion with the attending neonatologist, site principal investigator and a paediatric endocrinologist. This requires unblinding of treatment allocation, which will generally not occur before 2 weeks of age. If emergency unblinding occurs, the intervention will be revealed only to the senior medical staff caring for the infant. Study personnel collecting outcome data will remain blinded to intervention allocation.

Assessments

Demographic, obstetric and relevant family medical history are collected at study entry. Neonatal clinical data are obtained from the electronic health record and bedside charts. The study schedule is summarised in Table 2.

Blood is collected at baseline and sent to the hospital laboratories to measure plasma concentrations of insulin, beta-hydroxybutyrate, free fatty acids, creatinine, and blood gases. All infants will have a standard metabolic screen by Guthrie card at ≥48 hours. Additional heparinised blood is collected before the third study maintenance dose (36 hours after commencing the intervention) and plasma is stored for latter measurement of insulin, creatinine, and diazoxide concentrations. Fasting tests are not part of the study protocol but may be considered on clinical grounds, for example, if transitional hypoglycaemia is unusually severe or prolonged, or other diagnoses are suspected.

To assess if low dose diazoxide has any effect on cardiac function, infants at the primary site (Middlemore Hospital) will undergo cardiac ultrasound at ≥72 hours after commencing the study intervention to assess a) ductal patency, flow and shunt; b) pulmonary arterial pressure; and c) cardiac function. Infants with suspected congestive heart failure will also undergo formal echocardiography.

Outcomes

The primary outcome is time to resolution of hypoglycaemia, defined as the first time point at which all of the following criteria are met concurrently:

- No intravenous fluids for ≥24 h (time recorded at the end of the 24-hour period).
- Enteral bolus feeding for ≥24 h defined as a) breastfeeding without supplements; or b) breastfeeding with supplements at >2 hourly intervals, or c) if not breastfeeding, gastric tube or bottle feeds at 3 to 4 hourly intervals (time recorded at the end of the 24-hour period).
- Normoglycaemia for ≥24 h, defined as a minimum of four pre-feed BGC in the target range of 2.6 to 5.4 mmol/L (last BGC measured within 4 hours of primary outcome time point); four pre-feed BGC spanning >20 hours; no BGC out of range for ≥24 hours; time recorded at the end of the period).

The following secondary outcomes will be assessed from the time of randomisation:

- Time to achieve normoglycaemia (as per primary outcome)
- Time to establish enteral bolus feeding (as per primary outcome)
- Time to establish full sucking feeds defined as ≥five full breastfeeds (≥10 minutes) in 24 hours or ≥120 ml/kg/d of expressed breast milk or formula by bottle (up to discharge to home)
- Type of feeding at discharge from hospital and to home (breast milk, formula, mixed)
- Use of intravenous fluids and type
- Duration of intravenous fluids (up to discharge from hospital)
- Episodes of hypoglycaemia (BGC <2.6 mmol/L), elevated glucose concentration (BGC 5.5 to 6.9 mmol/L) and hyperglycaemia (BGC ≥7 mmol/L), including frequency, duration, timing and treatment before, during and after the episode (up to discharge from hospital)
- Number of blood glucose tests: during the study intervention and during hospital admission

- Duration of admission to first discharge home: neonatal care, postnatal ward, community birthing unit
- Duration of study intervention (up to discharge from hospital)
- Guthrie metabolic screen (≥48 hours from birth)
- Plasma insulin, creatinine and diazoxide concentrations at ≥36 hours after commencing the intervention
- Death (up to discharge from hospital)
- Seizures (total; presumed hypoglycaemic) (up to discharge from hospital)
- Discontinuation of study intervention due to elevated BGC or hyperglycaemia (up to discharge from hospital)
- Discontinuation of study intervention due to another adverse event (serious; non-serious) (up to discharge from hospital)
- Congestive heart failure (respiratory distress as evidenced by tachypnoea, recession, or use of oxygen or positive pressure support with consistent chest x-ray findings, including cardiomegaly, plethora, interstitial fluid or effusions) (up to discharge from hospital)
- Commencement of low flow oxygen or positive pressure respiratory support (up to discharge from hospital)
- Cardiac ultrasound (Middlemore Hospital) at (≥72 hours)
    - Ductus arteriosus: closed; trivial (<1.5 mm and a constricted pattern on Doppler); patent (≥1.5 mm, growing, pulsatile or bidirectional pattern on Doppler)
    - Pulmonary hypertension: pulmonary artery pressure ≥systemic as estimated by tricuspid regurgitant jet (RV-RA gradient +5 mmHg) or ductal shunt right to left (>20%) with characteristic pulmonary Doppler envelope (TPV/ RVET <20%)

- Cardiac impairment: left ventricular internal diameter diastolic z-score >2 and reduced systolic function (fractional shortening <25% or myocardial performance index >0.41)

Data management

Web-based data management is provided by the Clinical Data Research Hub at the Liggins Institute, University of Auckland. This includes a bespoke online randomisation system, with intervention stock management, that is integrated with the REDCap system.[27] Study data are collected directly into electronic case record forms (eCRF). Range and logic checks are used to reduce data entry errors. CGM data are captured in a secure cloud account and subsequently uploaded to the REDCap system.

A data monitor checks all eCRF for completeness and logic errors, after which eCRFs are locked. If the data monitor identifies potential errors, an electronic query is raised and referred to the site for checking.

Statistical analysis

Data analysis will be performed in SAS 9.4 (SAS Institute). Customised birthweight centiles will be calculated using GROW software (Perinatal Institute, United Kingdom). Population z-scores for weight, length, and head circumference at birth will be calculated using UK-WHO centiles.[28]

Categorical data will be presented as number and percent, and continuous data as mean and standard deviation or median and inter-quartile range, as appropriate. Count data will be presented as median and inter-quartile range or grouped into ordinal categories. Denominators will be given for all outcomes.

In the primary analysis, intervention groups will be compared for the primary outcome using Cox's proportional hazard regression analysis, with treatment effect expressed as adjusted hazards ratio with a 95% confidence interval (CI). The analysis will be right censored at 4 weeks. Proportionality assumptions will be assessed by inspecting Kaplan-Meier curves and Schoenfeld residuals. Secondary outcomes will be compared between groups using generalised linear models (normal, binomial or Poisson) with treatment effect presented as adjusted odds ratio, count ratio, mean difference, or ratio of geometric means (positively skewed data), as appropriate, with 95% CI. Regression models will be adjusted for stratification variables

(centre and customised birthweight centile, fixed effects), gestation length (fixed effect) and non-independence of multiples (random effect). If models fail to converge, the analysis algorithm will be optimised and the maximum number of iterations increased to get convergence with minimum Akaike Information Criteria (AIC). If this is unsuccessful, adjustment variables may be collapsed or excluded if necessary, for model convergence. For significance tests, the alpha level will be set at 0.05 (two-tailed). No adjustment will be made for multiple comparisons but results for secondary outcomes will be interpreted cautiously. All infants who meet eligibility will be included in the primary analysis (modified intention-to-treat analysis). Secondary exploratory analysis may include per protocol analysis of the primary outcome.

Sample size

A trial of 74 babies randomised in 1:1 ratio (37 per group) will give 80% power to detect a relative hazard of 2.0 (two-tailed alpha 0.05), assuming 90% of infants in each group have a primary outcome event within the study period (PASS Software 16). A hazard ratio of 2.0 indicates that the diazoxide group reaches the primary outcome at twice the rate (events per unit of time) of the control group. An adaptive sample size approach will be adopted where the number of randomised participants will be increased by the number of participants who withdraw or who are lost to follow-up.

Data and safety monitoring

An independent Data Monitoring and Safety Committee (DMSC) is monitoring recruitment, completeness of data acquisition and participant safety. The DMSC advises the Trial Steering Committee (TSC) on trial continuation or protocol modification. DMSC Terms of Reference were agreed before commencement of trial.

The following Serious Adverse Events (SAE) are reported to the DMSC for immediate review:

- Death
- Seizure
- Congestive heart failure
- Discontinuation of study intervention due to another serious adverse event, as judged by the site principal investigator or attending neonatologist (an adverse event is

considered serious if it is immediately life-threatening, requires prolongation of hospitalisation or substantial escalation in care, or results in persistent or significant disability or incapacity)

SAE are reported until the time of primary hospital discharge. The TSC Chair notifies the DMSC Chair of all SAE within 72 hours of onset. The DMSC reviews SAE within 1 week of receiving the SAE report, to determine if participation in the trial is likely to be a causative factor and reports back to the TSC with the findings.

The DMSC will undertake an interim safety review when the primary outcome is known for 25% and 60% of participants, including rates of SAE and the following Adverse Events (AE) by masked treatment group:

- Hyperglycaemia (≥7 mmol/L)
- Discontinuation of study intervention due to elevated BGC (5.5 to 6.9 mmol/L) or hyperglycaemia
- Discontinuation of study intervention due to another adverse event (non-serious)
- Commencement of low flow oxygen or positive pressure respiratory support

There is no planned interim efficacy analysis.

Patient and public involvement

The NeoGluCO Study was presented and developed at an ON TRACK Network (https://ontrack.perinatalsociety.org.nz/) clinical trials workshop, Auckland, New Zealand in February 2020, which was attended by consumers, including parents of infants admitted to neonatal intensive care. Consumer input was received about study design and participant information.

Ethics and dissemination

Approval has been obtained from the Central Health and Disability Ethics Committee of New Zealand (reference 19CEN189) and by the local institutional research review committees at each centre.

The primary and secondary outcomes will be published in an international peer-reviewed journal and disseminated via presentations at local and international conferences to researchers

and clinicians. The decision to publish is the responsibility of the Trial Steering Committee, which will have full access to the final data set. A lay summary of the research findings will be made available to those parents who indicated a wish to receive these on their consent forms.

Data availability

For each main publication, the corresponding data set will be electronically archived with the Clinical Data Research Hub, Liggins Institute, University of Auckland. Anonymised data may be shared with external researchers upon request, according to the Data Sharing Protocol of Research Hub (https://wiki.auckland.ac.nz/display/ontrack/Data+Sharing).

Discussion

Despite current management, infants with severe or recurrent transitional hypoglycaemia continue to have higher rates (approximately four-fold) of adverse neurological outcome than at-risk infants without hypoglycaemia.[11] In addition, they often have prolonged neonatal admission, ongoing blood glucose instability despite the provision of intravenous fluids, and can be difficult to establish on enteral feeds.[10] New treatment approaches are needed that target the underlying pathophysiology, especially dysregulated insulin secretion, such as low dose diazoxide.

A systematic review found low certainty evidence from one randomised trial that early use of diazoxide in SGA infants receiving intravenous dextrose for transitional neonatal hypoglycaemia decreased the duration of intravenous fluids and time to full enteral feeding by approximately 2 days.[29] Although there no apparent adverse effects in this trial, several case series have highlighted a range of possible side effects, including pulmonary hypertension, oedema, heart failure, neutropenia, reopening of the ductus arteriosus, and necrotizing enterocolitis.[30-33] However, in other reports, serious side effects in otherwise well infants were rare,[16,34-36] suggesting that some of the conditions associated with diazoxide may reflect confounding. Randomised controlled trials are needed to generate unbiased effect estimates.

The NeoGluCO Study will provide high-quality evidence to determine if early use of low-dose oral diazoxide for severe or recurrent transitional hypoglycaemia in late preterm and term infants reduces time to resolution of hypoglycaemia.

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Author contributions

CJDM, DL conceived and developed the study design, drafted the original study protocol, approved the final study protocol and drafted and reviewed the article for publication. EW contributed to study design, approved the final study protocol and drafted and reviewed the article for publication. JMA, SMH, MPM, JA, WSC, JR, GJC and JEH contributed to the study design, approved the final version of the study protocol and reviewed the article for publication. GDG assisted with the sample size calculation and statistical analysis plan, contributed to study design, approved the final version of the study protocol and reviewed the article for publication. All Authors are part the Trial Steering Committee. The authors have no financial or other competing interests to declare.

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Competing interests

None

Patient consent for publication

Not required

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Table 1: Intervention bedside algorithm

BGC	Action
≤2.5 mmol/L	Increase maintenance dose to 0.25 ml/kg (diazoxide 2.5 mg/kg) every 12 h and adjust fluids and feeds as clinically appropriate. If hypoglycaemia persists after two doses of study drug at 0.25 ml/kg, increase maintenance dose to 0.5 ml/kg (diazoxide 5.0 mg/kg) every 12 h. If further hypoglycaemia occurs after 2 doses of study drug at 0.5 ml/kg, discuss with the site principal investigator and a paediatric endocrinologist. Consider congenital hyperinsulinism in refractory infants, in which case unblinding may be required.
2.6 to 5.4 mmol/L	Continue maintenance dose every 12 h while weaning intravenous fluids and grading up feeds. Give one more dose after the primary outcome point is reached.
5.5 to 6.9 mmol/L	If on intravenous dextrose, stop or wean fluids more rapidly. If on supplementary feeds (formula or EBM) and the mother is planning to breastfeed, stop or wean supplementary feeds. Withhold intervention dose.

	If glucose returns to the target range (2.6-5.4 mmol/L), recommence the next maintenance at 0.1 ml/kg (diazoxide 1 mg/kg) every 12 h. If glucose remains elevated for ≥12 h, discontinue the intervention.
≥7 mmol/L	Discontinue intervention; wean any intravenous dextrose

BGC, blood glucose concentration; EBM, expressed breast milk. The intervention algorithm commences before the third maintenance dose.

Table 2: Study schedule

TIMEPOINT	Pre-randomisation	Randomisation	*Week 1*	*Week 2-4*	*Discharge*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Baseline data	X				
Demographics and contacts	X				
Baseline metabolic bloods	X				
Allocation		X			
INTERVENTIONS:					
Study drug			X	±	
ASSESSMENTS:					
Continuous glucose monitor			X		
Primary outcome assessment			X	±	
Blood collection (≥36 hours)			X		
Echocardiogram (≥72 hours)			X		
Secondary outcome assessment			X	X	X

Table 3: Continuous glucose monitor trend alarms

Trend Alarm	Medtronic Guardian setting	Interpretation
Low	Low Alert SGC=3.1 mmol/L AND Fall Alert ≥1 for 10 min*	BGC expected to be 2.5 mmol/L
	Low Alert SGC=3.1 AND ≤2.5 mmol/L after 20 min**	BGC falling by 0.03 mmol/L/min
High	High Alert SGC=5.6 mmol/L AND Rise Alert ≥1 for 10 min*	BGC expected to be 6.2 mmol/L
	High Alert SGC=5.6 mmol/L AND ≥6.1 mmol/L after 20 min***	BGC rising by 0.03 mmol/L/min

SGC/BGC, sensor/blood glucose concentration. Medtronic Guardian provides an SGC reading ever 5 min. *Fall/Rise Alert 1 indicates SGC is changing by 0.06 mmol/L/min; Fall/Rise Alert 2 indicates SGC is changing by 0.11 mmol/L/min; Fall/Rise Alert 3 indicates SGC is changing by 0.17 mmol/L/min. **If the SGC is ≥2.6 after 20 min, no Trend Alert is signalled. Snooze time for device Low Alert set to 20 min. ***The BGC 97th percentile for healthy breastfed babies >72 h is 6.0 mmol/L.[23]

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	*Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) Study; a randomised controlled trial.*	1
Trial registration	2a	*Trial registration ACTRN12620000129987*	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	*version 2.5, date 2021.11.11*	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors *All authors contributed to protocol development.*	1
	5b	Name and contact information for the trial sponsor *The trial sponsor is the corresponding author's listed institution (University of Auckland)*	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16-17
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8 and table 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) *Intervention is administered by hospital nurses and midwives from hospital drug charts*	7, 8 and table 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Table 1
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *This is an inpatient study*	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *There is no interim efficacy analysis.*	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Participant information sheet
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Protocol and participant information sheet

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) Study; a randomised controlled trial.

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Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) Study; a randomised controlled trial.

Authors:

Don Laing[1]*

Eamon Walsh[1]*

Jane M Alsweiler[2,3]

Sara M Hanning[4]

Michael P Meyer[2,5]

Julena Ardern[5]

Wayne S Cutfield[1]

Jenny Rogers[1]

Greg D Gamble[1]

J Geoff Chase[6]

Jane E Harding[1]

Christopher JD McKinlay[1,5]

*Joint first authors

1. Liggins Institute, University of Auckland, New Zealand
2. Department of Paediatrics: Child and Youth Health, University of Auckland, New Zealand
3. Starship Child Health, Auckland District Health Board, New Zealand
4. School of Pharmacy, University of Auckland, New Zealand
5. Kidz First Neonatal Care, Counties Manukau Health, Auckland, New Zealand
6. College of Engineering, University of Canterbury, Christchurch, New Zealand

Corresponding author: Christopher JD McKinlay +64274725099

c.mckinlay@auckland.ac.nz

Liggins Institute, University of Auckland, Private Bag 92019, Victoria Street West, Auckland 1142, New Zealand

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Abstract

Introduction: Infants with severe or recurrent transitional hypoglycaemia continue to have high rates of adverse neurological outcomes and new treatment approaches are needed that target the underlying pathophysiology. Diazoxide is one such treatment that acts on the pancreatic β-cell in a dose-dependent manner to decrease insulin secretion.

Methods and analysis: Phase IIB, double-blind, two-arm, parallel, randomised trial of diazoxide versus placebo in neonates ≥35 weeks' gestation for treatment of severe (blood glucose concentration [BGC] <1.2 mmol/L or BGC 1.2 to <2.0 mmol/L despite two doses of buccal dextrose gel and feeding in a single episode) or recurrent (≥3 episodes <2.6 mmol/L in 48 hours) transitional hypoglycaemia. Infants are loaded with diazoxide 5 mg/kg orally and then commenced on a maintenance dose of 1.5 mg/kg every 12 hours, or an equal volume of placebo. The intervention is titrated from the third maintenance dose by protocol to target BGC in the range of 2.6 to 5.4 mmol/L. The primary outcome is time to resolution of hypoglycaemia, defined as the first point at which the following criteria are met concurrently for ≥24 hours: no intravenous fluids, enteral bolus feeding and normoglycaemia. Groups will be compared for the primary outcome using Cox's proportional hazard regression analysis, expressed as adjusted hazards ratio with a 95% confidence interval.

Ethics and dissemination: This trial has been approved by the Health and Disability Ethics Committees of New Zealand (19CEN189). Findings will be disseminated in peer-reviewed journals, to clinicians and researchers at local and international conferences, and to the public.

Registration: 11 February 2020, ACTRN12620000129987.

Strengths and limitations of study methods

- The main strength of the NeoGluCO Study is its two-arm, parallel, randomised, double-blind design, comparing low-dose diazoxide with placebo.
- The interventions have been shown to have sensory equivalence, thus enhancing blinding.
- Other strengths include measurement of all blood glucose concentrations by gas analyser and targeting of blood glucose concentrations within a normal range (2.6 to 5.4 mmol/L) rather than just a minimum threshold.

- The main limitation of the study is that the primary outcome is a short-term measure.
- Other limitations are that infants are only being recruited from neonatal units and the study will have inadequate power to assess rare side effects.

Introduction

At least 30% of all newborn infants are at risk of transitional hypoglycaemia or low blood glucose concentration (BGC) due to being born small, large, preterm, or the infant of a women with diabetes.[1,2] They require regular testing of BGC in the first 24 to 48 hours after birth and approximately 50% develop hypoglycaemia and require further testing and intervention. Optimal management of transitional neonatal hypoglycaemia is important not only because of its impact on breastfeeding,[3,4] and the use of health care resources,[5,6] but also because of the potential for hypoglycaemia to cause permanent brain injury. We have shown that infants with asymptomatic hypoglycaemia have a two- to three-fold increased likelihood of later neurocognitive difficulties by 4 to 5 years of age, especially in executive function and visual-motor integration.[7] These functions are critical for learning, and even brief transitional neonatal hypoglycaemia has been associated with a two-fold increased likelihood of poor school achievement.[8] Moreover, in moderately preterm infants, transitional hypoglycaemia is the main modifiable risk factor for developmental delay at preschool age.[9]

If oral dextrose gel and additional feeding do not correct hypoglycaemia or if there are recurrent episodes, infants are typically admitted to the neonatal unit for frequent or continuous feeding by gastric tube or intravenous dextrose, to correct BGC to a normal range.[1] These infants often have prolonged neonatal admission, ongoing hypoglycaemia despite the provision of intravenous fluids, and can be difficult to establish on enteral feeds due to glucose instability.[10] Even with standard management, infants with severe or recurrent transitional hypoglycaemia continue to have higher rates (approximately four-fold) of adverse neurological outcomes.[11]

An important cause of severe or recurrent transitional hypoglycaemia is dysregulated insulin secretion, especially the inability to suppress insulin secretion at low BGC.[10,12,13] If insulin secretion remains inappropriately high during the transition period after birth, hepatic glucose output is inadequate for metabolic requirements, and hypoglycaemia ensues. Increasing delivery of exogenous glucose, either with formula or intravenous dextrose, may stimulate additional insulin secretion and cause ongoing suppression of endogenous glucose production, further delaying normal metabolic transition. Thus, alternative management strategies are needed for infants with severe or recurrent transitional hypoglycaemia that address the underlying pathophysiology and promote metabolic transition.

Diazoxide is one such potential treatment that acts on the pancreatic β cell in a dose-dependent manner to decrease insulin secretion by interacting with the sulfonylurea receptor (SUR1).[14]

Advantages of diazoxide include rapid onset of action, oral formulation, and low cost. Diazoxide has been used for many decades as a first-line treatment for certain forms of congenital (genetic) hyperinsulinism with a good efficacy and safety profile, although reversible congestive heart failure has been occasionally reported with prolonged high-dose treatment.[15]

Diazoxide has also been used selectively in babies with transient hyperinsulinism. Hoe *et al.* described 21 hyperinsulinaemic babies without known genetic defects, 20 (95%) of whom were responsive to diazoxide (5 to 15 mg/kg/day), when commenced at a median age of 13 days.[16] Additionally, in a randomised trial of 30 small-for-gestational-age (SGA) neonates with transient hyperinsulinism in the first 5 days of age, diazoxide at 6 to 12 mg/kg/day reduced the median time to achieve hypoglycaemic control (40 vs. 72 hours, P=0.02), the total duration of intravenous fluids (114 vs. 164 hours, P=0.04) and time to achieve full feeds (74 vs. 124 hours, P=0.02).[17] There were no apparent adverse events, although episodes of hyperglycaemia were not reported. Together these data suggest that diazoxide may have a role in the early management of severe neonatal hypoglycaemia to reduce the need for intravenous glucose, shorten neonatal unit admissions and facilitate the earlier introduction of enteral feeds.

We are therefore undertaking the Neonatal Glucose Care Optimisation (NeoGluCO) Study to determine if early use of low-dose oral diazoxide is beneficial for the treatment of severe or recurrent transitional neonatal hypoglycaemia. This trial was registered with the Australian New Zealand Clinical Trials Registry on 11 February 2020 (ACTRN12620000129987).

Aim

To determine if early use of diazoxide in late preterm and term neonates with severe or recurrent transitional hypoglycaemia reduces time to resolution of hypoglycaemia, defined as achieving enteral bolus feeding and normal BGC without intravenous fluids.

Hypothesis

Diazoxide therapy will improve glycaemic stability, allowing earlier weaning of intravenous fluids and establishment of enteral feeds.

Methods and analysis

Study design

The NeoGluCO Study is a phase IIB, double-blind, two-arm, parallel randomised trial of diazoxide versus placebo for treatment of severe or recurrent transitional hypoglycaemia in late preterm and term neonates.

Participants

Infants are eligible for this study if they are born at ≥35 weeks' gestation, are admitted to the neonatal care unit in the first week after birth with recurrent or severe hypoglycaemia, and their parents have provided informed written consent. Severe hypoglycaemia is defined as any BGC <1.2 mmol/L or BGC 1.2 to <2.0 mmol/L despite two doses of buccal dextrose gel and feeding in a single episode; recurrent hypoglycaemia is defined as ≥3 episodes (one or more consecutive BGC <2.6 mmol/L) of hypoglycaemia in 48 hours. Infants must also be receiving ongoing management for hypoglycaemia at the time of randomisation, e.g., intravenous dextrose, carbohydrate supplements, continuous or frequent feeding (≤2 hourly intervals), or inability to wean off formula due to hypoglycaemia. Eligibility is based on BGC measured by a gas analyser (portable or laboratory) or plasma glucose concentration measured on a laboratory chemical analyser.

Infants are excluded if they have a confirmed major congenital malformation or chromosomal disorder, suspected genetic syndrome associated with hypoglycaemia, gastrointestinal disorder likely to affect feed tolerance, confirmed sepsis (culture of a pathogenic organism from blood, cerebrospinal fluid or urine) or hypoxic-ischaemic encephalopathy; are planned or likely to have neonatal surgery; there is a family history of congenital hyperinsulinism; are suspected of suffering from an inborn error of metabolism; or are a triplet.

Recruitment, randomisation and allocation concealment

Recruitment commenced on 14 May 2020. Infants are being recruited at Middlemore Hospital, Counties Manukau Health, South Auckland and Auckland City Hospital, Auckland District Health Board, Auckland, New Zealand. These hospitals provide all tertiary neonatal services for the wider Auckland region. At both sites, neonatal care focuses on supporting breastfeeding, skin-to-skin care, keeping mother and baby together where possible and the use of dextrose buccal gel as the first-line management of neonatal hypoglycaemia.[18] Neonatal medical advice

is sought if an infant has severe or recurrent hypoglycaemia (as defined above), at which point the infant may be given artificial feed supplements or admitted to the neonatal care unit for intravenous dextrose, depending on caregiver preference and infant risk factors. BGC screening of at-risk infants is commenced between 1 and 2 hours of age using capillary whole-blood and a gas analyser (portable or laboratory).

Infants are recruited after birth by investigators, study personnel and clinical staff. Following written, informed parental consent and once all eligibility criteria are met, infants are allocated via an online randomisation system (Clinical Data Research Hub, Liggins Institute, University of Auckland) to one of two masked interventions, diazoxide or placebo. The allocation ratio is 1:1. The allocation sequence was computer-generated with random permuted blocks of 4 and 6, stratified by centre and SGA status (<10th customised centile).[19] Twins are individually randomised.

The interventions are provided in opaque bottles labelled with a four-digit random number. At randomisation, the web-based system assigns the appropriate bottle number according to the allocation sequence. Only the data manager and trial pharmacists have access to the allocation sequence and know the content of bottles; study personnel, clinical staff and parents are blinded to the allocation.

Interventions

The active intervention is prepared by hospital trial pharmacists by adding five 100 mg diazoxide capsules to 50 ml of Ora Blend sugar-free paediatric compounding solution, giving a concentration of 10 mg/ml. Infants are loaded with 5 mg/kg (0.5 ml/kg) orally or by gastric tube and then commenced on a maintenance dose of 1.5 mg/kg (0.15 ml/kg) every 12 h. The intervention is prescribed on hospital medication charts as "NeoGluCO study drug" in ml along with the bottle allocation number and is administered by hospital nurses or midwives. The active intervention is physically and chemically stable for up to 35 days at room temperature (25°) and when refrigerated (2°C to 8°C).

The maintenance dose is at the lower end of the range recommended in the New Zealand Formulary for Children. Although infants with congenital hyperinsulinism usually receive higher maintenance doses of 5 to 10 mg/kg/day, our clinical experience has shown that this dose is often too high for infants with transitional hypoglycaemia and may cause hyperglycaemia, whereas lower doses appear to be similarly efficacious but avoid high BGC.

Adverse effects, such as congestive heart failure, are also likely to be rare with low-dose treatment.

A bedside algorithm is used to titrate the study drug according to BGC, commencing immediately before the third maintenance dose (Table 1**Error! Reference source not found.**). Once the primary outcome is reached, one further dose of the study drug is given and then the intervention is discontinued. The intervention may also be stopped before the primary outcome is reached as per the titration protocol. Weekly dose adjustment for weight is made if required, once the infant returns to birthweight.

Table 1: Intervention bedside algorithm

BGC	Action
≤2.5 mmol/L	Increase maintenance dose to 0.25 ml/kg (diazoxide 2.5 mg/kg) every 12 hours and adjust fluids and feeds as clinically appropriate. If hypoglycaemia persists after two doses of the study drug at 0.25 ml/kg, increase the maintenance dose to 0.5 ml/kg (diazoxide 5.0 mg/kg) every 12 hours. If further hypoglycaemia occurs after 2 doses of the study drug at 0.5 ml/kg, discuss with the site principal investigator and a paediatric endocrinologist. Consider congenital hyperinsulinism in refractory infants, in which case unblinding may be required.
2.6 to 5.4 mmol/L	Continue maintenance dose every 12 hours while weaning intravenous fluids and grading up feeds. Give one more dose after the primary outcome point is reached.
5.5 to 6.9 mmol/L	If on intravenous dextrose, stop or wean fluids more rapidly. If on supplementary feeds (formula or EBM) and the mother is planning to breastfeed, stop or wean supplementary feeds. Withhold intervention dose. If glucose returns to the target range (2.6-5.4 mmol/L), recommence the next maintenance at 0.1 ml/kg (diazoxide 1 mg/kg) every 12 hours. If glucose remains elevated for ≥12 hours, discontinue the intervention.

≥7 mmol/L	Discontinue intervention; wean any intravenous dextrose

BGC, blood glucose concentration; EBM, expressed breast milk. The intervention algorithm commences before the third maintenance dose.

The control intervention consists of an equal volume of Ora Blend (0.5 ml/kg load, 0.15 ml/kg maintenance), combined with a small amount of cornstarch (4 g per 50 mL) to ensure that the placebo is identical in appearance to the diazoxide solution. The glucose load from the cornstarch is trivial (0.03 g per maintenance dose) and will not affect BGC. Dosing, administration and discontinuation are as per diazoxide.

Blinding

Tetrad testing was used to validate the comparability of the control and active interventions in 42 neonatal staff volunteers (36 females; 27 nurses).[20] Four bottles of study drug, two diazoxide and two placebo, were presented to the staff who were asked to examine the bottles and draw up the study drug into a clear syringe. Staff were then asked to group the bottles into two groups of two based on perceived similarities, after which staff were asked to identify the diazoxide and control pairs, using a forced-choice procedure. Only nine participants (21%) correctly paired the study interventions, corresponding to a Thurstonian effect size (95% CI) for sensory discrimination of 0.00 (0.00, 0.24).[21] This outcome indicates sensory equivalence of the interventions (an effect size ≤0.61 represents differences too small to be noticed).[22] Of those who identified the correct pairings, only two (22%) correctly identified the diazoxide pair, which is less than the percentage expected by chance alone of 50%.

Blood glucose target and monitoring

The target BGC range for infants in the NeoGluCO Study is 2.6 to 5.4 mmol/L, which represents the 10th and 90th centiles, respectively, over the first week in healthy breastfed infants.[23] Management decisions are based on BGC by gas analyser (portable or laboratory) or plasma glucose concentration by laboratory chemical analyser. Capillary, arterial, or venous blood samples are acceptable. Because gas analysers provide plasma-equivalent glucose concentration, whole-blood gas analyser and laboratory plasma measurements are used interchangeably without adjustment and are referred to in this protocol as BGC.[24] BGC are measured at least every 6 hours (pre-feed if on enteral bolus feeding) until the primary outcome is reached. Once the primary outcome is achieved, BGC measurement frequency is at clinical discretion but is performed at least every 12 hours while the infant is receiving the intervention.

Episodes of hypoglycaemia after randomisation (BGC ≤2.5 mmol/L) are managed according to local practice, which could include buccal dextrose gel, increasing enteral feed volume or frequency, and starting or increasing intravenous dextrose fluids. If hypoglycaemia occurs after the intervention titration algorithm has commenced (immediately before the third maintenance dose), the maintenance dose may be increased according to the titration protocol (Table 1**Error! Reference source not found.**).

Wherever possible, episodes of elevated blood glucose (5.5 to 6.9 mmol/L) or hyperglycaemia (≥7 mmol/L)[25] will be avoided. If this occurs before commencing the intervention titration algorithm (immediately before the third maintenance dose) intravenous fluids are weaned by 50% or stopped, or if the infant is receiving formula while establishing breastfeeding, the supplementary feed volume is halved or stopped. Once the intervention titration algorithm has commenced, intravenous fluids and supplementary feeds are weaned as soon as possible.

Co-interventions

Management of fluids and feeding is as per local practice but with the aim of weaning intravenous fluids and introducing enteral feeds as soon as possible once BGC have stabilised.

Glucagon injections are to be used only in emergencies when intravenous access cannot be obtained and BGC persists at <1.2 mmol/L. Glucagon infusions are not permitted. Glucocorticoids are not permitted for the treatment of hypoglycaemia but may be used if deemed essential for the management of other conditions, e.g., adrenal insufficiency.

Where possible, infants enrolled in the trial will have subcutaneous real-time continuous glucose monitoring (CGM) (Guardian Connect System, Enlite 3 sensor, Medtronic) to help identify the need for additional BGC testing (Supplement). The CGM is calibrated against BGC by a gas analyser, four times in the first 24 hours, then every 12 hours while *in situ*.[26] Using Bluetooth transmission to a bedside tablet computer and remote cloud monitoring with text alerts, research staff will use pre-defined Trend Alarm criteria to inform the bedside nurse that a BGC measurement is indicated, i.e., sensor glucose concentration (SGC) is trending out of range (Table 2). Clinical management decisions are based solely on BGC. The CGM will remain in place for 24 hours after either discontinuation of the study drug or attainment of the primary outcome, whichever is longer, up to a maximum of 7 days. CGM alert and SGC data are recorded along with all BGC measurements for later agreement analysis.

Table 2: Study schedule

TIMEPOINT	Pre-randomisation	Randomisation	*Week 1*	*Week 2-4*	*Discharge*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Baseline data	X				
Demographics and contacts	X				
Baseline metabolic bloods	X				
Allocation		X			
INTERVENTIONS:					
Study drug			X	±	
ASSESSMENTS:					
Continuous glucose monitor			X		
Primary outcome assessment			X	±	
Blood collection (≥36 hours)			X		
Echocardiogram (≥72 hours)			X		
Secondary outcome assessment			X	X	X

All other neonatal care will occur according to local practice. Open-label diazoxide may be considered in refractory cases once other management strategies have been maximised and after discussion with the attending neonatologist, site principal investigator and a paediatric endocrinologist. This requires unblinding of treatment allocation, which will generally not occur before 2 weeks of age. If emergency unblinding occurs, the intervention will be revealed only to the senior medical staff caring for the infant. Study personnel collecting outcome data will remain blinded to intervention allocation.

Assessments

Demographic, obstetric and relevant family medical history is collected at study entry. Neonatal clinical data are obtained from the electronic health record and bedside charts. The study schedule is summarised in Table 3.

Table 3: Continuous glucose monitor trend alarms

Trend Alarm	Medtronic Guardian setting	Interpretation
Low	Low Alert SGC=3.1 mmol/L AND Fall Alert ≥1 for 10 minutes*	BGC expected to be 2.5 mmol/L
	Low Alert SGC=3.1 AND ≤2.5 mmol/L after 20 minutes**	BGC falling by 0.03 mmol/L/minute
High	High Alert SGC=5.6 mmol/L AND Rise Alert ≥1 for 10 minutes*	BGC expected to be 6.2 mmol/L
	High Alert SGC=5.6 mmol/L AND ≥6.1 mmol/L after 20 minutes***	BGC rising by 0.03 mmol/L/minute

SGC/BGC, sensor/blood glucose concentration. Medtronic Guardian provides an SGC reading every 5 minutes. *Fall/Rise Alert 1 indicates SGC is changing by 0.06 mmol/L/minute; Fall/Rise Alert 2 indicates SGC is changing by 0.11 mmol/L/minute; Fall/Rise Alert 3 indicates SGC is changing by 0.17 mmol/L/minute. **If the SGC is ≥2.6 after 20 minutes, no Trend Alert is signalled. Snooze time for device Low Alert set to 20 minutes. ***The BGC 97th percentile for healthy breastfed babies >72 hours is 6.0 mmol/L.[23]

Blood is collected at baseline and sent to the hospital laboratories to measure plasma concentrations of insulin, beta-hydroxybutyrate, free fatty acids, creatinine, and blood gases. All infants will have a standard metabolic screen by Guthrie card at ≥48 hours. Additional heparinised blood is collected before the third study maintenance dose (36 hours after commencing the intervention) and plasma is stored for later measurement of insulin, creatinine, and diazoxide concentrations. Fasting tests are not part of the study protocol but may be considered on clinical grounds, for example, if transitional hypoglycaemia is unusually severe or prolonged, or if other diagnoses are suspected.

To assess if low dose diazoxide has any effect on cardiac function, infants at the primary site (Middlemore Hospital) will undergo a cardiac ultrasound at ≥72 hours after commencing the study intervention to assess a) ductal patency, flow and shunt; b) pulmonary arterial pressure; and c) cardiac function. Infants with suspected congestive heart failure will also undergo formal echocardiography.

Outcomes

The primary outcome is time to resolution of hypoglycaemia, defined as the first time point at which all of the following criteria are met concurrently:

- No intravenous fluids for ≥24 hours (time recorded at the end of the 24-hour period).
- Enteral bolus feeding for ≥24 hours is defined as a) breastfeeding without supplements; or b) breastfeeding with supplements at >2 hourly intervals, or c) if not breastfeeding, gastric tube or bottle feeds at 3 to 4 hourly intervals (time recorded at the end of the 24-hour period).
- Normoglycaemia for ≥24 hours, defined as a minimum of four pre-feed BGC in the target range of 2.6 to 5.4 mmol/L (last BGC measured within 4 hours of primary outcome time point); four pre-feed BGC spanning >20 hours; no BGC out of range for ≥24 hours; time recorded at the end of the period).

The following secondary outcomes will be assessed from the time of randomisation:

- Time to achieve normoglycaemia (as per primary outcome)
- Time to establish enteral bolus feeding (as per primary outcome)
- Time to establish full sucking feeds defined as ≥five full breastfeeds (≥10 minutes) in 24 hours or ≥120 ml/kg/d of expressed breast milk or formula by bottle (up to discharge to home)
- Type of feeding at discharge from hospital and to home (breast milk, formula, mixed)
- Use of intravenous fluids and type
- Duration of intravenous fluids (up to discharge from hospital)
- Episodes of hypoglycaemia (BGC <2.6 mmol/L), elevated glucose concentration (BGC 5.5 to 6.9 mmol/L) and hyperglycaemia (BGC ≥7 mmol/L), including frequency, duration, timing and treatment before, during and after the episode (up to discharge from hospital)
- Number of blood glucose tests: during the study intervention and hospital admission
- Duration of admission to first discharge home: neonatal care, postnatal ward, community birthing unit
- Duration of study intervention (up to discharge from hospital)

- Guthrie metabolic screen (≥48 hours from birth)
- Plasma insulin, creatinine and diazoxide concentrations at ≥36 hours after commencing the intervention
- Death (up to discharge from hospital)
- Seizures (total; presumed hypoglycaemic) (up to discharge from hospital)
- Discontinuation of study intervention due to elevated BGC or hyperglycaemia (up to discharge from hospital)
- Discontinuation of study intervention due to another adverse event (serious; non-serious) (up to discharge from hospital)
- Congestive heart failure (respiratory distress as evidenced by tachypnoea, recession, or use of oxygen or positive pressure support with consistent chest x-ray findings, including cardiomegaly, plethora, interstitial fluid or effusions) (up to discharge from hospital)
- Commencement of low flow oxygen or positive pressure respiratory support (up to discharge from hospital)
- Cardiac ultrasound (Middlemore Hospital) at (≥72 hours)
    - Ductus arteriosus: closed; trivial (<1.5 mm and a constricted pattern on Doppler); patent (≥1.5 mm, growing, pulsatile or bidirectional pattern on Doppler)
    - Pulmonary hypertension: pulmonary artery pressure ≥systemic as estimated by tricuspid regurgitant jet (RV-RA gradient +5 mmHg) or ductal shunt right to left (>20%) with characteristic pulmonary Doppler envelope (TPV/ RVET <20%)
    - Cardiac impairment: left ventricular internal diameter diastolic z-score >2 and reduced systolic function (fractional shortening <25% or myocardial performance index >0.41)

Data management

Web-based data management is provided by the Clinical Data Research Hub at the Liggins Institute, University of Auckland. This includes a bespoke online randomisation system, with intervention stock management, that is integrated with the REDCap system.[27] Study data are collected directly into electronic case record forms (eCRF). Range and logic checks are used to reduce data entry errors. CGM data are captured in a secure cloud account and subsequently uploaded to the REDCap system.

A data monitor checks all eCRF for completeness and logic errors, after which eCRFs are locked. If the data monitor identifies potential errors, an electronic query is raised and referred to the site for checking.

Statistical analysis

Data analysis will be performed in SAS 9.4 (SAS Institute). Customised birthweight centiles will be calculated using GROW software (Perinatal Institute, United Kingdom). Population z-scores for weight, length and head circumference at birth will be calculated using UK-WHO centiles.[28]

Categorical data will be presented as number and percent, and continuous data as mean and standard deviation or median and inter-quartile range, as appropriate. Count data will be presented as median and inter-quartile range or grouped into ordinal categories. Denominators will be given for all outcomes.

In the primary analysis, intervention groups will be compared for the primary outcome using Cox's proportional hazard regression analysis, with treatment effect expressed as adjusted hazards ratio with a 95% confidence interval (CI). The analysis will be right censored at 4 weeks. Proportionality assumptions will be assessed by inspecting Kaplan-Meier curves and Schoenfeld residuals. Secondary outcomes will be compared between groups using generalised linear models (normal, binomial or Poisson) with treatment effect presented as adjusted odds ratio, count ratio, mean difference, or ratio of geometric means (positively skewed data), as appropriate, with 95% CI. Regression models will be adjusted for stratification variables (centre and customised birthweight centile, fixed effects), gestation length (fixed effect) and non-independence of multiples (random effect). If models fail to converge, the analysis algorithm will be optimised and the maximum number of iterations increased to get convergence with minimum Akaike Information Criteria (AIC). If this is unsuccessful,

adjustment variables may be collapsed or excluded if necessary, for model convergence. For significance tests, the alpha level will be set at 0.05 (two-tailed). No adjustment will be made for multiple comparisons but results for secondary outcomes will be interpreted cautiously. All infants who meet eligibility will be included in the primary analysis (modified intention-to-treat analysis). Secondary exploratory analysis may include per protocol analysis of the primary outcome.

Sample size

A trial of 74 babies randomised in a 1:1 ratio (37 per group) will give 80% power to detect a relative hazard of 2.0 (two-tailed alpha 0.05), assuming 90% of infants in each group have a primary outcome event within the study period (PASS Software 16). A hazard ratio of 2.0 indicates that the diazoxide group reaches the primary outcome at twice the rate (events per unit of time) of the control group. An adaptive sample size approach will be adopted where the number of randomised participants will be increased by the number of participants who withdraw or who are lost to follow-up.

Data and safety monitoring

An independent Data Monitoring and Safety Committee (DMSC) is monitoring recruitment, completeness of data acquisition and participant safety. The DMSC advises the Trial Steering Committee (TSC) on trial continuation or protocol modification. DMSC Terms of Reference were agreed upon before commencement of trial.

The following Serious Adverse Events (SAE) are reported to the DMSC for immediate review:

- Death
- Seizure
- Congestive heart failure
- Discontinuation of study intervention due to another serious adverse event, as judged by the site principal investigator or attending neonatologist (an adverse event is considered serious if it is immediately life-threatening, requires prolongation of hospitalisation or substantial escalation in care, or results in persistent or significant disability or incapacity)

SAE are reported until the time of primary hospital discharge. The TSC Chair notifies the DMSC Chair of all SAE within 72 hours of onset. The DMSC reviews SAE within 1 week of receiving the SAE report, to determine if participation in the trial is likely to be a causative factor and reports back to the TSC with the findings.

The DMSC will undertake an interim safety review when the primary outcome is known for 25% and 60% of participants, including rates of SAE and the following Adverse Events (AE) by masked treatment group:

- Hyperglycaemia (≥7 mmol/L)
- Discontinuation of study intervention due to elevated BGC (5.5 to 6.9 mmol/L) or hyperglycaemia
- Discontinuation of study intervention due to another adverse event (non-serious)
- Commencement of low flow oxygen or positive pressure respiratory support

There is no planned interim efficacy analysis.

Patient and public involvement

The NeoGluCO Study was presented and developed at an ON TRACK Network (https://ontrack.perinatalsociety.org.nz/) clinical trials workshop, Auckland, New Zealand in February 2020, which was attended by consumers, including parents of infants admitted to neonatal intensive care. Consumer input was received about study design and participant information.

Ethics and dissemination

Approval has been obtained from the Central Health and Disability Ethics Committee of New Zealand (reference 19CEN189) and by the local institutional research review committees at each centre.

The primary and secondary outcomes will be published in an international peer-reviewed journal and disseminated via presentations at local and international conferences to researchers and clinicians. The decision to publish is the responsibility of the Trial Steering Committee, which will have full access to the final data set. A lay summary of the research findings will be made available to those parents who indicated a wish to receive these on their consent forms.

Data availability

For each main publication, the corresponding data set will be electronically archived with the Clinical Data Research Hub, Liggins Institute, University of Auckland. Anonymised data may be shared with external researchers upon request, according to the Data Sharing Protocol of Research Hub (https://wiki.auckland.ac.nz/display/ontrack/Data+Sharing).

Discussion

Despite current management, infants with severe or recurrent transitional hypoglycaemia continue to have higher rates (approximately four-fold) of adverse neurological outcomes than at-risk infants without hypoglycaemia.[11] In addition, they often have prolonged neonatal admission, ongoing blood glucose instability despite the provision of intravenous fluids, and can be difficult to establish on enteral feeds.[10] New treatment approaches are needed that target the underlying pathophysiology, especially dysregulated insulin secretion, such as low-dose diazoxide.

A systematic review found low certainty evidence from one randomised trial that early use of diazoxide in SGA infants receiving intravenous dextrose for transitional neonatal hypoglycaemia decreased the duration of intravenous fluids and time to full enteral feeding by approximately 2 days.[29] Although there are no apparent adverse effects in this trial, several case series have highlighted a range of possible side effects, including pulmonary hypertension, oedema, heart failure, neutropenia, reopening of the ductus arteriosus, and necrotizing enterocolitis.[30-33] However, in other reports, serious side effects in otherwise well infants were rare,[16,34-36] suggesting that some of the conditions associated with diazoxide may reflect confounding. Randomised controlled trials are needed to generate unbiased effect estimates.

The NeoGluCO Study will provide high-quality evidence to determine if early use of low-dose oral diazoxide for severe or recurrent transitional hypoglycaemia in late preterm and term infants reduces the time to resolution of hypoglycaemia.

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Author contributions

CJDM, DL conceived and developed the study design, drafted the original study protocol, approved the final study protocol and drafted and reviewed the article for publication. EW contributed to the study design, approved the final study protocol and drafted and reviewed the article for publication. JMA, SMH, MPM, JA, WSC, JR, GJC and JEH contributed to the study design, approved the final version of the study protocol and reviewed the article for publication. GDG assisted with the sample size calculation and statistical analysis plan, contributed to the study design, approved the final version of the study protocol and reviewed the article for publication. All Authors are part of the Trial Steering Committee. The authors have no financial or other competing interests to declare.

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Competing interests

None

Patient consent for publication

Not required

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	*Oral diazoxide versus placebo for severe or recurrent neonatal hypoglycaemia: Neonatal Glucose Care Optimisation (NeoGluCO) Study; a randomised controlled trial.*	1
Trial registration	2a	*Trial registration ACTRN12620000129987*	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	*version 2.5, date 2021.11.11*	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors *All authors contributed to protocol development.*	1
	5b	Name and contact information for the trial sponsor *The trial sponsor is the corresponding author's listed institution (University of Auckland)*	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16-17
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8 and table 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) *Intervention is administered by hospital nurses and midwives from hospital drug charts*	7, 8 and table 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Table 1
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *This is an inpatient study*	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *There is no interim efficacy analysis.*	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Participant information sheet
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	Protocol
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Protocol and participant information sheet

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.