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Paediatric endocrinology

Critical illness — another trial but are we any wiser?

Jan Gunst and Greet Van den Berghe

Refers to Agus, M. S. *et al.* Tight glycemic control in critically ill children. *N. Engl. J. Med.* <http://dx.doi.org/10.1056/NEJMoa1612348> (2017)

Standfirst

A recent trial in critically ill children found no benefit over tolerating hyperglycaemia from lowering blood glucose levels to 4.4–6.1 mmol/l. The achieved glucose levels, 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.

The Heart and Lung Failure–Paediatric Insulin Titration (HALF–PINT) study investigated whether targeting blood glucose levels of 4.4–6.1 mmol/l improved the clinical outcome of critically ill children, compared with tolerating hyperglycaemia up to 10.0 mmol/l¹. 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 glucose levels >8.3 mmol/l. Second, to suffer from 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 enroll 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 healthcare-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 ($n = 700$), which demonstrated reduced mortality, a reduced incidence of new infections and an improved long-term neurocognitive outcome by targeting age-adjusted normal fasting glucose levels 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 glucose levels in those not undergoing cardiac surgery⁴; a subgroup that was more severely ill than the cardiac subgroup and which 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 study¹. Patients in the Leuven trial received early parenteral nutrition as part of routine treatment, which subsequently turned out to be harmful⁵. Patients in the HALF–PINT study, however, also received parenteral nutrition during the first days in ICU, and at a similar dose as in the Leuven study. Indeed, 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 min¹. 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 glucose levels on patient outcomes in the HALF-PINT study is the very large overlap in achieved blood glucose levels 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 h¹. By that time, blood glucose levels in the majority of patients had already spontaneously decreased to levels well below the threshold for eligibility (glucose levels >8.3 mmol/l). As a consequence, after randomization, the median achieved blood glucose levels 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 glucose levels — was much lower than in the HALF-PINT study². This approach resulted in a rapid and large difference in achieved blood glucose levels and a clear separation between the two experimental groups. Indeed, in the Leuven study, the median achieved blood glucose levels 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 study¹, 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.

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 healthcare-associated infections in the tight glycaemic control group compared with the liberal glycaemic control group, and concluded that this could be a sign of harm¹. However, 95% of all patients in the HALF-PINT trial were treated with 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 healthcare-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 likely underdiagnosed in the HALF-PINT study, which confounds this important study endpoint. Furthermore, the scoring of infections could have been suboptimal. For example, zero ventilator-associated pneumonias per 1,000 ventilator-days

seems 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 results⁷⁻⁹. Two single-centre studies performed in Leuven found decreased morbidity and mortality by targeting glucose levels of 4.4–6.1 mmol/l in critically ill adults as compared with tolerating hyperglycaemia up to 12 mmol/l^{7,8}. In contrast, a large, pragmatic multicentre study subsequently showed harm by this treatment, as compared with insulin infusion to target blood glucose levels of 7.8–10.0 mmol/l⁹. 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 (which subsequently turned out to be harmful), could also account for the differences in outcome¹⁰.

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. Until evidence from new randomized controlled trials becomes available, avoiding severe hyperglycaemia in all critically ill patients seems prudent.

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Competing interests

The authors declare no competing interests.

Figure legend

Figure 1 | Different outcomes related to different levels of TGC.

The figure displays achieved blood glucose concentrations in the HALF-PINT study¹ (right panel) and in the paediatric Leuven study² (left panel). Blood glucose concentrations from the qualifying blood glucose level until day 8 after randomization (day 0) are shown. Dark lines represent the median values, shaded areas indicate the interquartile ranges. Redrawn using data obtained from elsewhere^{1,2}. Qual, qualifying blood glucose level. TGC, tight blood glucose control. LGC, liberal blood glucose control.

Pullquotes

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

“...avoiding severe hyperglycaemia in all critically ill patients seems prudent”

Author biographies

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Leuven trial

HALF-PINT trial