A randomized, controlled trial of Diazoxide and Glucagon in neonates with significant hypoglycaemia: THE GLAD study

Short title: Treating hypoglycaemia early with Glucagon And Diazoxide

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Study Design and Protocol

Aim

To determine if treatment with oral Diazoxide is more effective or easier to use than IV Glucagon in preventing treatment failure defined as the requirement for high concentration glucose infusion in hypoglycaemic infants of diabetic mothers.

Hypothesis

We hypothesise that oral Diazoxide treatment will reduce treatment failure defined as the need for high concentration glucose infusion in hypoglycaemic infants of diabetic mothers.

Methods/Design

Ethics

Ethics approval will be sought from the Women's and Children's Health Network Human Ethics Committee and from the local institutional research review committee. The ethics committee will be notified of any amendments to the study protocol.

Study Design

A randomised, controlled trial comparing continuous intravenous Glucagon infusion with oral Diazoxide as adjunctive therapy for neonatal hypoglycaemia in the first week of life in babies born of diabetic mothers (any type of diabetes).

Study population

Inclusion criteria

1. Infants of diabetic mothers (any type of diabetes)

AND satisfy ALL of the following:

1. Diagnosis of neonatal hypoglycaemia with requirement of >90ml/kg/day IV 10% glucose to maintain BGL >3.5
2. ≥ 35 weeks' gestation
3. Birth-weight more than 2.2 kg
4. Less than 12 hours old
5. Unlikely to require admission to NICU for any other reason e.g. respiratory distress

Exclusion criteria

1. Major congenital abnormality

Primary outcome

Treatment failure in allocated study arm defined as:

- requirement for continuous intravenous glucose infusion with >10% glucose to maintain blood glucose measurement ≥3.5mmol/l
- and/or failure to obtain central venous access if required
- and/or additional therapies (Diazoxide/Glucagon) required

Secondary outcomes

1. Serum Sodium ≤132 in the first 24 hours of treatment
2. Need for peripheral central venous catheter (hours)
3. Weight at 24 hours
4. Number of hypoglycaemic episodes (defined as ≤3.5mmol/l)
5. Length of stay in the nursery

Trial entry

Informed consent

Parents of babies who are likely to become eligible (maternal diabetes) will be identified through lead maternity carers and antenatal clinics and provided with an information sheet as early as is feasible. Written informed consent will be obtained when a diagnosis of neonatal hypoglycaemia is made, with a requirement for ≥90ml/kg/day intravenous 10% Glucose to maintain a blood glucose measurement ≥3.5mmol/l.

Randomisation

Participants will be randomly assigned to either the Diazoxide or Glucagon treatment groups with a 1:1 allocation according to computer generated block randomisation schedule. The block sizes will not be disclosed to ensure concealment.
Upon consent, the infant will be assigned a unique study number.

Discontinuation of randomised treatment

The allocated treatment can be stopped at any time at the request of the parents, or by the neonatologist caring for the baby if (s)he feels that stopping the treatment would be in the best interest of the baby. The baby will still be followed up and analysed according to the intention-to-treat principle.

Study groups

Starting doses:
Diazoxide – 5mg/kg/dose 8 hourly orally
Glucagon – 10microgram/kg/hr continuous intravenous infusion
Titrated to BGL response.

Blood glucose analysis

The blood glucose concentration will be measured at 1-2 and 4 hours of age, as per unit practice. Subsequent management will be according to hospital standard practices. All blood glucose concentrations will be analysed by the gold standard glucose oxidase method by a combined metabolite/ blood gas analyser (e.g. ABL 700, Radiometer Ltd, Copenhagen, Denmark).

Data analysis

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 blood glucose concentrations, will be compared using mixed model techniques, modelling the main effect of treatment group allocation, time and their interaction, with significant main effects and interactions tested using the method of Tukey. All tests will be two-tailed, with $P < 0.05$ considered significant. The data will be analysed on an intention-to-treat basis.

Economic evaluation

The cost-effectiveness of Diazoxide to prevent primary treatment failure will be compared with glucagon within the period to discharge. Resource utilisation will be obtained from a clinical record form identifying both length of stay (LOS) and relevant Diagnostic Related Group (DRG) code for the mother, plus any subsequent operative procedure (DRG), respiratory problem requiring treatment (DRG), and NICU admission for the baby (plus LOS). Costs will be assessed using Australian Department of Health cost weights and purchase unit prices.

Power and sample size

Typically, 50% of term infants of mothers with diabetes (gestational or insulin dependent) will be diagnosed as hypoglycaemic in our institution. Assuming a similar 10% rate of admission to NICU for intensive treatment, this would still result in 90 nursery admissions per year. In 2015-16 42 infants were prescribed Diazoxide for the management hypoglycaemia. We predict a 25% reduction in the rate of treatment failure in the Diazoxide arm of the study. This will require 100 infants who meet the eligibility criteria and a recruitment period of 2 years.

No head to head trial has been previously undertaken and there is no data on the effectiveness of either medication for this outcome. As such, a more pragmatic approach has been taken based on both clinical experience and available trial information. The authors propose the current trial size as a representative sample, being similar to the annual experience in our centre. We will recalculate sample size after enrolment of the first 25 babies.