CORRESPONDENCE

A Trial of Hyperglycemic Control in Pediatric Intensive Care

TO THE EDITOR: In reporting the results of the Control of Hyperglycaemia in Paediatric Intensive Care (CHiP) trial, Macrae et al. (Jan. 9 issue)[1] define "normoglycemia" in children in the intensive care unit (ICU) as a blood glucose level of 72 to 126 mg per deciliter (4.0 to 7.0 mmol per liter), and thus only two thirds of patients in the tight-glycemic-control group required insulin. The number of days that children were free from mechanical ventilation at 30 days was unaffected, but kidney failure was prevented, the length of stay in the hospital was reduced, and the mean costs of hospital and community health services were lowered by tight glucose control. An earlier randomized, controlled trial involving a similar patient population targeted healthy fasting blood glucose ranges (in infants younger than 1 year, 50 to 80 mg per deciliter [2.8 to 4.4 mmol per liter], and in children 1 year of age or older, 70 to 100 mg per deciliter [3.9 to 5.6 mmol per liter]). That trial, in which all patients required insulin, showed reduced morbidity and mortality and, subsequently, improved neurocognitive development.[2,3] In CHiP, most children in the control group were spontaneously "normoglycemic" according to the authors' definition (blood glucose level, 122 mg per deciliter [6.8 mmol per liter] on day 1 and 114 mg per deciliter [6.3 mmol per liter] thereafter). Hence, the population at risk was diluted by a population not at risk, rendering statistical power insufficient. Since tight glucose control prevents later complications,[4] only the more critically ill patients who had more severe hyperglycemia and longer stays in the hospital — just a fraction of the patients in this study — may possibly benefit. The length of hospital stay in this study was 5 days shorter with tight glycemic control than with conventional treatment. This effect occurred late and was confirmed by the analysis of costs in the 12 months after randomization, so that more weight was given to patients with longer stays in the hospital.[5] Future trials of tight glucose control in children in ICUs should therefore select only patients "at risk" (with hyperglycemia) or increase the sample size. Follow-up should not be limited to 30 days.

Greet Van den Berghe, M.D., Ph.D.
Dieter Mesotten, M.D., Ph.D.

KU Leuven
Leuven, Belgium
greet.vandenberghe@med.kuleuven.be

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5. Vanderheyden S, Casaer MP, Kesteloot K, et al. Early versus late parenteral nutrition in ICU patients: cost analysis of the EPaNIC trial. Crit Care 2012;16:R96.

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TO THE EDITOR: After more than a decade of tight glycemic control in critically ill patients, whether this should be considered a best practice remains a controversial subject, mainly in pediatric patients.[1,2] The study by Macrae et al. appears to be relevant to this topic, since, in addition to assessment of the financial impact of this treatment, it evaluated patients after cardiac surgery and with other clinical conditions.

Other studies have suggested that hyperglycemia can result in worse outcomes.[1,2] However, a recent study has emphasized stress hyperglycemia as an evolutionarily preserved adaptive response that increases the survival rate.[3]

The incidence of hypoglycemia varies in studies comparing tight glucose control and conventional treatment, mainly because of different populations and discrepant glycemic ranges. The incidence is higher in studies of tight glucose control[1,2] such as the study by Macrae et al. Despite the occurrence of seizures in patients in this trial, there was no long-term follow-up to evaluate the possible sequelae.

Advanced forms of technology such as computerized glucose control[4] have paved the way for future research and better clinical practices to distinguish groups that can really benefit from tight glucose control. Which path should be followed? New pediatric trials of tight glucose control should be considered, with the use of physiological mechanisms to reduce the occurrence of adverse effects.

Thalita G.S. Vasques, M.D.
Juliana F. Ferranti, M.D.
Werther B. de Carvalho, M.D., Ph.D.
University of São Paulo
São Paulo, Brazil
thalita_vasques@hotmail.com

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Van den Berghe and Mesotten describe the variability that we noted in our article in the four pediatric randomized, controlled trials of glucose control that used insulin; these trials involved a total of 3438 patients.[1,2] However, the most marked difference in each study is the use of insulin, not the glucose concentrations. We therefore question the usefulness of further randomized, controlled trials focused solely on glucose control.

Van den Berghe and Mesotten suggest that a future randomized, controlled trial should focus on children with marked hyperglycemia. Our trial was not limited to such a population. Rather, it answered the practical question of whether a glucose level of 72 to 126 mg per deciliter should be targeted in children in the pediatric ICU who required placement of an arterial catheter, mechanical ventilation, and vasoactive drug therapy. We concluded that in those circumstances, tight glycemic control had no effect on major clinical outcomes 30 days after randomization. A subgroup analysis based on severity-of-illness scores to determine the risk of death did not suggest that the effect was influenced by risk status, though that analysis had low power.

We fully agree that follow-up should not be limited to 30 days. We followed our patients for up to 1 year. The main benefits of glucose control were for patients in the non–cardiac-surgery subgroup, in whom hospital stay and costs up to 1 year were reduced.

Other than for a small number of children who had traumatic brain injury, our follow-up of children who did not remain in or who were not readmitted to the ICU on day 30 was only to determine how many patients had died and to assess for parent-reported use of health services, which could be seen as indicators of morbidity. We strongly agree that a range of clinically relevant longer-term end points should be part of any future randomized, controlled trials involving children in the pediatric ICU, and we agree with Vasques et al. that future applications or trials of glucose control should embrace new

forms of technology to ensure the safest delivery of the intervention.

Duncan Macrae, F.R.C.A.

Royal Brompton and Harefield NHS Foundation Trust
London, United Kingdom
d.macrae@rbht.nhs.uk

Robert C. Tasker, M.D.

Harvard Medical School
Boston, MA

Diana Elbourne, Ph.D.

London School of Hygiene and Tropical Medicine
London, United Kingdom

Since publication of their article, the authors report no further potential conflict of interest.

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Targeted Temperature Management after Cardiac Arrest

TO THE EDITOR: Nielsen and coauthors (Dec. 5 issue)[1] show the importance of avoiding hyperthermia in patients who have had a cardiac arrest. However, if the clinical objective is to improve the neurologic outcome, it is important to define the expected neurologic outcome in individual patients. Studies have shown that the severity of neuronal lesions is dependent on the delay in initiation of cooling after reperfusion.[2]

In the article by Nielsen et al., the studied patients had a median return of spontaneous circulation of 25 minutes, with a wide interquartile range of 18 to 40 in the hypothermic group and 16 to 40 in the normothermic group. In prolonged cardiac arrest, we do not expect that a reduction of neurologic metabolism by hypothermia will have a real effect on already damaged structures.

We should not conclude, on the basis of this trial, that hypothermia is simply an antihyperthermic strategy. Not all cardiac arrests are equal in terms of the time to return of spontaneous circulation. We should identify the subgroups of patients who can benefit from this form of therapy.

Gaetano Perchiazzi, M.D., Ph.D.
Nicola D'Onghia, M.D.
Tommaso Fiore, M.D.

University of Bari
Bari, Italy
gaetano.perchiazzi@uniba.it

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Nielsen et al. confirm that fever should be avoided in resuscitated patients. However, several unanswered questions remain before abandoning therapeutic hypothermia in patients after cardiac arrest. One key issue is the potential benefit of early cooling initiated during cardiopulmonary resuscitation (CPR).

Pathophysiological mechanisms[1] as well as experimental data suggest a benefit of early cooling, with intra-arrest cooling clearly superior to postresuscitation cooling.[2] Thus, when moving from very early cooling in the experimental setting to several hours of delay in clinical practice, we might miss the time window for the greatest effectiveness of hypothermia.[3]

Transnasal evaporative cooling can be induced in field conditions during CPR.[4] The method induces continuous cooling, primarily to the brain, without the hemodynamic side effects recently seen with cold saline. Ongoing and future studies may add important knowledge to this field of research.[5]

Nielsen et al. permitted a time to initiate cooling of 4 hours. We suggest that this time window may be crucial to influence outcome.

Per Nordberg, M.D.

Karolinska Institutet
Stockholm, Sweden
per.nordberg@sodersjukhuset.se