PAEDIATRIC ENDOCRINOLOGY

Critical illness — another trial, but are we any wiser?

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A recent trial in critically ill children found no benefit from lowering blood levels of glucose to 4.4–6.1 mmol/l compared with tolerating hyperglycaemia. The achieved levels of glucose, however, overlapped considerably between the tight and liberal glycaemic control groups, which might explain the lack of benefit. Moreover, liberal use of antibiotics could have resulted in a false low rate of infections.

Refers to Agus, M. S. *et al.* Tight glycemic control in critically ill children. *N. Engl. J. Med.* **376**, 729–741 (2017)

The Heart and Lung Failure–Paediatric INsulin Titration (HALF–PINT) study investigated whether targeting blood levels of glucose of 4.4–6.1 mmol/l improved the clinical outcome of critically ill children, compared with tolerating hyperglycaemia up to 10.0 mmol/l (REF. 1). To be eligible for inclusion in the study, patients needed to meet two criteria. First, to have confirmed hyperglycaemia, as defined by two consecutively recorded blood levels of glucose >8.3 mmol/l. Second, to be diagnosed with haemodynamic or respiratory failure, as defined by the need for vasoactive drugs or mechanical ventilation, respectively. Patients who were admitted to the intensive care unit (ICU) following cardiac surgery were not included in the study. The investigators planned to enrol 1,880 patients in order to detect a 1-day reduction in ICU length of stay and a 20% relative reduction in mortality. After inclusion of 713 patients, however, the study was stopped prematurely for reasons of futility and a potential, albeit questionable, sign of harm (a slight increase in health-care-associated infections in the tight glycaemic control group).

The results of the present study contrast with findings from an earlier single-centre trial performed in Leuven, Belgium, (n = 700), which demonstrated reduced mortality, a reduced incidence of new infections and an improved long-term neurocognitive outcome by targeting age-adjusted normal fasting blood levels of glucose in critically ill children (2.8–4.4 mmol/l target range for children aged <1 year; 3.9–5.6 mmol/l for older children)[2,3]. Subgroup analyses of a subsequent multicentre study of critically ill children also suggested a benefit from lowering blood levels of glucose in those not undergoing cardiac surgery[4]; a subgroup that was more severely ill than the cardiac subgroup and that more or less corresponded to the population of the HALF–PINT trial.

In their discussion, Agus *et al.* attribute the difference in results between studies to the omission of early parenteral nutrition in the HALF–PINT study[1]. Patients in the Leuven study received early parenteral nutrition as part of routine treatment, which subsequently turned out to be harmful[5]. Patients in the HALF–PINT study, however, were also prescribed a similar dose of parenteral nutrition during the first days in ICU. Energy intake in these patients was ~40 kcal/kg per day, and 70–100% of these calories were delivered by the parenteral route in the first 4 days; the glucose infusion rate was ~4 mg/kg per min[1]. Hence, the effect of blood glucose control in the absence of early parenteral nutrition remains to be investigated.

An alternative and more plausible explanation for the neutral effect of lowering levels of glucose on patient outcomes in the HALF–PINT study is the very large overlap in achieved blood levels of glucose between the tight and liberal glycaemic control groups. Although patients were only eligible for inclusion in the study after hyperglycaemia was confirmed, randomization occurred following a substantial delay of ~20 h (REF. 1). By that time, blood levels of glucose in most patients had already spontaneously decreased to levels well below the threshold for eligibility (threshold blood levels of glucose defined as >8.3 mmol/l). As a consequence, after randomization, the median achieved blood levels of glucose largely overlapped between the two groups (6.1 mmol/l versus 6.8 mmol/l for the tight and liberal glycaemic control groups, respectively; FIG. 1).

In the Leuven study, patients were randomly assigned to glucose-target groups immediately upon admission to the ICU, and the target range — age-adjusted normal fasting blood levels of glucose — was much lower than in the HALF–PINT study[2]. This approach resulted in a rapid and large difference in achieved blood levels of glucose and in a clear separation between the two experimental groups. Indeed, in the Leuven study, the median achieved blood levels of glucose were 4.9 mmol/l and 7.0 mmol/l for the tight and liberal glycaemic control groups, respectively (a difference of 2.1 mmol/l)[2]. With a median difference of only 0.7 mmol/l in the HALF–PINT study[1], any potential difference in outcome was likely to be small or even negligible. Furthermore, the HALF–PINT study was not statistically powered to detect such a small difference.

> “…blood glucose control in the absence of early parenteral nutrition remains to be investigated”

Another important concern relates to how the effect of the intervention on new infections was reported in the HALF–PINT study. Agus *et al.* reported a slightly higher incidence of health-care-associated infections in the tight glycaemic control group compared with the liberal glycaemic control group and concluded that this could be a sign of harm[1]. However, 95% of all patients in the HALF–PINT trial were treated with

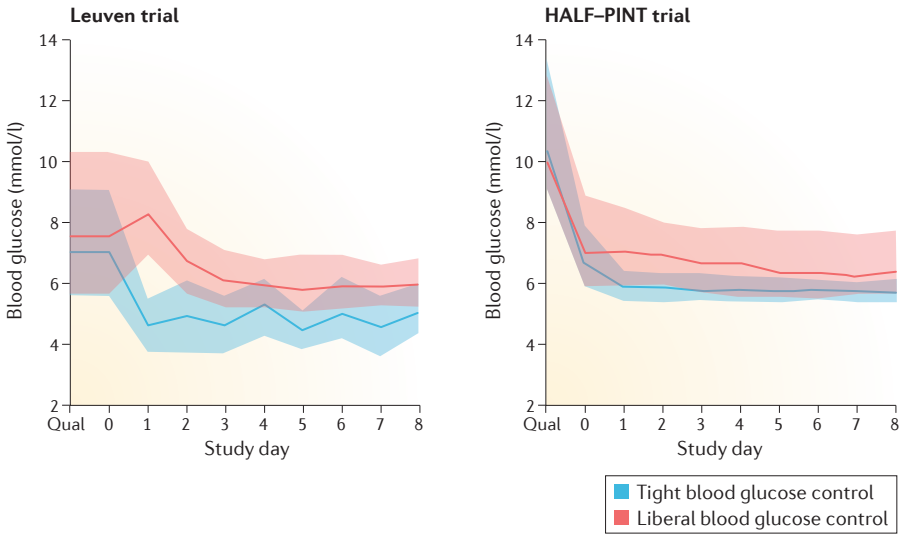

Figure 1 | **Different outcomes related to different levels of tight blood glucose control.** The figure displays achieved blood concentrations of glucose in the paediatric Leuven study[2] (left panel) and in the HALF–PINT study[1] (right panel). Blood concentrations of glucose from the qualifying blood level of glucose until day 8 after randomization (day 0) are shown. The lines represent the median values, and shaded areas indicate the interquartile ranges. Redrawn using data obtained from elsewhere[1,2]. Qual, qualifying blood glucose level.

antibiotics, with ~4% more patients treated in the liberal glycaemic control group than in the tight glycaemic control group — a difference that was statistically significant. In contrast to the high use of antibiotics, the incidence of health-care-associated infections was extremely low (~2%)[1]. It is highly probable that the liberal use of antibiotics produced culture-negative results. Therefore, ICU-acquired infections were probably underdiagnosed in the HALF–PINT study, which confounds this important study end point. Furthermore, the scoring of infections could have been suboptimal. For example, zero ventilator-associated pneumonias per 1,000 ventilator-days seems to be implausible according to the Centers for Disease Control and Prevention criteria, which were followed in the trial but do not require identification of the causative microorganism.

Altogether, the results from the HALF–PINT trial add to the ongoing controversy surrounding tight blood glucose control in critically ill patients in general. Indeed, as in critically ill children[1–3,6], randomized controlled trials in critically ill adults have yielded, at first sight, conflicting results[7–9]. Two single-centre studies performed in Leuven found decreased morbidity and mortality by targeting levels of glucose of 4.4–6.1 mmol/l in critically ill adults compared with tolerating hyperglycaemia up to 12 mmol/l (REFS 7,8). By contrast, a large, pragmatic multicentre study subsequently showed harm by this treatment, compared with insulin infusion to target blood levels of glucose of 7.8–10.0 mmol/l (REF. 9). Although harm in the adult multicentre study could be explained by the use of inaccurate glucose meters and a non-validated glucose control algorithm (with a high risk of undetected and prolonged hypoglycaemia as a consequence), the use of early parenteral nutrition in the Leuven studies[7,8] (which subsequently turned out to be harmful) could also account for the differences in outcome[10].

Currently, no adequately powered randomized controlled trials have investigated tight glucose control (using accurate monitoring tools and a reliable algorithm that minimizes the risk of hypoglycaemia) in the context of withholding early parenteral nutrition. Future trials should investigate this issue. Until evidence from new randomized controlled trials becomes available, avoiding severe hyperglycaemia in all critically ill patients seems to be prudent.

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Competing interests statement
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