Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study

Dirk Vlasselaers, Ilse Milants*, Lars Desmet*, Pieter J Wouters, Ilse Vanhorebeek, Ingeborg van den Heuvel, Dieter Mesotten, Michael P Casaer, Geert Meyfroidt, Catherine Ingels, Jan Muller, Sophie Van Cromphaut, Miet Schetz, Greet Van den Berghe*

Summary

Background **Critically ill infants and children often develop hyperglycaemia, which is associated with adverse outcome; however, whether lowering blood glucose concentrations to age-adjusted normal fasting values improves outcome is unknown. We investigated the effect of targeting age-adjusted normoglycaemia with insulin infusion in critically ill infants and children on outcome.**

Methods **In a prospective, randomised controlled study, we enrolled 700 critically ill patients, 317 infants (aged <1 year) and 383 children (aged ≥1 year), who were admitted to the paediatric intensive care unit (PICU) of the University Hospital of Leuven, Belgium. Patients were randomly assigned by blinded envelopes to target blood glucose concentrations of 2·8–4·4 mmol/L in infants and 3·9–5·6 mmol/L in children with insulin infusion throughout PICU stay (intensive group [n=349]), or to insulin infusion only to prevent blood glucose from exceeding 11·9 mmol/L (conventional group [n=351]). Patients and laboratory staff were blinded to treatment allocation. Primary endpoints were duration of PICU stay and inflammation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00214916.**

Findings **Mean blood glucose concentrations were lower in the intensive group than in the conventional group (infants: 4·8 [SD 1·2] mmol/L *vs* 6·4 [1·2] mmol/L, p<0·0001; children: 5·3 [1·1] mmol/L *vs* 8·2 [3·3] mmol/L, p<0·0001). Hypoglycaemia (defined as blood glucose ≤2·2 mmol/L) occurred in 87 (25%) patients in the intensive group (p<0·0001) versus five (1%) patients in the conventional group; hypoglycaemia defined as blood glucose less than 1·7 mmol/L arose in 17 (5%) patients versus three (1%) (p=0·001). Duration of PICU stay was shortest in the intensively treated group (5·51 days [95% CI 4·65–6·37] *vs* 6·15 days [5·25–7·05], p=0·017). The inflammatory response was attenuated at day 5, as indicated by lower C-reactive protein in the intensive group compared with baseline (–9·75 mg/L [95% CI –19·93 to 0·43] *vs* 8·97 mg/L [–0·9 to 18·84], p=0·007). The number of patients with extended (>median) stay in PICU was 132 (38%) in the intensive group versus 165 (47%) in the conventional group (p=0·013). Nine (3%) patients died in the intensively treated group versus 20 (6%) in the conventional group (p=0·038).**

Interpretation **Targeting of blood glucose concentrations to age-adjusted normal fasting concentrations improved short-term outcome of patients in PICU. The effect on long-term survival, morbidity, and neurocognitive development needs to be investigated.**

Funding **Research Foundation (Belgium); Research Fund of the University of Leuven (Belgium) and the EU Information Society Technologies Integrated project "CLINICIP"; and Institute for Science and Technology (Belgium).**

Lancet 2009; 373: 547–56

Published Online January 27, 2009 DOI:10.1016/S0140-6736(09)60044-1

See Comment page 520

*These authors contributed equally

Department of Intensive Care Medicine (Paediatric Intensive Care Unit), Catholic University Leuven, Leuven, Belgium (D Vlasselaers MD, I Milants RN, L Desmet MD, P J Wouters MSc, I Vanhorebeek PhD, I van den Heuvel MD, D Mesotten MD, M P Casaer MD, G Meyfroidt MD, C Ingels MD, J Muller MD, S Van Cromphaut MD, M Schetz MD, Prof G Van den Berghe MD)

Correspondence to: Prof Greet Van den Berghe, Department of Intensive Care Medicine, University Hospital Gasthuisberg, Catholic University Leuven, B-3000 Leuven, Belgium **greet.vandenberghe@med.kuleuven.be**

Introduction

Many studies have shown an association between hyperglycaemia and adverse outcome of a critical illness, both in adult and paediatric patients in an intensive care unit (ICU).[1–11] However, randomised, controlled intervention studies are needed to assess a causal relation. In adults, such studies have shown that maintenance of normoglycaemia with insulin infusion reduces morbidity of surgical and medical ICU patients, and reduces mortality of surgical ICU patients.[12–14] A study of patients with severe sepsis, which was stopped early for risk of hypoglycaemia, was not powered to confirm this benefit, fuelling controversy about generalisability of the findings.[15] A literature review confirmed that no randomised controlled studies investigating glucose control with insulin in populations in the paediatric ICU (PICU) have been done.[16]

Hyperglycaemia is prevalent in patients in PICU, with more than 80% having a blood glucose concentration greater than 6·1 mmol/L, more than 60% a concentration greater than 8·3 mmol/L, and more than 30% a concentration exceeding 11·1 mmol/L.[5] The extent of hyperglycaemia correlates with risk of organ failure, length of stay in the PICU, and risk of death.[5–9,11] Furthermore, variability of blood glucose concentrations and hypoglycaemia are associated with adverse outcome.[5] Whether these associations are an indicator of the severity of the underlying illness, or rather that hyperglycaemia or hypoglycaemia in itself are risk factors, is unclear. Potential mechanisms

underlying a risk of hyperglycaemia include pro-inflammatory effects and the toxic effect of increased circulating glucose concentrations on vulnerable vital organ systems. Normal fasting values for blood glucose concentrations in infants and children are lower than in adults.[17,18]

We postulated that targeting age-adjusted normoglycaemia with insulin infusion in critically ill infants and children in the PICU would improve outcome, and designed a randomised controlled study to test our hypothesis.

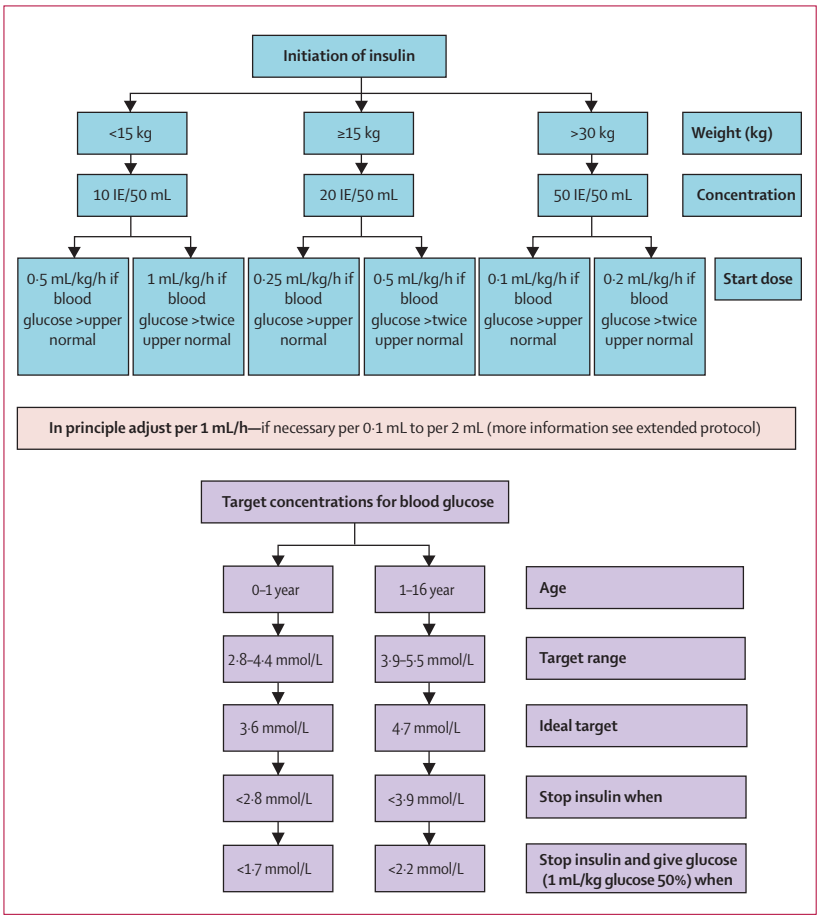

Figure 1: **Insulin titration guideline for intensive insulin therapy in the paediatric intensive care unit**

	Conventional insulin group (N=351)	Intensive insulin group (N=349)
Infant (age <1 year)*	160 (45·6%)	157 (45·0%)
Age (years)	1·3 (0·3–4·6)	1·4 (0·3–5·5)
Weight* (kg)	9 (5–18)	10 (5–18)
Male sex*	199 (56·7%)	202 (57·9%)
Malignancy*	15 (4·3%)	21 (6·0%)
Diabetes mellitus	3 (0·9%)	3 (0·9%)
Diagnostic category*		
Cardiac surgery for congenital heart defects	265 (75·5%)	261 (74·8%)
Cyanotic lesions	54 (20·4%)	61 (23·4%)
RACHS score, median	3 (2–3)	3 (2–3)
Complicated/high-risk surgery or trauma	38 (10·8%)	36 (10·3%)
Neurological medical disorders	8 (2·3%)	13 (3·7%)
Infectious medical diseases	16 (4·6%)	16 (4·6%)
Other medical disorders	17 (4·8%)	17 (4·9%)
Solid organ transplants	7 (2·0%)	6 (1·7%)

(Continues on next page)

Methods

Study population

All infants and children (aged 0–16 years inclusive) who were admitted to the PICU of the University Hospital of Leuven, Belgium were eligible for inclusion. Exclusion criteria were expected PICU stay less than 24 h, inability to obtain frequent blood samples because of the absence of an arterial line, a do-not-resuscitate or therapy restriction order before PICU admission, a medical disorder that the treating physician regarded as unsuitable for this study, and enrolment in another study protocol. We obtained written informed consent from the parents or legal guardians of all children. The protocol and consent forms were approved by the Institutional Review Board (approval number ML2586). Patients were recruited between Oct 1, 2004, and Dec 14, 2007.

Study design

A single-centre design was decided for safety reasons, in view of the risk of hypoglycaemia with lower target ranges for blood glucose, necessitating an ICU nursing team with extensive experience in blood glucose control. Patients were randomly assigned to intensive or conventional insulin treatment on a 1:1 basis. Assignment to treatment groups was done before surgery or at admission to PICU by envelopes that blinded allocation, stratified according to diagnostic category and age group (table 1), and balanced with the use of permuted blocks of ten.

In the conventional group, continuous insulin infusion was started only when blood glucose concentration exceeded 11·9 mmol/L twice, and the dose was adjusted by the PICU nurses to keep blood glucose between 10·0 and 11·9 mmol/L. When blood glucose concentration fell to less than 10·0 mmol/L, insulin infusion was tapered down and stopped.

In the intensive insulin group, insulin was infused to target age-adjusted normoglycaemia. Normal fasting blood glucose concentrations range in healthy neonates (aged <4 weeks) from 1·7 to 3·3 mmol/L, in infants (aged 4 weeks–1 year) from 2·2 to 5·0 mmol/L, in children younger than 2 years from 3·3 to 5·5 mmol/L, and in children older than 2 years from 3·9 to 5·9 mmol/L.[17,18] For reasons of simplicity and safety, we defined only two age-adjusted target ranges for blood glucose concentrations: 2·8–4·4 mmol/L for infants aged 0–1 year and 3·9–5·5 mmol/L for children aged 1–16 years (figure 1). These targets are not only normal fasting values, but they are also above the lower ranges

of normal in all patients, which we regarded as safer. Insulin infusion was started when blood glucose concentration exceeded the upper normal limit, and the dose was adjusted to maintain values within the defined targets. At discharge from intensive care, the study intervention ended.

Insulin infusions were prepared as 10 IU Actrapid HM (Novo Nordisk, Bagsværd, Denmark) in 50 mL NaCl 0·9% for patients weighing less than 15 kg, as 20 IU Actrapid HM in 50 mL NaCl 0·9% for those weighing 15–30 kg, and as 50 IU Actrapid HM in 50 mL NaCl 0·9% for those weighing more than 30 kg. We used a syringe-driven infusion pump (B/Braun-Perfusor-Space, B Braun, Melsungen, Germany). We set the starting insulin dose at 0·1 IU/kg/h for a first measurement above upper normal limit and at 0·2 IU/kg/h for a first measurement above twice the upper normal limit. The insulin dose was adjusted by 0·02 IU/h to 1 IU/h increments, on the basis of measurement of blood glucose concentration in undiluted arterial blood at 1–4 h intervals with the ABL700 analyser (Radiometer Medical A/S, Copenhagen, Denmark). The ABL700 analyser reported results as corrected to plasma concentrations.

For infants, insulin infusions were stopped when blood glucose fell to less than 2·8 mmol/L, and 1 mL/kg of a 50% dextrose solution was given when blood glucose fell to less than 1·7 mmol/L. For children, we stopped insulin infusions when blood glucose fell to less than 3·9 mmol/L, and 1 mL/kg of a 50% dextrose solution was given when blood glucose fell to less than 2·2 mmol/L (figure 1).

Blood sampling, blood glucose determination, and subsequent insulin dose adjustments were made by the bedside PICU nurses (one nurse per two patients), after extensive training and guided by a simple one-page guideline (figure 1), as an integral part of the clinical nursing workload.

On admission, patients who could not be fed enterally received intravenous nutrition with a mixture of glucose 20% and Vamin-glucose 10% (Fresenius-Kabi, Bad Homburg, Germany) in equal amounts, consisting of 150 mg/mL glucose and 4·7 mg/mL nitrogen. For patients who required temporary fluid restriction, total fluid intake was 50 mL/m²/h on day 1 and 2, and 60 mL/m²/h on day 3 (including intravenous drugs). Patients not requiring fluid restriction received 100 mL/kg per day for the first 10 kg bodyweight, 50 mL/kg for the next 10 kg, and 20 mL/kg for bodyweight greater than 20 kg. For all patients receiving intravenous nutrition, and within the fluid limitation described above, lipids (Intralipid [20 g/100 mL]; Fresenius-Kabi) were added from day 4 onward, initially at a dose of 5 mL/kg per day, increasing to a maximum of 15 mL/kg per day. Enteral feeding was attempted as soon as indicated by the medical disorder.[19] In infants, we used breastmilk or the patient's home milk formula. Older children received a standard feeding formula (Pediasure 1 kcal/mL; Abbott, Zwolle, Netherlands) unless contraindicated by the medical disorder. Enteral feeding was administered through the gastric tube in a continuous way for 10 h followed by 2 h rest, and was gradually increased as dictated by tolerance. Switch to oral intake was made as soon as deemed safe by the treating physician.

	Conventional insulin group (N=351)	Intensive insulin group (N=349)
(Continued from previous page)		
Allocation before surgery*	45 (12·8%)	39 (11·2%)
Mechanical ventilation*	337 (96·0%)	336 (96·3%)
ECMO or other assist device*	9 (2·6%)	8 (2·3%)
Mean blood glucose* (mmol/L [95% CI])	8·31 (7·88–8·74)	7·94 (7·54–8·34)
PELOD first 24h in PICU*	11 (2–12)	11 (2–12)
CRP (mg/L)		
Median	29 (14–48)	27 (17–51)
Mean (95%CI)	40·72 (35·8–45·64)	42·17 (37·14–47·2)

Data are number (%) or median (IQR), unless otherwise stated. RACHS=risk adjustment in congenital heart surgery. ECMO=extracorporeal membrane oxygenation. PELOD=paediatric logistic organ dysfunction score. CRP=C-reactive protein concentration on day 1 of stay at paediatric intensive care unit. *These parameters are the clinically relevant risk factors used in the multivariate logistic regression model for mortality.

Table 1: **Baseline demographics**

Data collection and definitions

At baseline, we obtained demographic and clinical information, including the necessary information from

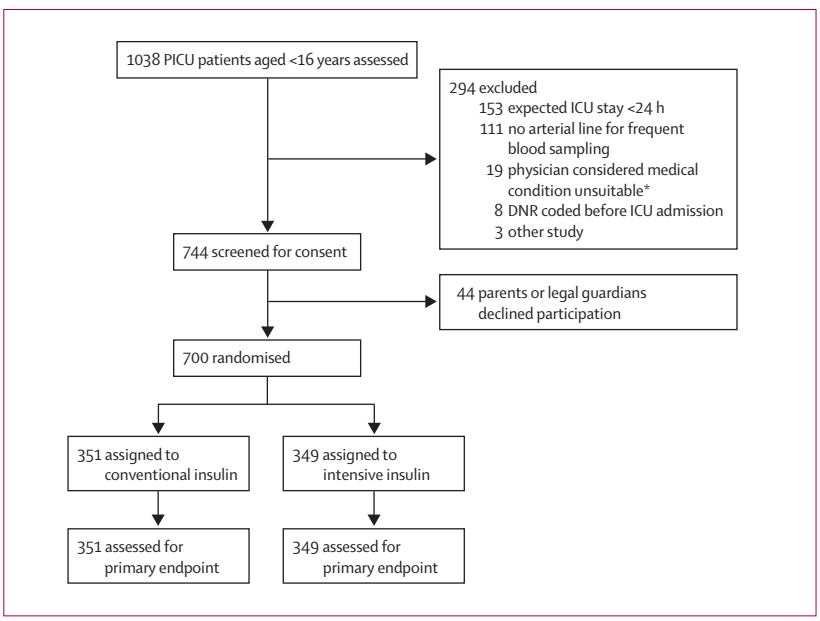

Figure 2: **Trial profile**

PICU=paediatric intensive care unit. ICU=intensive care unit. DNR=do not resuscitate. *The 19 medical disorders that were considered unsuitable by the treating physician consisted of two patients dependent on home ventilation, six metabolic disorders, two patients for whom it was the personal opinion of the treating physician that it would be inappropriate to participate in a study in view of poor prognosis (although the patients formally did not have a DNR code), and nine patients who had already been treated with intensive insulin therapy elsewhere before assessment for participation.

the first day of intensive care to calculate the paediatric logistic organ dysfunction (PELOD) score.[20,21] The paediatric risk of mortality (PRISM) score on day 1 (mean 12 [SD 6]) in the PICU was not suitable for this study, since the highest concentration of blood glucose occurring during the first 24 h of PICU stay is included in the score, which is affected by the randomised intervention. Modified PRISM scores—calculated with only the admission value of blood glucose, which is unaffected by the study intervention—were a mean of 11 (SD 6) in both insulin therapy groups. For the congenital cardiac surgery subgroup, we also measured the risk adjustment in congenital heart surgery (RACHS) score.[22]

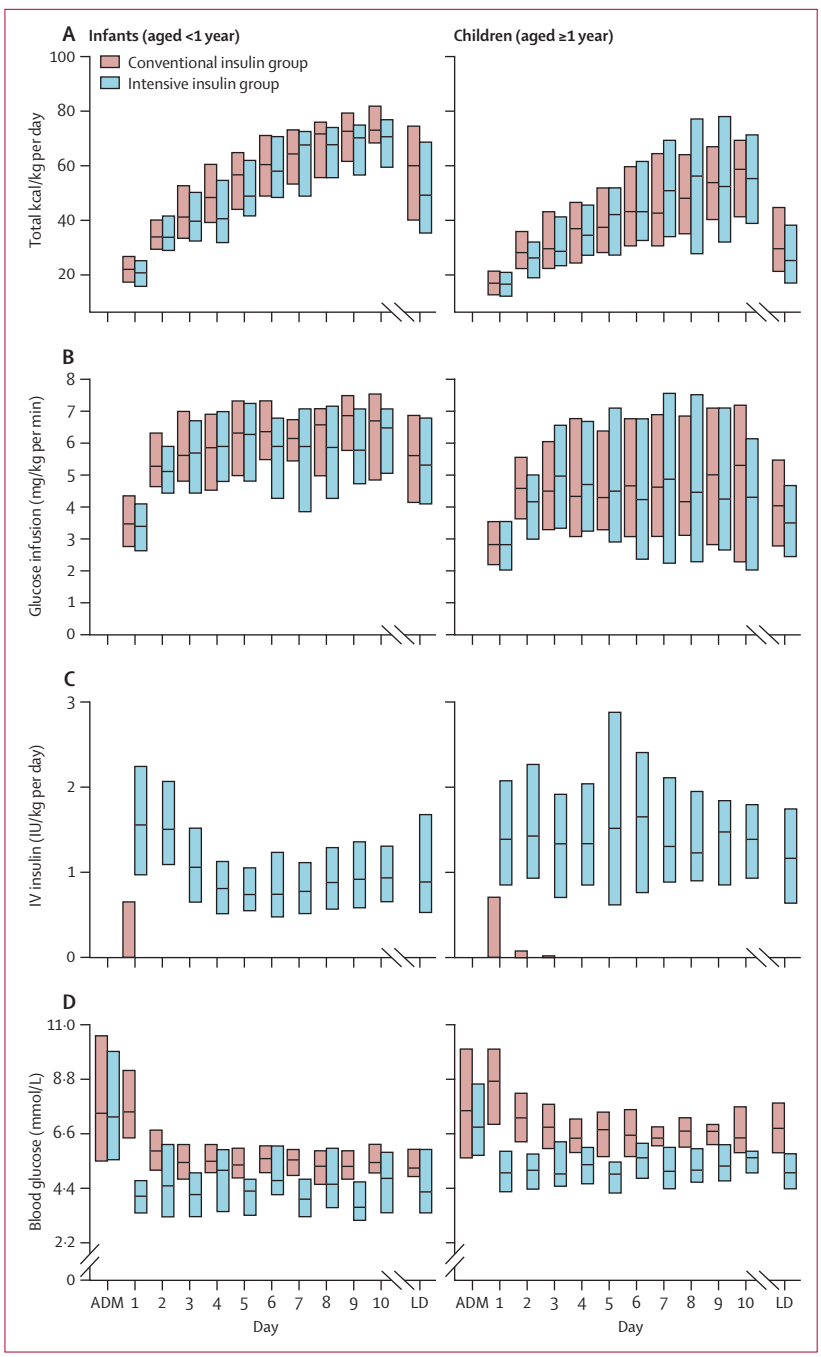

Figure 3: **Nutrition and blood glucose control**
The middle horizontal lines within the boxes represent medians, boxes show IQR. Data are shown for the first 10 days and the last day (LD) in PICU. (A) Daily amounts of total kcal/kg per day for each age group. (B) Daily amounts of infused glucose (mg/kg per min). The two groups were comparable for the feeding strategy on all time points. (C) Daily doses of insulin (IU/kg per day). (D) Morning blood glucose concentrations for each age group. ADM=admission.

We systematically sampled blood on admission and subsequently every hour until blood glucose target was reached; thereafter it was sampled every 4 h, or more often when required according to the guidelines for blood glucose control (figure 1). We analysed the blood glucose concentration measured on admission, the mean of all blood glucose concentrations measured at 0600 h, and the mean of all blood glucose concentrations per patient.

Hypoglycaemia was defined, as in adults, as a blood glucose result of 2·2 mmol/L or less. Since normal fasting blood glucose concentrations range to 1·7 mmol/L in healthy neonates, we also reported hypoglycaemia as blood glucose concentration less than 1·7 mmol/L.[17,18,23]

Secondary infection was defined as any suspected or documented secondary infection that was diagnosed after PICU admission by the attending senior intensive care physician and treated with systemic antimicrobials for more than 48 h. The site of the most severe infection per patient was used to define the type of infection.

To minimise bias in the analysis of duration of ICU stay—caused by variable availability of a bed on a regular paediatric ward—patients were defined as dischargeable from the PICU when they were no longer in need of vital organ support and receiving at least two-thirds of the calculated caloric needs through the normal enteral route, or earlier when sent to a ward.

For deaths in the PICU, cause of death was determined by the senior treating intensive care physician and subsequently categorised as cardiogenic, neurological, or pulmonary.

Outcome measures

In view of the low mortality in PICU, we chose morbidity as the primary endpoint. The sample size was calculated on the basis of a hypothesised decrease in C-reactive protein (CRP)—a quantifiable indicator of an anti-inflammatory effect of the study intervention, which at the study start was assumed to have a role in contributing to any morbidity benefit.[24] The duration of stay in intensive care was the clinical primary outcome measure. Secondary outcome measures were duration of (invasive or non-invasive) mechanical ventilatory support and of other vital organ support (vaso-active intravenous drugs, temporary pacemaker, inhaled nitric oxide, extracorporeal membrane oxygenation [ECMO] or ventricular assist devices, dialysis); biochemical

markers of organ dysfunction (plasma creatinine, urea, bilirubin, and troponin measured by routine clinical chemistry, and heart-type fatty acid binding protein [HFABP] measured by a commercial ELISA [Hycult Biotechnology, Uden, Netherlands]); and the number of patients with secondary infections. We assessed mortality in the PICU as a safety secondary endpoint. Patients and laboratory staff were blinded to treatment assignment.

We recorded hypoglycaemic episodes and immediate symptoms related to hypoglycaemia (sweating, agitation, arrhythmia or other haemodynamic deterioration, neurological deterioration, convulsions, or death) as safety endpoints, as well as the time to normalisation of blood glucose and the highest blood glucose concentration reached within 4 h of a hypoglycaemic event.

Statistical analysis

We calculated that a sample size of 700 patients would be needed to detect the hypothesised decrease in CRP (two-sided alpha level <0·05 and a power of 80%). We did not plan any interim analyses. An independent safety board monitored yearly PICU mortality compared with that before the start of the study, as well as complications attributed to hypoglycaemia.

We compared baseline and outcome variables with Student's *t* test, repeated measures ANOVA, χ^2 test, and Mann-Whitney *U* test. We analysed cumulative incidence of death in the PICU with Kaplan-Meier analysis and significance testing with the log-rank test. Odds ratios for mortality were estimated with logistic regression analysis and were subsequently corrected for all clinically relevant baseline risk factors (table 1) with multivariate logistic regression analysis. Data are presented as means (95% CI) or medians (IQR) unless otherwise indicated. All analyses were done on an intention-to-treat basis. We made no corrections for multiple comparisons. Statistical analysis was done with StatView (version 5.0.1).

The study is registered with ClinicalTrials.gov, number NCT00214916.

Role of the funding source

The sponsors of the study had no role in study design, patient enrolment, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 2 shows the trial profile. Treatment groups were well matched at randomisation (table 1). Almost half of the 700 patients were younger than 1 year (table 1). Three-quarters of patients had been admitted after cardiac surgery for congenital heart defects, with equal

	Conventional insulin group (N=351)	Intensive insulin group (N=349)	p value
CRP change from baseline to day 5 (mg/L)			
Median	0 (–12 to 29)	–6 (–28 to 15)	0·007
Mean	8·97 (–0·9 to 18·84)	–9·75 (–19·93 to 0·43)	..
Dependency on intensive care			
Days in ICU			
Median	3 (2 to 7)	3 (2 to 6)	0·017
Mean	6·15 (5·25 to 7·05)	5·51 (4·65 to 6·37)	..
Extended* stay in ICU (>3 days)	165 (47·0%)	132 (37·8%)	0·013
Dependency on mechanical ventilatory support			
Number of patients ventilated	337 (96·0%)	335 (96·0%)	0·987
Days on mechanical ventilatory support			
Median	2 (1 to 5)	2 (1 to 4)	0·366
Mean	4·66 (3·82 to 5·5)	4·33 (3·57 to 5·09)	..
Extended* mechanical ventilation (>2 days)	129 (36·8%)	120 (34·4%)	0·512
Organ failure: cardiovascular system			
Dependency on vasoactive IV drugs†			
Number of patients on vasoactive IV drugs	244 (69·5%)	223 (63·9%)	0·114
Days on vasoactive IV drugs			
Median	2 (0 to 4)	2 (0 to 3)	0·017
Mean	3·73 (2·98 to 4·48)	2·95 (2·4 to 3·5)	..
Extended* vasoactive IV drugs (>2 days)	140 (39·9%)	103 (29·5%)	0·003
Dependency on temporary pacemaker			
Number of patients requiring temporary pacemaker	79 (22·5%)	66 (18·9%)	0·240
Days on pacemaker when requiring one			
Median	3 (2 to 5)	2 (1 to 4)	0·122
Mean	4·00 (3·33 to 4·67)	4·92 (2·92 to 6·92)	..
Extended pacemaker requirement (>2 days)	47 (13·4%)	28 (8·0%)	0·021
Dependency on NO inhalation			
Number of patients receiving iNO	29 (8·3%)	27 (7·7%)	0·797
Days on iNO when requiring it			
Median	3 (2 to 6)	4 (2 to 5)	0·555
Mean	4·62 (3·06 to 6·18)	4·48 (3·19 to 5·77)	..
Extended iNO requirement (>2 days)	16 (4·6%)	20 (5·7%)	0·482
Dependency on ECMO or assist device at any time			
Number of patients on ECMO or assist	12 (3·4%)	10 (2·9%)	0·674
Days on ECMO/assist when requiring one			
Median	6 (3 to 17)	6 (5 to 8)	0·791
Mean	8·67 (4·38 to 12·96)	7·00 (3·94 to 10·06)	..
Lactate (mmol/L) 12–18 h after randomisation			
Median	1·3 (1·0 to 1·7)	1·0 (0·7 to 1·3)	<0·0001
Mean	1·53 (1·41 to 1·65)	1·20 (1·09 to 1·31)	..
Troponin (µg/L) 12–18 h after randomisation in cardiac patients (N=526)			
Median	11·1 (5·8 to 19·7)	8·9 (3·8 to 15·3)	0·011
Mean	16·02 (13·50 to 18·54)	12·02 (10·29 to 13·75)	..
HFABP (ng/mL) 12–18 h after randomisation in cardiac patients (N=526)			
Median	16·0 (7·4 to 35·8)	11·7 (6·0 to 26·9)	0·026
Mean	29·34 (24·27 to 34·41)	22·31 (19·08 to 25·54)	..

(Continues on next page)

	Conventional insulin group (N=351)	Intensive insulin group (N=349)	p value
(Continued from previous page)			
Organ failure: kidney			
Dialysis	6 (1·7%)	2 (0·6%)	0·157
Maximum concentration of serum creatinine (μmol/L)	52·16 (42·43 to 66·30)	51·27 (42·43 to 65·42)	0·652
Peak:d1 creatinine concentration, mean	1·14 (0·56 to 1·72)	1·19 (0·78 to 1·60)	0·170
Maximum concentration of serum urea (mmol/L)	13·57 (10·00 to 17·85)	13·57 (10·00 to 19·64)	0·571
Organ failure: liver			
Peak level of bilirubin (μmol/L)	12·31 (8·38 to 23·94)	11·12 (7·52 to 20·69)	0·109
Secondary infections			
Number of patients with secondary infections	129 (36·8%)	102 (29·2%)	0·034
Type of infection			
Pulmonary	90 (25·6%)	68 (19·5%)	..
Bloodstream	26 (7·4%)	20 (5·8%)	..
Wound	5 (1·4%)	6 (1·7%)	..
Urinary tract	4 (1·1%)	5 (1·4%)	..
CNS	3 (0·9%)	1 (0·3%)	..
Gastrointestinal tract	1 (0·3%)	2 (0·6%)	..
Hypoglycaemia			
Number of patients with hypoglycaemia (≤2·2 mmol/L)	5 (1·4%)	87 (24·9%)	<0·0001
Blood glucose concentration when hypoglycaemic (mmol/L), mean	1·62 (1·28 to 1·96)	1·84 (1·77 to 1·91)	0·387
Peak blood glucose ≤4 h after hypoglycaemia (mmol/L), mean	7·99 (4·14 to 11·84)	6·17 (5·75 to 6·59)	0·097
Number of patients with hypoglycaemia (<1·7 mmol/L)	3 (0·9%)	17 (4·9%)	0·001

Data are median (IQR), mean (95% CI), or number (%), unless otherwise indicated. CRP=C-reactive protein. (P)ICU=(paediatric) intensive care unit. IV=intravenous. iNO=inhaled nitric oxide. ECMO=extracorporeal membrane oxygenation. HFABP=heart-type fatty acid binding protein. ARDS=acute respiratory distress syndrome. *Longer than median number of days of the conventional group. †Vasoactive intravenous drugs include dobutamine, milrinone, enoximone, dopamine, adrenaline, noradrenaline, and isuprenaline.

Table 2: **Morbidity outcomes**

distribution of cyanotic heart lesions (table 1), which was representative of the total case-mix in the PICU (data not shown). Most patients were randomly assigned on PICU admission (table 1). 259 (82%) infants and 279 (73%) children had blood glucose concentrations at admission greater than the upper limit of normal for the age group of 5·0 mmol/L and 5·8 mmol/L, respectively.

Nutritional intake was similar in the intensive and the conventional insulin group (figure 3). In 207 (59%) patients in the conventional group and 194 (56%) in the intensive group, at least partial enteral nutrition was tolerated (p=0·37).

Figure 3 shows blood glucose control in both treatment groups. Mean morning blood glucose concentrations were higher in the conventional group than in the intensive group in infants (6·4 [SD 1·2] mmol/L *vs* 4·8 [1·2] mmol/L, p<0·0001), and in children (8·2 [3·3] mmol/L *vs* 5·3 [1·1], mmol/L p<0·0001). Intensive insulin therapy reduced the mean of all measured glucose values from 7·1 (1·3) mmol/L to 5·2 (1·0) mmol/L in infants (p<0·0001) and from 8·8 (1·9) mmol/L to 6·3 (1·3) mmol/L in children (p<0·0001). At all time points, insulin doses were higher (all p<0·0001) and blood glucose concentrations lower (all p<0·010) in the intensive than the conventional insulin groups, apart from infants on day 8 (p=0·064) (figure 2).

In the intensive insulin group, virtually every patient required insulin (n=345 [99%]). In the conventional group, 163 (46%) patients received insulin. The average daily insulin dose was a median 0·0 (IQR 0·0–0·6) IU/kg bodyweight in the conventional group and 1·3 (0·9–1·8) IU/kg bodyweight in the intensive group.

The inflammatory response to critical illness was attenuated, as evidenced by the time course of CRP (table 2, figure 4). Secondary infections were also reduced, most importantly pulmonary and bloodstream infections (table 2). When present, infections were treated with systemic antimicrobial drugs for 6 (IQR 4–10) days in the conventional group and 7 (4–11) days in the intensive group (p=0·77).

Intensive insulin therapy reduced the duration of PICU stay (p=0·017), and more specifically, the need for extended (>median of the conventional group) intensive care dependency (p=0·013) (table 2). The duration of mechanical ventilation did not differ significantly between the two groups (table 2). Intensive insulin therapy reduced extended requirement of haemodynamic (intravenous, inhaled or mechanical) support from 145 of 351 (41%) to 108 of 349 (31%) (p=0·004). Early indicators of myocardial damage in the reperfusion phase among cardiac surgery patients—such as the serum concentrations of troponin (p=0·011), HFABP (p=0·026) measured between 12 and 18 h after randomisation, and blood lactate concentrations (p<0·0001)—were lowered by the intervention (table 2). Clinical indicators of kidney and liver function were not significantly affected by treatment (table 2).

Hypoglycaemia (≤2·2 mmol/L) occurred in 87 (25%) patients in the intensive insulin group (70 infants and 17 children) and in five (1%) in the conventional group (three infants and two children) (p<0·0001). Hypoglycaemia defined as blood glucose concentration less than 1·7 mmol/L occurred in 17 patients (5%) in the intensive insulin group (15 infants and two children) and in three (1%) in the conventional group (two infants and one child) (p=0·001). Hypoglycaemia (≤2·2 mmol/L) occurred at a median of day 2 (IQR 1–5) in the PICU in the intensive insulin group versus day 1 (1–3) in the conventional group (p=0·29). Hypoglycaemia (≤2·2 mmol/L) on more than two occasions occurred in 18 patients (5%) treated with intensive insulin compared with none in the conventional group.

Within 1 h of detection of hypoglycaemia, blood glucose was normalised in 82 (89%) patients; within

2 h, 89 (97%) of the cases were normalised. The highest blood glucose level within 4 h of a hypoglycaemic episode was 8·0 (SD 3·9) mmol/L in the conventional group and 6·2 (2·0) mmol/L in the intensive group (p=0·097).

In three patients of the intensive insulin group, an event of hypoglycaemia was associated in time with arrhythmia. In two of these patients, the event was a period of supraventricular tachycardia that occurred already before the episode of hypoglycaemia and which re-occurred in the absence of hypoglycaemia; in the third patient, transient bradycardia was evoked by an erroneous flush of intravenous potassium associated with the correction of hypoglycaemia. No patients had convulsions nor died after an event of hypoglycaemia. In 16 (one in the conventional and 15 in the intensive insulin groups) of all 92 patients who had hypoglycaemia, one dose of neuromuscular blocking agents had been given on the day of this event. The attending physicians on the paediatric ward did not report any problems that could have been related to hypoglycaemia.

In the intensive insulin group, nine (2·6%) patients died versus 20 (5·7%) in the conventional group (p=0·038) (uncorrected odds ratio 0·44 [95% CI 0·19–0·97]; p=0·043) (table 3 and figure 3). Corrected for the baseline risk factors listed in table 1, the odds ratio was 0·28 (95% CI 0·09–0·79; p=0·016). A post-hoc analysis showed that intensive insulin therapy reduced mortality from 4·3% to 1·5% in patients receiving enteral nutrition, and from 7·6% to 3·8% in those not receiving enteral nutrition. 30-day mortality was also reduced by intensive insulin therapy (table 3).

The fewer deaths with intensive insulin therapy occurred in two cause-of-death categories: neurological (complications or deterioration) and pulmonary (intractable acute respiratory distress syndrome or terminal weaning failure). The number of deaths due to a cardiogenic cause (non-recovery of initial vitium or intractable shock) did not differ between the groups. Mortality was 7·4% in patients with secondary infections compared with 2·6% for those without infections (p=0·003).

Patients who developed hypoglycaemia had a risk of death of 6·5% compared with 3·8% for those who did not develop hypoglycaemia (odds ratio 1·7 [95% CI 0·7–4·4]; p=0·225). In multivariate logistic regression analysis, correcting for ICU stay, which highly significantly and independently determined the risk of death, the odds ratio of death for hypoglycaemia was reduced to 1·2 (95% CI 0·4–3·3; p=0·66). After correction for other baseline risk factors, hypoglycaemia (defined as ≤2·2 mmol/L or <1·7 mmol/L) was not an independent risk factor for mortality (defined as ≤2·2 mmol/L: odds ratio 1·7 [95% CI 0·3–8·1], p=0·52; defined as <1·7 mmol/L: odds ratio 2·9 [0·4–21·7], p=0·29).

Discussion

In this randomised controlled study of 700 critically ill infants and children in PICU, targeting blood glucose concentrations to an age-adjusted normal fasting concentration with insulin infusion throughout intensive care improved morbidity and reduced mortality, despite a substantial risk of biochemical hypoglycaemia. Intensive insulin therapy protected the

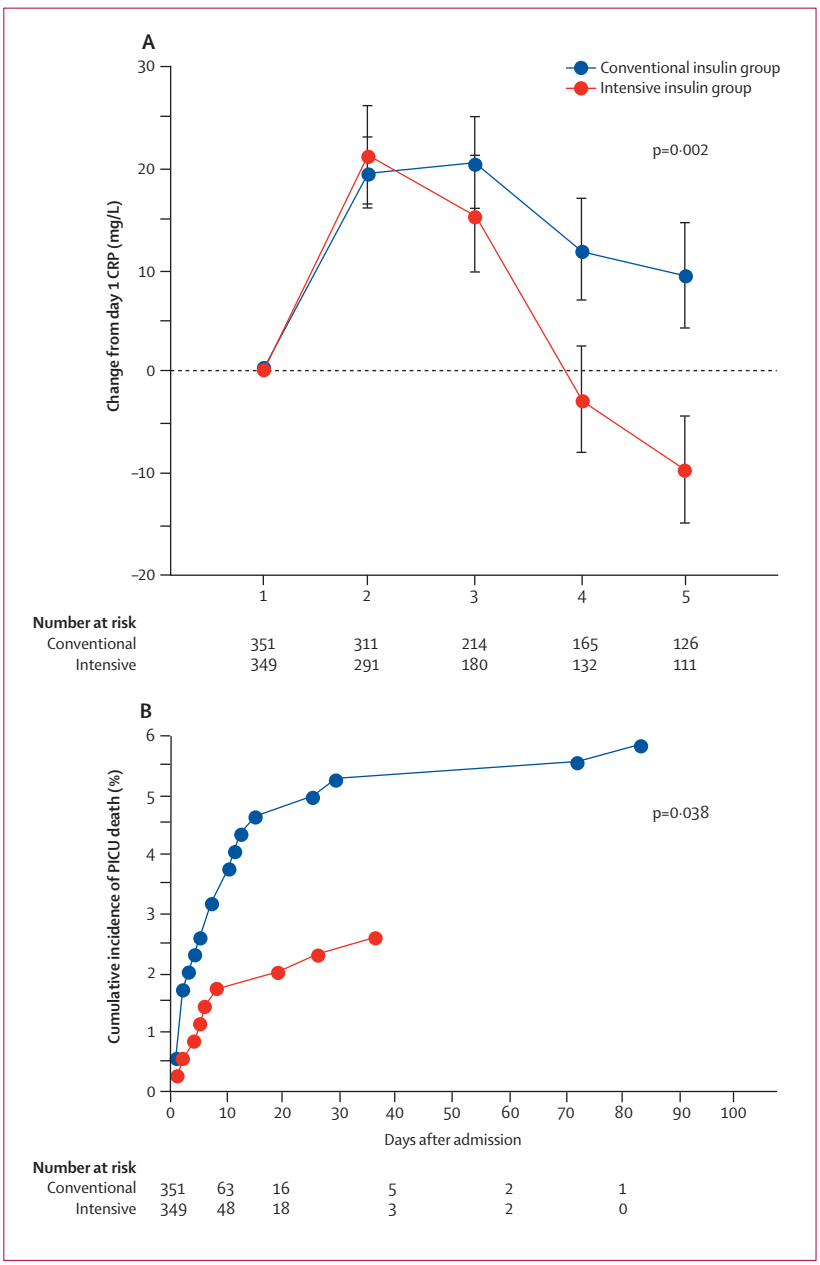

Figure 4: **Effect on inflammation and mortality**
(A) Mean changes from day 1 concentrations of C-reactive protein (CRP) in the conventional and intensive insulin groups for the first 5 days in PICU. Error bars indicate SE. p value was obtained by repeated measures ANOVA for overall significance of the difference in time course of CRP (time*treatment interaction). The p value for the change in CRP on day 5, calculated by Mann-Whitney *U* test, was 0·007. (B) Kaplan-Meier analysis depicting cumulative incidence of PICU death (%) for time (days) in PICU in the conventional and intensive insulin groups. The p value was obtained by log-rank testing.

	Conventional insulin group (N=351)	Intensive insulin group (N=349)	p value
Number of PICU deaths	20 (5·7%)	9 (2·6%)	0·038
Causes of PICU death (n)	..	..	0·024
Cardiogenic (non-recovery of initial vitium or intractable shock)	7	8	..
Neurological complications or deterioration	8*	1†	..
Pulmonary (intractable ARDS or terminal weaning failure)	5‡	0	..
Odds ratio PICU mortality (95% CI) (uncorrected)	0·44 (0·19–0·97)	..	0·043
Odds ratio PICU mortality (95% CI) (corrected for baseline risk§)	0·28 (0·09–0·79)	..	0·016
30-day PICU mortality	18 (5·1%)	8 (2·3)	0·047
Odds ratio 30-day mortality (95% CI) (uncorrected)	0·43 (0·19–1·01)	..	0·053
Odds ratio 30-day mortality (95% CI) (corrected for baseline risk§)	0·23 (0·07–0·74)	..	0·014

*Eight neurological causes of death, of which four were in the upon-admission category complicated/high-risk surgery or trauma, two in the upon-admission category cardiac surgery, one in the upon-admission category neurological medical disorders, and one in the upon-admission category other medical disorders. The admission Glasgow coma scale was 15/15 in five of these eight patients, 6/15 in one, and 3/15 in two. †One neurological cause of death in the upon-admission category cardiac surgery. The admission Glasgow coma scale of this patient was 3/15. ‡Five pulmonary causes of death, of which one was in the upon-admission category cardiac surgery, two in the upon-admission category infectious medical, and two in the upon-admission category other medical. §Corrected for baseline age group, weight, sex, diagnostic category, malignancy, ventilation, extracorporeal membrane oxygenation/assist, glucose, PELODd1 (indicated in table 1).

Table 3: **Mortality in the two treatment groups**

cardiovascular system, prevented secondary infections, and attenuated the inflammatory response, reducing the need for extended stay in intensive care. Mortality was lowered by an absolute 3·1% (95% CI 0·2–6·0) due to prevention of lethal neurological and pulmonary damage, and possibly prevention of infection. The risk of hypoglycaemia with insulin therapy in this young patient population necessitates a long-term follow-up study to quantify late survival and morbidity, especially the effect of hyperglycaemia and hypoglycaemia on the developing brain.[25,26]

The clinical primary endpoint of this study was the duration of stay in intensive care; the inflammatory response had been the quantifiable indicator of a process contributing to such clinical benefit. The CRP time course indicated an attenuated inflammatory response, as reported in the adult study.[23] Prevention of secondary infections with intensive insulin therapy also occurred in the paediatric study cohort. Hence, whether the anti-inflammatory effect is mediated directly by insulin or prevention of hyperglycaemia, or is (partly) due to infection prevention, remains unclear.

Extended stay in intensive care was reduced by intensive insulin therapy, which was mainly explained by reduced need for haemodynamic support. Two reasons could explain why the cardiovascular system is most affected in this study cohort. First, in a predominantly paediatric population undergoing cardiac surgery, the heart is the organ most vulnerable to so-called ischaemia reperfusion and thus might benefit most from prevention of secondary injury during the reperfusion phase.[27] Protection of the heart seems to occur early with intensive insulin therapy, as shown by reduced concentrations of troponin and HFABP. Furthermore lactate concentrations, despite being in the normal range, were lowered, which can be partly explained by a circulatory benefit, by an improved mitochondrial function, or by a reduction of glycolysis.[28–32] We are unable to distinguish these causes without pyruvate concentrations. Second, prevention of septic complications might have played a part. The kidney and the liver seemed less affected in young children than in adults.

In view of the low PICU mortality, we did not study mortality as a primary efficacy endpoint. However, recording the same 3% absolute risk reduction as in the adult populations[12,13] was noteworthy. To confirm this mortality benefit, with a type-1 error of 0·05 and 80% power, repeat studies should include 1200–1700 patients, dependent on the baseline mortality. For a 2% absolute difference, 3000–4000 PICU patients would be needed. If a mortality benefit is confirmed, it would suggest that for infants and children in the ICU, lethal non-recovery of secondary organ damage, or lethal reperfusion injury to vital organs, can be reduced by prevention of hyperglycaemia with insulin. This result would be a major breakthrough in paediatric intensive care.

The risk of hypoglycaemia defined as blood glucose concentration of 2·2 mmol/L or less (25%) was higher than in the adult ICU populations (5% for surgical and 18% for medical patients).[12,13] This finding is mostly explained by the lower normal ranges, and thus the lower targets set out for blood glucose control in infants and children, which were inevitably closer to this conventional hypoglycaemic threshold. Less pronounced counter-regulatory responses in infants and children might also play a part. With hypoglycaemia defined as blood glucose concentration less than 1·7 mmol/L, incidence of hypoglycaemia was much lower (5%). We noted possible symptoms of hypoglycaemia in only three patients (arrhythmia, no convulsions). However, sedation in ICU might obscure diagnosis of early symptoms preceding arrhythmia, and neuromuscular blocking agents could mask convulsions. Although patients who developed hypoglycaemia had a higher risk of death than did those who did not develop hypoglycaemia, this association was not significant and was explained by the duration of stay in ICU, which captures both the exposure time to insulin and, independently, the severity of illness. This result is in line with that of a nested case–control study showing no causal relation between hypoglycaemia and lethality in adult patients in ICU.[33]

Furthermore, the excess neurological deaths in this study occurred in the conventional, not the intensive, insulin group. Thus the short-term benefits of preventing hyperglycaemia in an ICU environment

seem to outweigh the short-term risks of biochemical hypoglycaemia, provided that hypoglycaemia is diagnosed and treated promptly and adequately. Preclinical studies have shown that glucose reperfusion after hypoglycaemia, rather than hypoglycaemia itself, triggers neuronal death.[26] Hence, prevention of rebound hyperglycaemia in our study could have been very important in prevention of brain damage. However, long-term consequences on neurocognitive development, both of hypoglycaemia and of hyperglycaemia, need to be investigated in great detail.[25,26] Such a follow-up study has been initiated in the studied patient cohort.

The hypothesis tested in this study was that targeting age-normal fasting blood glucose concentrations during intensive care is beneficial in paediatric patients. Therefore, the age-adapted target ranges set out for this study were important. Indeed, the control group that was treated conventionally displayed much lower blood glucose concentrations than did the adult population, although these values were abnormally high for age.[17,18] If the study had targeted blood glucose concentrations that were comparable with the adult population (4·4–6·1 mmol/L), the blood glucose concentrations for infants in the intervention group would not have differed from those in the control group.

The study has some important limitations. First, as for all studies on tight blood glucose control, the study could not feasibly be done in a blinded manner, since insulin titration requires careful blood glucose monitoring. Second, the study was undertaken in one centre, with three-quarters of patients admitted to PICU after cardiac surgery. Thus findings cannot be generalised to paediatric patients with other types of illness or to other clinical settings. Third, the expertise with tight blood glucose control of the nursing team could have been essential. Indeed, this trial was a proof-of-concept study in the paediatric ICU population, and long-term follow-up and multicentre studies should follow. Our study, therefore, cannot be considered yet as evidence for general implementation in clinical practice. For future studies, an accurate continuous blood glucose sensor for use in the PICU, which was not available when we undertook our study, would be preferable to keep the risk of hypoglycaemia to a minimum.

Contributors

GVdB and DV designed and coordinated the study. IM and PJW were responsible for patient screening and enrolment. DV, LD, IvdH, DM, MC, GM, CI, JM, SVC, and MS provided patient care and requested informed consent from the parents or legal guardians. IM and PJW collected the clinical and laboratory data and IV contributed to the biochemical analyses. GVdB did the statistical analyses. GVdB, DV, and DM contributed to the interpretation of the results and the writing and critical review of the report. All authors have seen and approved the final version of the report.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We thank the clinical fellows and the PICU nursing staff for excellent patient care and protocol compliance; Magaly Boussemaere, Nathalie Rubbens, Nele Nijs, and Mona Eerdekens for technical support; An Andries, Jenny Gielens, and Myriam Vandenbergh for secretarial help; and Peter Lauwers, Roger Bouillon, and Marc Van den Berghe for critical manuscript review. This research was fully supported by official research grants from the Research Foundation—Flanders, Belgium (FWO) (G.0533.06); the Research Fund of the University of Leuven (OT/03/56 and GOA/2007/14) and the EU Information Society Technologies Integrated project "CLINICIP" contract number 506965; and Institute for Science and Technology—Flanders, Belgium (IWT 070695). DV and GM are clinical PhD fellows and IV and SVC are post-doctoral fellows of the Research Foundation, Flanders, Belgium (FWO). DM is a post-doctoral fellow supported by the Clinical Research Fund of the University Hospital Gasthuisberg. GVdB, via the University of Leuven, receives structural research financing via the Methusalem programme, funded by the Flemish Government.

References

1 Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000; **355:** 773–78.

2 McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin* 2001; **17:** 107–24.

3 Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001; **32:** 2426–32.

4 Falciglia M. Causes and consequences of hyperglycemia in critical illness. *Curr Opin Clin Nutr Metab Care* 2007; **10:** 498–503.

5 Wintergerst KA, Buckingham B, Gandrud L, et al. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics* 2006; **118:** 173–79.

6 Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. *J Pediatr* 2005; **146:** 30–34.

7 Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. *Pediatr Crit Care Med* 2004; **5:** 329–36.

8 Branco RG, Garcia PC, Piva JP, Casartelli CH, Seibel V, Tasker RC. Glucose level and risk of mortality in pediatric septic shock. *Pediatr Crit Care Med* 2005; **6:** 470–72

9 Yung M, Wilkins B, Norton L, Slater A, for the Paediatric Study Group, Australian and New Zealand Intensive Care Society. Glucose control, organ failure, and mortality in pediatric intensive care. *Pediatr Crit Care Med* 2008; **9:** 147–52.

10 Piper HG, Alexander JL, Shukla A, et al. Real-time continuous glucose monitoring in pediatric patients during and after cardiac surgery. *Pediatrics* 2006; **118:** 1176–84.

11 Falcao G, Ulate K, Kouzakanani K, Bielefeld MR, Morales JM, Rotta AT. Impact of postoperative hyperglycemia following surgical repair of congenital cardiac defects. *Pediatr Cardiol* 2008; **29:** 628–36.

12 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; **345:** 1359–67.

13 Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354:** 449–61.

14 Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006; **55:** 3151–59.

15 Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358:** 125–39.

16 Skillman HE, Wischmeyer PE. Nutritional therapy in critically ill infants and children. *J Parent Enteral Nutr* 2008; **32:** 520–35.

17 Pagana KD, Pagana TJ. Mosby's diagnostic and laboratory test reference (6th edn). Philadelphia: Mosby, Elsevier Science, 2003: 457.

18 Brown TCK, Connelly JF, Dunlop ME, McDougall PN, Tibballs J. Fasting plasma glucose in children. *Aust Paediatr J* 1980; **16:** 28–29.

19 Mehta N, Castillo L. Nutrition in the critically ill child. In: Fuhrman BP, Zimmerman J, eds. Pediatric critical care. Philadelphia: Mosby Elsevier, 2006: 1069–84.

20 Leteurtre S, Martinot A, Duhamel A, et al. Development of a pediatric multiple organ dysfunction score: use of two strategies. *Med Decis Making* 1999; **19:** 399–410.

21 Leteurtre S, Martinot A, Duhamel A, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. *Lancet* 2003; **362:** 192–97.

22 Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Lezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg* 2002; **123:** 110–18.

23 Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics* 2000; **105:** 1141–45.

24 Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab* 2003; **88:** 1082–88.

25 Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007; **356:** 1842–52.

26 Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *J Clin Invest* 2007; **117:** 910–18.

27 Su H, Sun X, Ma H, et al. Acute hyperglycemia exacerbates myocardial ischemia/reperfusion injury and blunts cardioprotective effect of GIK. *Am J Physiol Endocrinol Metab* 2007; **293:** E629–35.

28 Ellger B, Debaveye Y, Vanhorebeek I, et al. Survival benefits of intensive insulin therapy in critical illness: impact of maintaining normoglycemia versus glycemia-independent actions of insulin. *Diabetes* 2006; **55:** 1096–105.

29 Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* 2004; **114:** 1187–95.

30 Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005; **115:** 2277–86.

31 Ellger B, Richir MC, van Leeuwen PA, et al. Glycemic control modulates arginine- and ADMA-levels during critical illness by preserving DDAH-activity. *Endocrinology* 2008; **149:** 3148–57.

32 Vanhorebeek I, De Vos R, Mesotten D, et al. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005; **365:** 53–59.

33 Vriesendorp TM, DeVries JH, van Santen S, et al. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med* 2006; **34:** 2714–18.