Continuous glucose monitoring in extremely preterm infants in intensive care: the REACT RCT and pilot study of 'closed-loop' technology

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Scientific summary

The REACT RCT and pilot study of 'closed-loop' technology

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Scientific summary

Background

Hyperglycaemia and hypoglycaemia have both been associated with increased mortality and morbidity for preterm infants. However, controversy remains regarding the optimal management. This relates to the unique challenges in the extremely preterm infant when aiming to optimise nutritional intake, while also avoiding the risks of insulin-induced hypoglycaemia. Continuous glucose monitors are widely used in adults and children with diabetes to target glucose control, and have been trialled in intensive care, but they are not approved for use in neonates. Computer algorithms are also used to guide glucose management in patients with diabetes and have been trialled in adult intensive care patients, with variable benefits. This REAl-time Continuous glucose moniToring in neonatal intensive care (REACT) project aimed to evaluate the potential role of continuous glucose monitoring to support the use of insulin and additional glucose to target glucose control in the extremely preterm infant, both alone and in combination with a bespoke computer algorithm.

Objectives

- To undertake a single-centre feasibility study of continuous glucose monitoring in preterm infants to inform the design of a multicentre randomised controlled trial.
- To evaluate the clinical role of continuous glucose monitoring in terms of efficacy, safety, utility and cost-effectiveness through a multicentre randomised controlled trial.
- To pilot the potential use of a 'closed-loop' system for glucose control using continuous glucose monitoring.

Feasibility study

Objectives

To inform the design of a multicentre randomised controlled trial through provisional assessment of accuracy, safety and utility of the intervention, and to explore the primary outcome measure of time in target (i.e. 2.6–10 mmol/l) to inform power calculations.

Methods

A single-centre study with eligibility criteria of birthweight $\leq$ 1200 g and aged $\leq$ 48 hours. The intervention lasted for up to 7 days. Infants had an Enlite™ sensor (Medtronic plc, Watford, UK) inserted in their lateral thigh and linked to a MiniMed™ Paradigm® Veo™ system (Medtronic plc). The sensor glucose data were used alongside a paper guideline to support the clinical management of glucose control. The study received all necessary ethics and regulatory approvals, and informed consent was received prior to any study interventions.

Results

Twenty-one infants were recruited and one infant was withdrawn because of failure of sensor insertion.

Accuracy

Comparative data demonstrated a mean absolute relative difference of 10% and 11% between blood glucose levels measured on the continuous glucose monitor and on the blood gas analyser and Novostat (Nova Biomedical, Waltham, MA, USA) meter, respectively.

Safety
There were no serious adverse device effects. Three infants had an episode of hypoglycaemia (i.e. blood glucose of < 2.6 mmol/l) related to the loss of intravenous access, and the infants were asymptomatic, clinically well and not on insulin. There were no concerns about skin integrity or infection at the sensor site.

Utility and staff acceptability
Nursing staff were positive about the impact on care in terms of feeling more empowered to manage the infant's glucose control and reported that the use of continuous glucose monitoring led to better care. However, staff found the use of both predictive and threshold alarms challenging. The median of the mean number of blood samples per day for an infant was 4.1 (range 3.3–4.3).

Efficacy data
Sensor data were available from 20 infants. The median percentage of time in the primary target range (i.e. 2.6–10 mmol/l) was 78% (interquartile range 59–94%) and the median percentage of time in the secondary target range (i.e. 4–8 mmol/l) was 46% (interquartile range 35–66%), with a standard deviation of sensor glucose of 2.39 mmol/l (95% confidence interval 1.78 to 3.67 mmol/l).

Conclusion
Based on the feasibility data, the standard deviation of the primary outcome (time in target range of 2.6–10 mmol/l) was conservatively estimated at 22% and, therefore, it was calculated that the sample size required to provide 90% power to detect a difference of 10%, at the 5% significance level, was 200 infants. Consensus was reached among expert opinion from the Trial Steering Committee and Data Monitoring and Ethics Committee that a 10% difference would be clinically meaningful.

Randomised controlled trial

Trial objectives
To evaluate the efficacy, safety, utility and cost-effectiveness of real-time continuous glucose monitoring in preterm infants in neonatal intensive care.

Methods

Study design
A multicentre interventional randomised controlled trial comparing the use of continuous glucose monitoring with standard clinical management of glucose control in preterm infants. Participants were recruited from 13 level 3 neonatal intensive care units across Europe. Infants were recruited within 24 hours of their birth and underwent continuous glucose monitoring for the first 6 days of life. Data were collected until 36 weeks' corrected gestational age.

Eligibility
Preterm infants were eligible for trial entry if they weighed ≤ 1200 g at birth, were aged ≤ 24 hours and ≤ 33^{+6} weeks gestation, and there was informed parental consent. Infants were excluded if they had a lethal congenital abnormality, any congenital metabolic disorder or no realistic prospect of survival at trial entry. Following consent, infants were randomised in a 1 : 1 ratio to either the control or the intervention arm of the study using a web-based randomisation system.

Intervention: continuous glucose monitoring with guideline
Each infant had a subcutaneous Enlite sensor inserted and linked to a MiniMed™ 640G (Medtronic plc). Clinical staff were advised to use the continuous glucose monitor glucose readings in combination with a written guideline for management of glucose control. The guideline was developed during the REACT feasibility study.

Control: standard care

Each infant had a subcutaneous Enlite sensor inserted and linked to a MiniMed™ 640G. The device collected glucose data continuously, but the display screen was masked to clinical staff. Glucose control was managed in accordance with local standard clinical care using point-of-care blood glucose monitoring.

Outcomes

The primary outcome measure was the percentage of time during which the sensor glucose level was in the target range of 2.6–10 mmol/l during the first 6 days of life.

The secondary outcome measures were categorised as efficacy, safety, acceptability or health economics outcomes, or as exploratory clinical outcomes:

- efficacy –
  - mean sensor glucose in the first 6 days of life
  - percentage of time sensor glucose is in the target range of 4–8 mmol/l within the first 6 days of life
  - sensor glucose variability within individuals, as assessed by within-patient standard deviation
  - percentage of time glucose levels are in the hyperglycaemic range (i.e. sensor glucose > 15 mmol/l)
- safety –
  - incidence of hypoglycaemia, defined as any episode of blood glucose of > 2.2 mmol/l and < 2.6 mmol/l
  - incidence of hypoglycaemia, defined as a continuous episode of sensor glucose of < 2.6 mmol/l for > 1 hour
  - incidence of hypoglycaemia, defined as any episode of blood glucose of ≤ 2.2 mmol/l
- acceptability –
  - clinical staff rating score of impact on clinical care
  - frequency of blood glucose monitoring
  - clinical use of guideline
- health economics –
  - cost-effectiveness expressed in terms of incremental cost per additional case of adequate glucose control (defined as > 80% time spent between 2.6 and 10 mmol/l)
- exploratory outcomes –
  - mortality and morbidity before 36 weeks' corrected gestational age.

An independent Data Monitoring Ethics Committee was established to review safety data from the trial and trial management was overseen by the Trial Steering Committee.

Results

A total of 182 infants were recruited to the trial. The mean time in the glucose target range of 2.6–10 mmol/l was 9% higher in infants in the continuous glucose monitoring group than in infants in the control arm (95% confidence interval 3% to 14%; $p = 0.002$). In the case of the glucose target level range of 4–8 mmol/l, the mean percentage of time in the target range was 12% higher in the intervention group (95% confidence interval 4% to 19%; $p = 0.004$). There was no difference in the number of episodes of hypoglycaemia between the arms. Exploratory outcomes showed a reduced risk of necrotising enterocolitis (odds ratio 0.33, 95% confidence interval 0.13 to 0.78; $p = 0.01$)

in the intervention arm compared with the control arm. Both staff and parents reported that the use of continuous glucose monitoring improved care and the continuous glucose monitoring was found to be dominant in health economic terms.

Conclusions

Continuous glucose monitoring in preterm infants can support the use of insulin and glucose to optimise glucose control, reducing exposure to hyperglycaemia without increasing the risk of hypoglycaemia. Staff and parents felt that the use of continuous glucose monitoring improved care. Economic evaluation demonstrated that, over the first 7 days, continuous glucose monitoring is, on average, more costly and more effective than standard care. Assuming cost-effectiveness thresholds of £1000, £5000 and £10,000, the probability of cost-effectiveness for continuous glucose monitoring reached 90% at approximately £6000, whereas the net monetary benefit associated with continuous glucose monitoring became positive at a cost-effectiveness threshold of £5000. However, in terms of clinical impact over a time horizon extending to 36 weeks' corrected gestational age, continuous glucose monitoring was, on average, less costly and more effective, and therefore dominant in health economic terms.

Closed-loop system

Objectives

Assessment of the potential for continuous glucose monitoring combined with a computer algorithm, 'closed loop', to be more effective in targeting glucose control in extremely preterm infants than the use of continuous glucose monitoring combined with a simple paper guideline.

Methods

A single-centre study with eligibility criteria of birthweight $\leq$ 1200 g and aged $\leq$ 48 hours. All infants underwent subcutaneous continuous glucose monitoring in the first week of life, with those in the intervention group receiving closed-loop insulin delivery between 48 and 72 hours of age. The primary outcome was percentage of time in target range (i.e. sensor glucose level of 4–8 mmol/l).

Results

Data from 20 infants showed the time in the target range increased from a median of 26% (interquartile range 6–64%) with paper guidance to 91% (interquartile range 78–99%) during closed-loop insulin delivery ($p < 0.001$), without increasing hypoglycaemia.

Conclusions

Closed-loop glucose control based on subcutaneous glucose measurements is feasible and has the potential to further target glucose control in extremely preterm infants.

Implications for health care

The findings of these studies demonstrate that continuous glucose monitoring in preterm infants can increase the time in the glucose target range of 2.6–10 mmol/l compared with standard clinical care. The study highlighted the challenges of using devices that are not designed for preterm infants, and the need for devices that can address the unique physiological and pathological challenges facing these infants, and the staff and parents caring for them. Robust pathways are needed to encourage the development and validation of devices for use in such vulnerable populations.

'Closed-loop' technology has the potential to provide a further personalised approach to targeting glucose control. The trial data clearly demonstrated the wide variability between infants, and it is in this context that such intelligent algorithms can help to optimise care. It could also help to address some of the challenges of providing optimal care in very busy neonatal intensive care units where it is acknowledged that there is sometimes a shortage of adequately trained nursing staff to deliver care. Importantly, despite

the potential additional workload of a clinical trial, the staff and parents reported that they felt that the use of continuous glucose monitors improved care. It will therefore be important to ensure that these devices can be introduced into clinical practice in a robust manner to ensure adequate support and training for staff so that the devices are used effectively and safely in this population.

Despite the challenges, the health economic analysis demonstrated the use of continuous glucose monitors to be favourable even over a relatively short time horizon. Exploratory analysis also showed a reduced risk of necrotising enterocolitis, but this trial was underpowered to determine the impact on other clinical outcomes, and larger studies are needed to confirm if this is a robust finding and to look at other impacts. Further studies are also needed to elucidate the optimal targets of glucose control to improve long-term health outcomes. Continuous glucose monitor technology is well placed to support such studies.

Recommendations for research

The findings of the REACT project raise the following important questions that need to be addressed in further studies.

Short term

- What is the optimal glucose target range for preterm infants at this time?
- What is the prevalence of glucose dysregulation throughout the preterm course on a neonatal intensive care unit?
- What is the role of continuous glucose monitoring in infants in the neonatal intensive care unit who are at risk of glucose dysregulation for other reasons, such as following hypoxic–ischaemic insults and during cooling?

Future

- Can we design a continuous glucose monitor that is better suited to the unique physiology and pathology of the newborn?
- Can we design 'closed-loop' systems that will support staff in further safely targeting glucose levels in these infants and save staff time?

Long term

- What is the impact of silent hypoglycaemia in preterm infants?
- What is the impact of 'optimising' glucose control in the preterm infant on health outcomes?

Trial registration

This trial is registered as ISRCTN12793535.

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This report

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