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Computer-determined dosage of insulin in the management of neonatal hyperglycaemia (HINT2): protocol of a randomised controlled trial

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ABSTRACT

Introduction: Neonatal hyperglycaemia is frequently treated with insulin, which may increase the risk of hypoglycaemia. Computer-determined dosage of insulin (CDD) with the STAR-GRYPHON program uses a computer model to predict an effective dose of insulin to treat hyperglycaemia while minimising the risk of hypoglycaemia. However, CDD models can require more frequent blood glucose testing than common clinical protocols. The aim of this trial is to determine if CDD using STAR-GRYPHON reduces hypoglycaemia in hyperglycaemic preterm babies treated with insulin independent of the frequency of blood glucose testing.

Methods and analysis: Design: Multicentre, non-blinded, randomised controlled trial. Setting: Neonatal intensive care units in New Zealand and Australia. Participants: 138 preterm babies ≤30 weeks' gestation or ≤1500 g at birth who develop hyperglycaemia (two consecutive blood glucose concentrations ≥10 mmol/L, at least 4 hours apart) will be randomised to one of three groups: (1) CDD using the STAR-GRYPHON model-based decision support system: insulin dose and frequency of blood glucose testing advised by STAR-GRYPHON, with a maximum testing interval of 4 hours; (2) bedside titration: insulin dose determined by medical staff, maximum blood glucose testing interval of 4 hours; (3) standard care: insulin dose and frequency of blood glucose testing determined by medical staff. The target range for blood glucose concentrations is 5–8 mmol/L in all groups. A subset of babies will have masked continuous glucose monitoring. Primary outcome: is the number of babies with one or more episodes of hypoglycaemia (blood glucose concentration <2.6 mmol/L), during treatment with insulin.

Ethics and dissemination: This protocol has been approved by New Zealand's Health and Disability Ethics Committee: 14/STH/26. A data safety monitoring committee has been appointed to oversee the trial. Findings will be disseminated to participants and carers, peer-reviewed journals, guideline developers and the public.

Trial registration number: 12614000492651

Strengths and limitations of this study

- This is the first randomised controlled trial to investigate the safety and effectiveness of computer-determined dosage of insulin (CDD) using the STAR-GRYPHON program in the management of neonatal hyperglycaemia.
- The trial's randomisation schedule incorporates three treatment groups to determine the independent effect of frequency of blood glucose sampling on outcomes.
- Blinded continuous glucose monitoring performed in a subset of participants will allow detailed assessment of glycaemic control and episodes of low interstitial glucose concentrations not detected on intermittent blood sampling.
- The trial intervention cannot be blinded.
- There is the potential for prescribing practices of clinicians in the control groups to change after exposure to the computer model. Analysis of pretrial and post-trial prescribing practices will allow detection of any contamination.

BACKGROUND

Approximately 2.4 million babies are born very preterm (<32 weeks' gestation) worldwide annually.[1 2] These babies have high rates of disability, including cerebral palsy and developmental delay.[3] Extremely preterm babies commonly develop hyperglycaemia in the neonatal period, with over 80% of babies weighing <1000 g developing blood glucose concentrations of >8 mmol/L.[4] Neonatal hyperglycaemia is associated with neonatal mortality and major neonatal morbidity including intraventricular haemorrhage,[5] retinopathy of prematurity[6] and a reduction in cerebral white matter volume,[7] all of which may lead to a poor neurodevelopmental outcome. However, it is not clear if the hyperglycaemia causes these morbidities or is

merely a marker for small sick babies who are at increased risk. There are no reliable data on the long-term neurodevelopmental outcomes of babies who experienced neonatal hyperglycaemia. A recent Cochrane review emphasised the need for large randomised trials to assess the effect of treatment of neonatal hyperglycaemia on long-term outcomes.[8]

Neonatal hyperglycaemia is often treated with an insulin infusion.[9] A randomised trial of tight glycaemic control in hyperglycaemic preterm babies (the Hyperglycaemia and Insulin in Neonates Trial (HINT) trial) showed that maintaining tight glycaemic control using insulin in hyperglycaemic babies facilitated weight gain, but increased the incidence of hypoglycaemia from 27% to 58%.[10] Similarly, the multicentre Neonatal Insulin Replacement Therapy in EURopE (NIRTURE) trial which randomised normoglycaemic very preterm babies to elective insulin therapy with dextrose replacement found hypoglycaemia incidence increased from 17% in the control to 29% in the insulin group.[11] Hypoglycaemia in preterm babies has been associated with adverse neurodevelopmental outcome.[12] Further, the development of hypoglycaemia during treatment with insulin has the potential to be particularly harmful as insulin also inhibits lipolysis and proteolysis, decreasing availability of alternative cerebral fuels. Observational studies in infants with congenital hyperinsulinism report that hypoglycaemic episodes are associated with poor neurodevelopmental outcomes and epilepsy.[13 14] However, there remains a paucity of data on long-term outcomes after hypoglycaemia secondary to an insulin infusion in preterm babies.

Current practice is for medical staff to titrate the insulin dose according to blood glucose measurements using a 'best guess' approach. As small sick babies often have rapid and unpredictable changes in insulin sensitivity,[15] this approach often leads to hypoglycaemia.[10] Computer-determined dosage of insulin (CDD) is a clinical decision support system that uses a computer model of metabolic physiology to calculate insulin dosing in hyperglycaemic patients. Trials of CDD using different models or algorithms have been shown to improve glycaemic control and reduce the incidence of hypoglycaemia in critically ill adults[16 17] and children.[18 19]

However, several trials have reported a high frequency of blood glucose testing with the use of some CDD.[20–23] Thus, it currently is unclear if the benefits of CDD are secondary to the CDD program itself or to the increased frequency of blood glucose testing which results in increased surveillance of the glycaemic control.

The CDD program, STAR-GRYPHON, has been developed specifically for preterm babies.[24–26] Unique to this CDD, STAR-GRYPHON uses a stochastic model to estimate the impact of future variability to determine a dose of insulin that minimises hypoglycaemic risk.[27] The prescribing clinician enters the current nutrition regimen and blood glucose concentration into the STAR-GRYPHON program. The STAR-GRYPHON program

estimates the baby's insulin sensitivity, forecasts the likely insulin sensitivity in the next few hours and calculates a range of insulin doses most likely to meet the targeted blood glucose concentration. A number of recommended treatment options, with the corresponding recommended blood glucose testing interval, are displayed for the clinician to choose from. A pilot study has shown this CDD program significantly improved glycaemic control and reduced episodes of hypoglycaemia in hyperglycaemic preterm babies on insulin compared with historic controls.[14]

We propose a randomised controlled trial to determine if CDD of insulin using STAR-GRYPHON for treatment of hyperglycaemic preterm babies reduces hypoglycaemia and improves neonatal growth and long-term outcome, independent of frequency of blood glucose testing.

AIMS
Primary aims
▶ To determine if hypoglycaemia can be reduced in hyperglycaemic preterm babies treated with insulin by means of CDD using STAR-GRYPHON.
▶ To determine the effect of frequency of blood glucose testing on the incidence of hypoglycaemia in these babies.

Secondary aims
▶ To determine the effect of CDD using STAR-GRYPHON on
 – the proportion of blood glucose measurements that remain in the target range (5–8 mmol/L);
 – neonatal growth and morbidity;
 – neurodevelopmental outcome.

STUDY DESIGN
Multicentre randomised controlled trial (see figure 1).

Entry criteria
Preterm babies ≤30 weeks' gestation or ≤1500 g at birth who develop hyperglycaemia (two consecutive blood glucose concentrations ≥10 mmol/L at least 4 hours apart) whose parents give written informed consent and in whom insulin is not contraindicated.

Exclusion criteria
Congenital abnormalities likely to affect life expectancy or neurological development; previous insulin treatment; judged to be at risk of imminent death.

Informed consent
All parents of babies who may become eligible because of their gestational age or birth weight will be provided with an information sheet. Written, informed consent will be obtained by a member of the research team either antenatally or as soon as is practical after birth. Babies will be randomised when they meet the criterion for hyperglycaemia. Parents or clinicians can withdraw

Figure 1 Flow chart of study pathway.
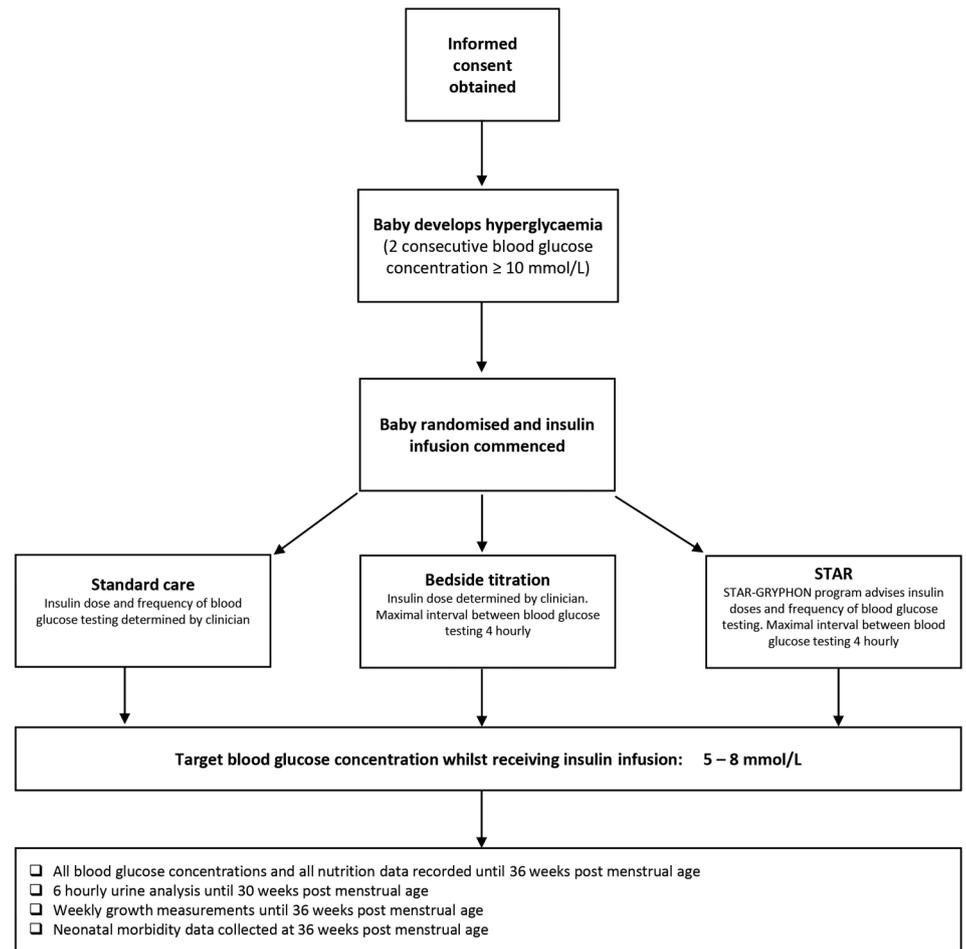
the baby from the study at any time. Should a baby be withdrawn from the trial, consent will be sought from the parents for ongoing data collection of blood glucose concentrations and urine analyses; nutrition and growth data; neonatal morbidities and neurodevelopment data.

TREATMENT ALLOCATION

Randomisation is by block randomisation with variable block size stratified by study centre and gestational age (<26 weeks vs ≥26 weeks). Assignment will be to one of three groups. The target blood glucose range for all treatment groups will be 5–8 mmol/L.

CDD using STAR-GRYPHON

Babies will have insulin dosing prescribed by clinicians using the dosage advice calculated by the computer model, STAR-GRYPHON, available on a computer tablet (Samsung Galaxy Tablet 3) at the bedside. Dosage and frequency of blood glucose testing are determined by the program, with a maximal interval between testing of 4 hours. *See earlier description of the program.*

Bedside titration

Babies will have the dose of insulin determined by the clinician. Once determined, the dose of insulin is entered into the bedside titration program on a tablet at the bedside. The bedside titration program displays the same interface as STAR-GRYPHON but does not perform calculations or give advice on insulin dosing. It is designed to record data in a similar format to the CDD STAR-GRYPHON group and capture the decision-making of the clinician in an electronic format. The program offers options for the frequency of blood glucose testing, with a maximal interval between testing of 4 hours, and the clinician selects from the options presented.

Standard care

Babies will have the dose of insulin and frequency of blood glucose testing determined by the clinician and local guidelines. No computer tablet is used and there are no restrictions placed on maximal time intervals between blood glucose testing.

Babies will remain in the same allocated randomisation group throughout their hospital stay. All concomitant care and interventions are permitted for the duration of the trial. If hyperglycaemia resolves but then recurs, the criteria for recommencing insulin are:

1. a single blood glucose concentration of ≥15 mmol/L, OR
2. two consecutive blood glucose concentrations ≥10 mmol/L at least 4 hours apart. Management will be according to randomisation group.

Justification for three treatment groups

Analysis of the three groups will allow the following questions to be addressed:

1. *CDD using STAR-GRYPHON v Standard Care*: Does STAR-GRYPHON reduce hypoglycaemia compared with 'best guess' approach to insulin titration?
2. *CDD using STAR-GRYPHON v Bedside Titration*: Does STAR-GRYPHON reduce hypoglycaemia compared with bedside titration independently of the effect of STAR-GRYPHON on blood glucose testing frequency?
3. *Bedside Titration v Standard Care:* Does an increased frequency of blood glucose testing by itself reduce hypoglycaemia?

OUTCOMES
Primary outcome

The number of babies who have one or more episodes of hypoglycaemia (any blood glucose concentration <2.6 mmol/L) detected by intermittent blood glucose testing, while receiving an intravenous insulin infusion.

Secondary outcomes

▶ Number of episodes of hypoglycaemia (one more consecutive blood glucose concentration <2.6 mmol/L) per baby, detected by intermittent blood glucose testing, while receiving an intravenous insulin infusion;
▶ time taken for the blood glucose concentration to reach target range (5–8 mmol/L), after beginning insulin infusion, detected by intermittent blood glucose testing;
▶ number of episodes of low interstitial glucose concentration (two or more consecutive interstitial glucose concentrations <2.6 mmol/L), detected by continuous glucose monitoring (CGM);
▶ area under the interstitial glucose concentration × time curve <2.6 mmol/L/min, while receiving an insulin infusion;
▶ time taken for interstitial glucose concentration to reach target range (5–8 mmol/L), after beginning insulin infusion, detected by CGM;
▶ proportion of measured blood glucose concentrations in the target range (5–8 mmol/L);
▶ proportion of time the interstitial glucose concentration is in the target range (5–8 mmol/L), detected by CGM;
▶ number of episodes of mild hypoglycaemia (one more consecutive blood glucose concentration <3.3 mmol/L) per baby, detected by intermittent blood glucose testing, while receiving an intravenous insulin infusion;
▶ severity of hypoglycaemia detected by intermittent blood glucose testing (the proportion of measured blood glucose concentrations below <2.2, <2.0 and <1.5 mmol/L);

▶ severity of low interstitial glucose concentrations detected by CGM (the proportion of time with interstitial glucose concentrations below <2.2, <2.0 and <1.5 mmol/L);
▶ number and volume of blood transfusions;
▶ glycosuria (number of days on which at least one urinalysis shows ≥2+ glucose while receiving treatment with insulin);
▶ growth: Z-score change from birth to 36 weeks' postmenstrual age and growth velocity of weight (calculated using the exponential method reported by Patel[28]), length and head circumference;
▶ neonatal morbidity: intraventricular haemorrhage, sepsis, retinopathy of prematurity, periventricular leucomalacia, chronic lung disease and necrotising enterocolitis;
▶ death before 36 weeks;
▶ death before discharge home;
▶ neurodevelopment at 2 years of age (Bayley III cognitive, language and motor scores; cerebral palsy and neurosensory impairment).

CLINICAL SURVEILLANCE
Blood sampling

Babies in the CDD using STAR-GRYPHON group will have the frequency of blood glucose testing determined by the clinician choosing one of the three recommendations calculated by the program based on the dosing options, at intervals of not <4 hours. Babies in the bedside titration group will have the frequency of blood glucose testing determined by the clinician, but at intervals not longer than 4 hourly. Babies in the standard care group will have the frequency of blood glucose testing determined solely by the clinician.

Blood glucose concentrations will be analysed by the glucose oxidase method only, using a blood gas machine (Radiometer , Copenhagen, Denmark) or a cotside portable gas machine (iSTAT, Abbot Laboratories, Abbott Park Ilinois, USA). Blood will be taken from arterial lines or capillary heel pricks. All blood glucose concentration measurements performed from starting insulin to stopping treatment will be analysed. We will collect data on the method of blood sampling, and do a sensitivity analysis to determine if this affects the primary outcome of hypoglycaemia.

Continuous glucose monitoring

In babies whose parents consent, CGM (iPro2 and Enlite sensor system, Medtronic, MiniMed, Northridge, CA, USA) will be in place for the first 2 weeks of insulin treatment to allow detection of low interstitial glucose concentrations that would not otherwise be detected by intermittent blood glucose monitoring.[29] The CGM data will not be displayed in real time and will therefore not influence clinical practice. Our previous work has shown that low interstitial glucose concentrations are more frequently detected by CGM than by intermittent blood

glucose sampling.[28] The CGM will be inserted by a member of the research team or a clinician trained in its use, preferably at least 1 hour before insulin is started but no later than 12 hours after the initiation of insulin. The CGM will be removed 12 hours after insulin treatment is discontinued. If the baby is restarted on insulin following the removal of the CGM, it will be reinserted on one further occasion only. The CGM sensor needs to be replaced after 7 days *in situ*. If the baby is on insulin for longer than 14 days, the CGM will be removed at the end of 14 days. The sensor site will be monitored frequently by the nursing staff for signs of possible infection or pressure trauma, and the sensor will be removed if there are any concerns.

Babies participating in HINT 2 outside of New Zealand will only have CGM sited if there is appropriate expertise with these devices available locally.

Growth
Babies will be weighed twice weekly and measured (occipito-frontal head circumference, and crown-heel length) weekly until 36 weeks' postmenstrual age.

Glycosuria
Urine will be tested for glycosuria with urine test strips (Multistix reagent strips, Bayer Healthcare, Bayer New Zealand, Auckland, New Zealand or equivalent strips if outside New Zealand) every 6 hours from enrolment in the study until 4 weeks' postnatal age or 30 weeks' postmenstrual age, whichever is the later.

Hypoglycaemia
Hypoglycaemia (<2.6 mmol/L) will result in cessation of an insulin infusion (if present) and additional interventions as per unit policy. Severe hypoglycaemia (<1.5 mmol/L) will be reported to the safety monitoring committee within 3 days.

Target range for blood glucose concentrations
Tighter glycaemic control has been shown to improve morbidity in some populations.[30] [31] However, the optimal target range for blood glucose concentrations in preterm babies has not been determined, leading to a wide variation in practice.[9] Previous studies of insulin use in preterm babies have used target ranges of 4–8 mmol/L[11] and 4–6 mmol/L.[10] A survey of practice in Australian and New Zealand tertiary neonatal units indicated that a target range with an upper limit of 8 mmol/L is commonly used, and a lower limit ranging from 3 to 6 mmol/L.[9] Two randomised controlled trials targeting glycaemic control using 4 mmol/L as the lower threshold had high rates of hypoglycaemia,[10] [11] suggesting that this lower limit of the target range could put babies at increased risk of low blood glucose concentrations. Therefore, in conjunction with the safety parameters set by the STAR-GRYPHON computer model from early trials, the target range for this trial was set slightly higher at a blood glucose concentration of 5.0–8.0 mmol/L. By analysing insulin sensitivity and using nutrition data, the CDD STAR-GRYPHON program predicts possible blood glucose outcomes and adjusts the dose of insulin to maximise overlap between the predicted blood glucose concentration band containing 90% of likely outcomes and the 5.0–8.0 mmol L target range. To ensure safety, the CDD STAR-GRYPHON program is designed to ensure a maximum 5% risk of blood glucose concentrations <4.4 mmol/L.[24] [32] [33] For babies not randomised to CDD using STAR-GRYPHON, clinicians will titrate the insulin dose to target a blood glucose concentration (BGC) between 5.0 and 8.0 mmol/L.

Risk of contamination
As clinical staff exposed to CDD using STAR-GRYPHON may alter their usual practice when treating a baby randomised to one of the other study arms, there is a potential risk of contamination. However, we did not experience significant contamination during our trial of tight glycaemic control,[10] with significant differences in the frequency of blood glucose testing and blood glucose concentrations maintained between the two groups. To address the potential for contamination, we will monitor the use of insulin and frequency of blood testing in the control group compared with historic controls to determine if contamination has occurred. In addition, we will record insulin dose used in all babies over the course of the trial to determine if staff practice in the control groups converges towards the CDD STAR-GRYPHON protocol.

ADVERSE EVENTS
All adverse events will be reported to an independent safety monitoring committee. Serious adverse events will be reported within 3 days.

Serious adverse events
▶ Severe hypoglycaemia (blood glucose concentration <1.5 mmol/L).
▶ Neonatal or infant death.

Adverse events
▶ A severe new intraventricular haemorrhage (grade III/IV).
▶ Sepsis (a positive bacterial or fungal culture of blood and/or cerebrospinal fluid, or a positive urine culture by sterile collection and after consideration of clinical and laboratory evidence, a decision is made to give the patient antibiotics with therapeutic intent against this organism for ≥5 days).

SAMPLE SIZE
In our previous study, 58% of babies in the tight glycaemic group with a target blood glucose concentration of 4–6 mmol/L experienced hypoglycaemia, compared with 38% of babies receiving insulin with a target blood

glucose concentration 8–10 mmol/L.[9] We estimate that 50% of babies receiving insulin with a target of 5–8 mmol/L will experience hypoglycaemia. Previous work with CDD has shown an incidence of hypoglycaemia of 22% in preterm babies receiving insulin.[15] To reduce the incidence of hypoglycaemia from 50% to 22% with 80% power, alpha 0.05 two tailed testing requires 46 babies in each group × 3 groups =138 babies. Recruitment to the trial will be monitored carefully and additional sites will be invited to join the trial to achieve adequate participant enrolment to reach the sample size.

DATA MANAGEMENT

Every baby randomised will be assigned a unique study number. All data will be collected using specific case report forms labelled with the allocated study number. Collected data will be double entered into a secure database to ensure data quality. All records will be secured in a locked drawer or password-protected computer database.

METHODS OF DATA ANALYSIS

The primary outcome of number of babies with one or more episodes of hypoglycaemia while receiving an insulin infusion will be analysed initially by χ^2 test. This will be followed by logistic regression analysis determining the effect of computer-determined dosage, frequency of blood sampling and their interaction on the primary outcome. Potentially confounding variables such as sex, birth weight Z-score and gestational age and any other prerandomisation likely confounders that differ between randomisation groups by 10% or more will be included in the regression models. Continuous data will be compared by student's t-test or the Mann-Whitney U test if the data are not normally distributed and cannot be converted to near normality by simple transformation. Data with repeated points, such as CGM data will be compared by repeated measures analysis of variance (ANOVA) or mixed models. Significance will be set at the 5% level. The data will be analysed initially on an intention to treat basis. A secondary, per protocol, analysis will then be performed.

The trial data set will be available to all the investigators with no limitations on access.

TRIAL IDENTIFICATION

The trial is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN: 12614000492651 12 May, 2014.

TRIAL OVERSIGHT AND DATA MONITORING

A trial steering group has been appointed to oversee the running of the trial. Any amendments to the protocol will be submitted to the ethics committee for approval. All approved amendments to the protocol will be communicated to the investigators and recorded at the front of the protocol. An independent data monitoring committee, consisting of two neonatologists and an experienced academic clinician will meet yearly to review trial recruitment, data quality, primary outcome and safety data. The data monitoring committee will report back to the trial steering group advising ongoing conduct of the trial.

COMPENSATION

Participants in New Zealand will be covered by the Accident Compensation Corporation (ACC) of New Zealand should any harm occur from trial participation.

DISCUSSION

Hyperglycaemia is common in preterm babies, and is often treated with insulin. The lack of high quality evidence to aid clinical decision-making during insulin treatment of hyperglycaemia in preterm babies has led to a wide variation in clinical practice.[9 34] Outcomes reported from the two published randomised controlled trials, HINT and NIRTURE, show insulin use in preterm babies is not without risk.[10 11] Both trials reported higher rates of hypoglycaemia in babies randomised to the interventions involving greater insulin use, with the potential for an increased risk of poor long-term neurodevelopmental outcome, although one trial was investigating insulin as a *treatment* for hyperglycaemia while the other was investigating insulin as *prevention* of hyperglycaemia.

The HINT trial[10] was designed to determine whether using insulin to treat and maintain tight glycaemic control in hyperglycaemic preterm babies improved growth without increasing hypoglycaemia. This trial reported that tight glycaemic control decreased linear growth but increased head circumference and weight gain. There were no differences in secondary outcomes of rates of mortality or neonatal morbidities between the two groups.[10] In contrast, the NIRTURE trial[11] investigated early elective insulin therapy in euglycaemic preterm babies to determine if insulin therapy prevented hyperglycaemia thus improving overall glycaemic control and mortality at expected date of delivery. Although a final analysis revealed no difference in mortality at expected date of delivery, an interim analysis found that death before 28 days was more common in the early insulin group. Non-protocol analysis of cranial ultrasound reports found an increased incidence of parenchymal lesions in the early intervention group (5.5% vs 0.7%) leading to suspension of the trial.[11] While additional subgroup analysis of the control arm of the NIRTURE has produced important information relating to prevalence and determinants of hyperglycaemia and CGM data,[4 35] early cessation of the trial means that it had limited statistical power. Thus the short-term outcome data from NIRTURE should be interpreted cautiously in considering potential risks and benefits of using insulin to *treat* hyperglycaemia in preterm babies.

We have defined the primary outcome of this trial as the number of babies who have one or more episodes of hypoglycaemia, defined as any blood glucose concentration <2.6 mmol/L, detected by intermittent blood glucose testing, while receiving an intravenous insulin infusion. The best definition of hypoglycaemia in preterm babies that leads to an increased risk of brain damage is currently unclear.[36] Two recently published guidelines from the American Academy of Pediatrics[37] and the American Pediatric Endocrine Society[38] have recommended different blood glucose concentrations; <2.6 and <3.3 mmol/L, respectively; as appropriate thresholds for intervention in newborns considered at risk of developing hypoglycaemia in the first few days after birth. Both identify the lack of high quality evidence to support the use of these thresholds, but recognise the need for a pragmatic approach in clinical care. Further, neither guideline provides specific guidance for preterm babies born <34 weeks gestational age. Two recent randomised controlled trials on insulin infusions in preterm babies defined hypoglycaemia as blood glucose concentration of <2.6 mmol/L,[10 11] and the commonly accepted definition of neonatal hypoglycaemia in the UK and Australasian neonatal units is also <2.6 mmol/L.[39 40]

HINT and NIRTURE have highlighted the need for insulin to be delivered effectively and safely if future studies are to be undertaken looking to improve glycaemic control and long-term outcomes in hyperglycaemic preterm babies. Our proposed trial aims to address this challenging issue. CDD using STAR-GRYPHON reduced the incidence of hypoglycaemia in preterm babies treated with insulin in comparison with historic controls, but there have been no randomised controlled trials of CDD using STAR-GRYPHON in this vulnerable very preterm population. A recent Cochrane review recommended trials to refine insulin algorithms in this population.[8] The approach of CDD using STAR-GRYPHON to reduce the incidence of hypoglycaemia in preterm babies treated with insulin needs to be formally tested by our proposed randomised controlled trial prior to being introduced into routine practice. If this technique is effective in preventing hypoglycaemia, it could provide a safe way of administering insulin in preterm babies and may improve neurodevelopmental outcome.

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