

❖ BACKGROUND

Hypoglycaemia (low blood glucose concentration [BGC]) is a common metabolic problem in newborns, affecting about 15% of all babies, and is a preventable cause of brain injury in infancy.¹ Buccal dextrose gel has been widely adopted as first-line management and is known to reduce admission to neonatal intensive care units (NICU) and to promote breastfeeding.² However, at least 20% of infants with neonatal hypoglycaemia still require admission to NICU due to severe or recurrent episodes (~2,000 per annum in New Zealand). These babies often have prolonged hospital admission, unstable glucose concentrations despite dextrose treatment, difficulty establishing enteral feeds and are at higher risk of neurological sequelae. The main cause of glucose instability in babies with severe or recurrent hypoglycaemia is dysregulated insulin due to prenatal exposures such as maternal diabetes and fetal growth restriction. New treatments are needed that target the underlying pathophysiology of this condition.

Early use of oral diazoxide is a potential new management strategy for transitional neonatal hypoglycaemia. Diazoxide acts on the pancreatic beta cell to slow insulin secretion, and preliminary evidence suggests that it improves the stability of BGC, reduces the duration of intravenous fluids and allows earlier introduction of feeds. Diazoxide has long been used for certain congenital (genetic) forms for hyperinsulinism, but it is currently not used for routine management of transitional neonatal hyperglycaemia.

❖ PURPOSE OF THE TRIAL

The **Neonatal Glucose Care Optimisation (NeoGluCO) Study** is a two-arm parallel, placebo-controlled randomised trial designed to investigate if early treatment of severe or recurrent neonatal hypoglycaemia with oral diazoxide reduces time to successful hypoglycaemia treatment, defined as achieving enteral bolus feeding and normal BGC concentrations without intravenous fluids

A secondary aim of the study is to evaluate the use of continuous glucose monitoring (CGM) Trend Alarms to determine when the BGC is out of target range and to indicate the need for a BGC check, potentially optimising glucose control and reducing heel-pricks for glucose monitoring.

❖ ENTRY CRITERIA

Inclusion Criteria:

1. Born at ≥ 35 weeks and admitted to NICU in the first week with recurrent or severe hypoglycaemia, defined by one or more of the following:
 - Any episode of hypoglycaemia < 1.2 mmol/L
 - BGC of 1.2 to < 2.0 mmol/L persisting after 2 doses of dextrose gel and feeding in a single episode
 - ≥ 3 episodes of hypoglycaemia < 2.6 mmol/L in 48 h
2. Babies must be receiving treatment for hypoglycaemia at the time of randomisation, e.g., IV dextrose, carbohydrate supplements, continuous or frequent feeding (≤ 2 hourly), or inability to wean off formula due to hypoglycaemia.
3. Prospective, written, informed consent.

Exclusion Criteria:

- Major congenital malformation or chromosomal disorder
- Suspected genetic syndrome associated with hypoglycaemia, e.g., Beckwith Wiedemann
- Gastrointestinal disorder affecting feeding
- Planned or likely neonatal surgery
- Confirmed sepsis (culture of pathogenic organism from blood, CSF or urine)
- Hypoxic ischaemic encephalopathy
- Family history of congenital hyperinsulinism
- Suspected inborn error of metabolism
- Triplet

❖ STUDY GROUPS

Eligible infants will be randomly allocated to either diazoxide (load 5 mg/kg, maintenance 1.5 mg/kg q12 h) or an equivalent volume of placebo, stratified by SGA status.

The study intervention will be titrated from the 3rd maintenance dose by algorithm, with the aim of targeting BGC 2.6 to 5.4 mmol/L. This range is based on normative data from the GLOW Study.³ If hypoglycaemia occurs > 24 h after commencing study drug, the maintenance dose may be increased according to the algorithm. The intervention will be stopped 12 h after the primary outcome is reached.

Feeds and fluid will be managed as per local protocol, but with the aim of weaning intravenous fluids and increasing enteral feeding as soon as possible.

❖ OUTCOMES

Primary:

The primary outcome is time to successful hypoglycaemia treatment, defined as achieving enteral bolus feeding and normal glucose concentrations without intravenous fluids. This is the first time point at which all the following occur concurrently:

1. Glucose stabilisation for ≥ 24 hours, defined as BGC in the target range of 2.6 to 5.4 mmol/L (minimum of four pre-feed BGC).
2. Enteral bolus feeding, for ≥ 24 hours defined as breastfeeding without supplements; or b) breastfeeding with supplements given at > 2 hourly intervals, or c) if not breastfeeding, gastric tube or bottle feeds at 3-4 hourly intervals.
3. No intravenous fluids for ≥ 24 hours.

Secondary:

1. Time to glucose stabilisation
2. Time to establish enteral bolus feeding
3. Time to establish full sucking feeds defined as \geq five full (code E/F) breastfeeds in 24 hours or ≥ 120 ml/kg/d of expressed breast milk or formula by bottle
4. Feeding at discharge from hospital and to home
5. Use of intravenous fluids and type
6. Duration of intravenous fluids
7. Episodes of hypoglycaemia (< 2.6 mmol/L), elevated glucose concentration (5.5 to 6.9 mmol/L) and hyperglycaemia (≥ 7 mmol/L)
8. Number of BGC tests
9. Duration of admission
10. Duration of study intervention
11. Plasma insulin, creatinine and diazoxide concentrations at ≥ 36 hours after commencing the intervention
12. Adverse Events

References

1. Harding JE, Harris DL, Hegarty JE, Alsweiler JM, McKinlay CJD. An emerging evidence base for the management of neonatal hypoglycaemia. *Early Hum Dev.* 2017;104:51-6.
2. Alsweiler JM, Harding JE, Crowther CA. Oral dextrose gel to treat neonatal hypoglycaemia: New Zealand clinical practice guidelines. 2015; Department of Paediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand.
3. Harris DL, Weston PJ, Gamble GD, Harding JE. Glucose profiles in healthy term infants in the first 5 days: the Glucose in Well Babies (GLOW) Study. *J Pediatr.* 2020; DOI: 10.1016/j.jpeds.2020.02.079

❖ 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 (2-tailed alpha 0.05), assuming 90% of infants in each group have a primary outcome event within the study period. A hazard ratio of 2.0 indicates that the diazoxide group reaches the primary outcome at twice the rate of the control group.

❖ GLUCOSE MONITORING

During weaning and stabilisation, and when defining the primary outcome, BGC should be measured at least every 6 hours (pre-feed if on enteral bolus feeding). Once glucose stability has occurred, BGC measurement frequency will be at clinical discretion but should be at least 12-hourly while on diazoxide or continuous glucose monitoring (CGM). Capillary, arterial or venous blood samples are acceptable and considered equivalent but must be tested by gas or laboratory analyser.

Babies enrolled in the trial will have a subcutaneous real-time CGM sensor inserted in the lateral thigh (Medtronic Guardian 3). It will be calibrated four times in the first 24 h, then every 12 h using BGC in the target range (2.6-5.4 mmol/L). Using Bluetooth transmission to a bedside tablet computer and remote cloud monitoring with text alerts, research staff will use pre-defined Trend Alert criteria to inform the clinical team that a BGC measurement is recommended, i.e., BGC is likely out of range.



CGM monitor insertion, lateral thigh.

NeoGluCO Investigators:

Dr Chris McKinlay (Principal Investigator, Site Investigator Middlemore Hospital), Dr Jane Alsweiler (Site Principal Investigator, Auckland City Hospital), Prof Jane Harding (Neonatologist), Prof Wayne Cutfield (Endocrinologist), Don Laing (Researcher), Jenny Rogers (Kaiarahi), Greg Gamble (Statistician), Prof Geoff Chase (Engineer), Dr Sara Hanning (Pharmacist), A/Prof Michael Myer (Neonatologist), Julena Ardern (Nurse Practitioner), Lisa Mravicich (Study Coordinator).

Funding:

This trial has been funded by the University of Auckland and Health Research Council.

Funding:

For more information contact Dr Chris McKinlay:

Email: c.mckinlay@auckland.ac.nz

Mobile: 0274725099



NEO GLU C O

Neonatal Glucose Care Optimisation Study



NEO GLU C O

Neonatal Glucose Care Optimisation Study

A Study to Optimise Care of Babies Admitted with Hypoglycaemia



Health Professional Brochure

CMH Study phone: 021897982