A clinical and economic evaluation of Control of Hyperglycaemia in Paediatric intensive care (CHiP): a randomised controlled trial

Duncan Macrae,[1]* Richard Grieve,[2] Elizabeth Allen,[3] Zia Sadique,[2] Helen Betts,[1] Kevin Morris,[4] Vithayathil John Pappachan,[5] Roger Parslow,[6] Robert C Tasker,[7] Paul Baines,[8] Michael Broadhead,[9] Mark L Duthie,[10] Peter-Marc Fortune,[11] David Inwald,[12] Paddy McMaster,[13] Mark J Peters,[9] Margrid Schindler,[14] Carla Guerriero,[2] Deborah Piercy,[3] Zdenek Slavik,[1] Claire Snowdon,[3] Laura Van Dyck[3] and Diana Elbourne[3]

[1]Royal Brompton Hospital, London, UK
[2]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK
[3]Medical Statistics Department, London School of Hygiene and Tropical Medicine, London, UK
[4]Birmingham Children's Hospital, Birmingham, UK
[5]Southampton General Hospital, Southampton, UK
[6]Faculty of Medicine and Health, University of Leeds, Leeds, UK
[7]Boston Children's Hospital, Boston, MA, USA
[8]Alder Hey Hospital, Liverpool, UK
[9]Great Ormond Street Hospital for Children, London, UK
[10]Glenfield Hospital and Leicester Royal Infirmary, Leicester, UK
[11]Royal Manchester Children's Hospital, Manchester, UK
[12]St Mary's Hospital, London, UK
[13]University Hospital of North Staffordshire, Stoke-on-Trent, UK
[14]Bristol Royal Hospital for Children, Bristol, UK

*Corresponding author

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Scientific summary

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Scientific summary

Background

Early research in adults admitted to intensive care suggested that tight control of blood glucose during acute illness can be associated with reductions in mortality, length of hospital stay and complications such as infection and renal failure. There was no clear information, however, about whether or not there were different effects for adults in surgical compared with medical intensive care; nor was there clear information concerning the longer-term economic implications of controlling blood glucose. In addition, despite over 10,000 children being admitted to paediatric intensive care units (PICUs) in England and Wales each year, the research did not include children.

Objectives

The objective of the Control of Hyperglycaemia in Paediatric intensive care (CHiP) trial was to determine if a policy of strictly controlling blood glucose [tight glycaemic control (TGC)] using insulin reduces mortality and morbidity and is cost-effective in children admitted to PICUs, whether or not admission follows cardiac surgery.

The primary hypothesis was that:

- TGC will increase the numbers of days alive and free of mechanical ventilation within 30 days of trial entry (VFD-30) for children aged ≤ 16 years on ventilatory support and receiving vasoactive drugs.

The secondary hypotheses were that:

- TGC will lead to improvement in a range of complications associated with intensive care treatment.
- TGC will be cost-effective.
- The clinical effectiveness of TGC will be similar whether children were admitted to a PICU following cardiac surgery or for other reasons.
- The cost-effectiveness of TGC will be similar whether children were admitted to a PICU following cardiac surgery or for other reasons.

Methods

Children were eligible for trial entry if they:

- were ≥ 36 weeks corrected gestational age and ≤ 16 years
- were admitted to the PICU following injury, following major surgery or in association with critical illness, and it was anticipated treatment would be required to continue for at least 12 hours
- had an arterial line in situ and were receiving both mechanical ventilation and vasoactive drugs.

Children were excluded prior to trial entry if they:

- were born preterm (≤ 36 weeks corrected gestational age)
- had diabetes mellitus
- had an established or suspected diagnosis of an inborn error of metabolism

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- were children for whom treatment withdrawal or limitation of intensive care treatment was being considered
- had been in a PICU for > 5 consecutive days
- had already participated in the CHiP study during a previous PICU admission.

After consent by parents/guardians, children were randomised to either of the following:

- TGC: insulin by intravenous infusion titrated to maintain a blood glucose between the limits of 4.0 and 7.0 mmol/l.
- Conventional management (CM): insulin by intravenous infusion only if blood glucose levels exceeded 12 mmol/l on two blood samples taken at least 30 minutes apart and discontinued once blood glucose fell to < 10.0 mmol/l.

Patients not entered into the trial received standard care.

Standard insulin solutions were used and changes in insulin infusion rates were guided by the glucose levels from arterial blood sampling using commercially available 'point-of-care' blood gas analysers. Training in the use of the glucose control protocol was provided.

To reduce the risk of selection bias at trial entry, allocation was carried out through a central computerised 24-hour, 7-day-a-week randomisation service. Minimisation with a probabilistic element was used to ensure a balance of key prognostic factors between arms. The minimisation criteria were centre; age ≤ 1 year compared with between 1 year and ≤ 16 years; admission following cardiac surgery or not; for children admitted for cardiac surgery, Risk-adjusted Classification for Congenital Heart Surgery 1 (RACHS1) categories 1–4 compared with 5–6; for children not admitted for cardiac surgery, Paediatric Index of Mortality version 2 (PIM2) score categorised by probabilities of death of < 5%, 5% to < 15% and ≥ 15%; and accidental traumatic brain injury (TBI) or not.

Following randomisation, care-givers and outcome assessors were no longer blind to allocation.

The primary outcome measure was VFD-30. A difference of 2 days in VFD-30 was considered clinically important. Taking a type I error of 1% (with a two-sided test), with an overall standard deviation across both cardiac and non-cardiac strata of 7 days, a total sample size of 750 patients would have 90% power to detect this difference. The target size was inflated to 1000 to take account of possible dilution of effect. The trial was powered to be able to detect whether or not any effect of tight glucose control differed between the cardiac surgery and non-cardiac surgery strata. To have 80% power for an interaction test to be able to detect a difference of 2 days in the effect of intervention between the strata at the 5% level of statistical significance, the sample size was increased to 1500.

Secondary outcomes were assessed at PICU discharge or 30 days after randomisation (if on PICU ≥ 30 days) and at 12 months. The short-term outcomes included mortality; duration of ventilation, length of PICU and hospital stay; readmission rates; renal replacement therapy; infection; transfusions; seizures; paediatric organ dysfunction score; and hypoglycaemia. The 12-month outcomes included mortality; attention and behaviour in TBI patients; and total duration of PICU and hospital stay. Additional outcomes for the economic evaluation included hospital costs within 30 days of trial entry; hospital and community health service costs within 12 months of trial entry; and lifetime incremental net benefits calculated by valuing quality-adjusted life-years (QALYs) at the recommended threshold of £20,000 per QALY. All future costs and life-years were discounted at the recommended rate of 3.5%.

Resource-use data were collected on the trial case report forms. Data on the level of care for PICU bed-days were available through the *Paediatric Critical Care Minimum Data Set*, extracted via the Paediatric Intensive Care Audit Network. Other data on hospital and community service use at 12 months were collected from parents by postal questionnaire for patients randomised before 30 October 2010. Unit costs were taken

from the 2011 NHS Payments by Results database. For children who survived to hospital discharge, vital status at 12 months post randomisation was recorded using information from the participating PICUs, the children's general practitioners (GPs) or the NHS Information Centre and the NHS Central Register.

Primary analyses were by intention to treat. For the primary outcome, linear regression models were used to estimate a mean difference in VFD-30 between the two arms of the trial. For the secondary outcomes, appropriate generalised linear models were used to examine the effect of the intervention. Odds ratios and mean differences are reported with 95% confidence intervals (CIs). Non-parametric bootstrapping was used when appropriate. Multiple imputation was used to handle missing data. Sensitivity analyses (SAs) were undertaken to investigate whether or not results were robust to alternative approaches, including the approaches taken to unit costing, handling missing data and extrapolating survival in the lifetime cost-effectiveness analysis.

Prespecified subgroup analyses were planned for cardiac surgical compared with non-cardiac surgical cases, age (< 1 year or between 1 and ≤ 16 years), TBI or not, RACHS1 (cardiac cases) (groups 1–4 vs. 5 and 6), PIM2 risk of mortality (non-cardiac cases) (categorised by probabilities of death of < 5%, between 5% and < 15% and ≥ 15%) and run-in cases (first 100 randomised) compared with non-run-in cases. Likelihood ratio tests for interactions were used to assess whether or not there was any difference in the effect of the intervention in the different subgroups.

An independent Data Monitoring and Ethics Committee (DMEC) was established to review data from the trial in strict confidence, using the Peto–Haybittle stopping rule.

Results

Trial recruitment began on 4 May 2008 and was slower than expected, mainly because of delays in trial initiation at some sites, clinical constraints and a 'research learning curve' in many of the participating units that had no previous experience of recruiting critically ill children to clinical trials. The DMEC confidentially reviewed unblinded interim analyses on two occasions. In addition, they met to discuss serious adverse events and recruitment rates on three further occasions. Recruitment closed on 31 August 2011. A total of 19,924 children were screened from 13 sites. Of these, 1384 were recruited and randomised (701 to TGC and 683 to CM). Of the 1384, 15 were subsequently found to be ineligible, leaving 1369 eligible children (694 to TGC and 675 to CM) randomised into the trial – 91% of the original target of 1500.

The randomised groups were broadly comparable at trial entry. Sixty-two per cent were randomised within 1 day of admission to PICU. In terms of the prespecified stratifying factors, two-thirds were aged under 1 year, and 60% of the children were in the cardiac surgery stratum. In the cardiac surgery stratum, 7% of children were considered to be undergoing surgical procedures associated with a high risk of mortality (RACHS1 score 5 or 6), and 19% of children in the non-cardiac group had a PIM2 score indicative of > 15% risk of PICU mortality.

The management of blood glucose differed between the two arms of the study. In the TGC arm, 461 of the 694 children (66%) received insulin compared with 109 of 675 (16%) in the CM arm. Children in the TGC arm received more insulin, received insulin treatment earlier and continued insulin treatment for longer.

The primary outcome, the mean VFD-30, was 23 in both trial arms (mean difference 0.36; 95% CI –0.42 to 1.14).

The secondary outcomes up to 30 days were similar between the arms, although less renal replacement therapy was carried out in the TGC arm (odds ratio 0.63; 95% CI 0.45 to 0.89). Hypoglycaemia occurred in a greater proportion of patients in the TGC arm than in the CM arm of the study (moderate, 12.5% vs. 3.1%, $p < 0.001$; severe, 7.3% vs. 1.5%, $p < 0.001$).

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None of the interaction tests between the intervention and prespecified subgroups for the primary outcome were statistically significant, suggesting that there was no difference in the effect of TGC on VFD-30 in the different strata.

For the index hospital episode, the mean number of PICU bed-days, the length of stay on general medical wards and the total length of stay were similar between arms. The mean total number of hospital days up to day 30, including both the initial episode and readmissions to the initial PICU before day 30, was also similar between arms. For the stratum admitted to PICUs following cardiac surgery, the mean total length of stay was again comparable between arms, but, for the non-cardiac surgery stratum, the mean numbers of PICU days and the length of stay on general medical wards and in total were lower for the TGC than the CM arm.

Overall, the mean total costs at 30 days post randomisation were similar between arms. For the cardiac surgery stratum, the mean total costs per patient were £16,228 (TGC) and £17,005 (CM). For the non-cardiac surgery stratum, the TGC arm had lower mean costs than the CM arm, with an incremental cost of –£2319 (95% CI –£4702 to £124).

Between 30 days and 12 months post randomisation, the mean numbers of days in a PICU, on general medical wards and in total were lower for the TGC than the CM arm. For the cardiac surgery stratum, the mean total length of stay at 12 months was similar between arms. For the non-cardiac surgery stratum, the TGC arm reported fewer days on PICUs, on general medical wards and in total at 12 months post randomisation (mean total hospital days at 12 months, 31.0 for the TGC arm vs. 44.5 for the CM arm).

Mortality at 12 months was similar between the randomised arms, and no differences were found between the two arms of the trial in attention and behaviour measures for the 13 patients with TBI.

The mean total costs at 12 months were lower in the TGC than in the CM arm (incremental costs –£3620, 95% CI –£7743 to £502). For the cardiac surgery stratum, the mean total costs were similar between arms (incremental costs £133, 95% CI –£3568 to £3833), but, for the patients not admitted for cardiac surgery, the mean costs were lower in the TGC than in the CM arm, with an incremental cost of –£9865 (95% CI –£18,558 to –£1172).

Sensitivity analyses showed that the results were robust to alternative approaches for calculating unit costs, or handling missing data.

Overall, the lifetime incremental net benefits were high (£3346, 95% CI –£11,203 to £17,894). For patients admitted for cardiac surgery, the incremental net benefits were close to zero (–£919, 95% CI –£16,661 to £14,823). For patients not admitted for cardiac surgery, the incremental net benefits were positive (£11,322, 95% CI –£15,791 to £38,615). The cost-effectiveness acceptability curves consider alternative thresholds of willingness to pay for a QALY gain, and show that overall, and for the cardiac surgery stratum, it is highly uncertain that TGC is cost-effective. For the non-cardiac stratum, the probability that TGC is cost-effective is relatively high. For example, at ceiling ratios of £10,000 to £30,000 per QALY, the probabilities that TGC is cost-effective range from 90% to 70%.

The SAs suggest that these findings are robust to alternative assumptions about the extrapolation of long-term survival, quality of life for PICU survivors or long-term costs.

Conclusions

Implications for health care

This study found no differences in the effectiveness of TGC compared with CM, according to the primary outcome measure, both overall and for prespecified subgroups. The secondary clinical outcomes were generally similar between the arms, but a lower proportion of the TGC arm had renal replacement therapy, and a higher proportion had hypoglycaemia. For the cardiac surgery subgroup, average costs at 12 months post randomisation were similar between arms, and TGC was unlikely to be cost-effective. For the subgroup not admitted for cardiac surgery, average costs at 12 months post randomisation were lower for the TGC than the CM arm. Therefore, TGC is likely to be cost-effective for patients not admitted for cardiac surgery.

The majority of PICUs in the NHS currently provide CM for patients who meet this study's inclusion criteria. For children following cardiac surgery, our study does not offer any evidence to suggest that PICUs should stop CM for these patients. For children admitted to PICUs for other reasons, TGC can reduce NHS costs. However, before a policy of TGC can be recommended for this subgroup, the potential for cost savings has to be weighed against the small increased risk of hypoglycaemia, and further investigation of the long-term clinical effectiveness and cost-effectiveness of TGC compared with CM is warranted.

Recommendations for research

The findings of the CHiP trial raise the following important questions to be addressed in follow-on studies:

1. Does the excess rate of moderate and severe hypoglycaemia during TGC for children admitted to PICUs for reasons other than cardiac surgery have an impact on long-term neurodevelopmental outcomes?
2. Can we improve the delivery of TGC to minimise the risk of hypoglycaemia?
3. Does TGC in critically ill children protect the kidneys from injury?
4. Do the findings from CHiP apply to routine clinical practice?
5. What can be learnt from triallists, clinicians, parents and older children about their experiences of participating in CHiP to aid the design and conduct of future PICU trials?

Trial registration

This trial is registered as ISRCTN61735247.

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