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PAEDIATRICS

Cognitive benefits of tight glucose control in critically ill children

Brief episodes of hypoglycaemia in children under critical care do not negatively affect cognitive development in subsequent years of life. These findings, reported in *JAMA*, challenge previous notions that the risk of hypoglycaemia would outweigh any benefit of preventing hyperglycaemia in children and adults treated in intensive care units (ICUs).

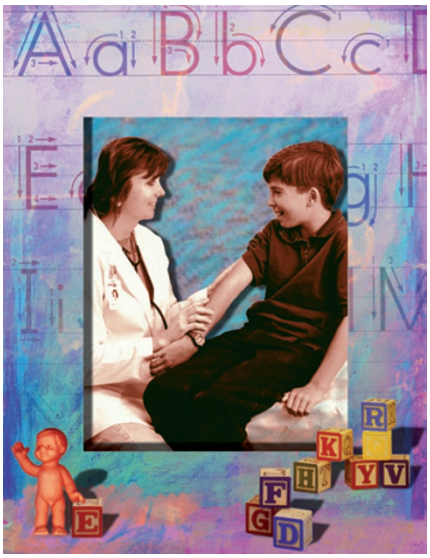
"Hyperglycaemia has long been known to be associated with adverse outcomes in critically ill adults and children," explains lead researcher Greet Van den Berghe. "My team has previously performed three pioneering prospective randomized controlled trials, two in adults and one in children, to address the causality of this association," she adds. These studies have shown that lowering blood glucose levels to healthy normal fasting ranges, compared with not treating hyperglycaemia unless blood glucose levels exceed 215 mg/dl (11.93 mmol/l), reduces mortality and morbidity. However, a marked increase in the percentage of episodes of hypoglycaemia was observed in the study of children (from 1% in the group receiving usual care to 25% in the group under tight glycaemic control) and concerns were raised that this hypoglycaemia could have harmful effects in a child's future neurocognitive development. Therefore, Van den Berghe and colleagues undertook a follow-up study of the children who took part in the trial to compare the long-term effects of the different glucose monitoring strategies.

The initial trial included 700 patients aged ≤16 years who were admitted to the paediatric ICU of the University Hospitals in Leuven, Belgium, between October 2004 and December 2007. Patients were randomly allocated to receive tight glucose control, defined as insulin infusion targeted to achieve normal age-adjusted glucose levels (50–80 mg/dl [2.78–4.44 mmol/l] for patients aged <1 year and 70–100 mg/dl [3.89–5.58 mmol/l] for those aged 1–16 years), or usual care (only treated when glucose levels rose above 215 mg/dl).

Follow-up analysis was performed 3 years after hospital stay for all patients except infants, who were assessed when they were aged 4 years to enable adequate data comparison. The median follow-up period was 3.9 years. Evaluation of cognitive development was possible in 569 of the original study participants. Neurocognitive testing included measurement of intelligence, visual–motor integration, attention, motor coordination, inhibitory control, cognitive flexibility, memory and behaviour. The presence of neurological abnormalities was also investigated. Importantly, the study included a control group of 216 children who had never needed intensive care.

Although the incidence of episodes of hypoglycaemia was higher among patients who received tight glucose control, hypoglycaemia was not independently associated with neurocognitive outcomes. Patients who received tight glucose control had comparable scores of intelligence, visual–motor integration and memory to those of patients who received usual care. The incidence of death or severe disability was also similar in the two groups. However, motor coordination and cognitive flexibility were significantly improved in the group who underwent tight glucose control.

"Hyperglycaemia appears to be more toxic to the developing brain than brief hypoglycaemia in ICU patients," comments Van den Berghe, "provided that hypoglycaemia is always quickly detected and adequately treated to prevent an overshoot of hyperglycaemia after hypoglycaemia." Nevertheless, Van den Berghe stresses the importance of using age-appropriate target blood glucose levels. "Insulin treatment for ICU patients only works when the normal healthy fasting ranges are achieved, and these are much lower in infants than in adults."



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Van den Berghe points out that the expertise of nurses and the use of accurate tools for blood glucose measurement are important factors to avoid extended periods of hypoglycaemia. "Hand-held meters for blood glucose monitoring are, in our view, not accurate enough to titrate such a normal range of blood glucose levels in ICU patients. Working towards a semi-closed loop will, in the future, help clinicians achieve the benefit of titrating insulin to normoglycaemia in the ICU."

Of note, children who received treatment at the ICU had worse cognitive performance scores than children in the control group. "What we do to these patients in intensive care can affect neurocognitive development," concludes Van den Berghe, calling for further study on the way children are cared for in the ICU and the effects of this care. "We will study the potential underlying mechanisms of the 'legacy' of critical illness long after childhood intensive care."

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Original article Mesotten, D. *et al.* Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. *JAMA* doi:10.1001/jama.2012.12424