Intensive insulin therapy: does it improve outcomes and is it safe?

Neil Orford

The two major questions regarding intensive insulin therapy (IIT) are: Does it improve outcomes? And is it safe? The article by Mitchell and colleagues[1] in this issue of the Journal (*page 289*) can be read with both these questions in mind.

Does intensive insulin therapy improve outcomes? Mitchell et al's article does not address this, as their study was designed to determine safety and effectiveness of an IIT protocol. However, the report is pertinent as it reviews the clinical application of the NICE-SUGAR trial protocol. The NICE-SUGAR trial is a large, multicentre, randomised controlled trial comparing IIT with conventional treatment in general intensive care patients. It may provide important information on the generalisability of the benefits of IIT reported in the Leuven medical (M-ICU) and surgical (S-ICU) trials.[2,3] The results reported in this issue suggest that the NICE-SUGAR protocol is an effective tool. The authors report comparable efficacy (IIT median blood glucose level [BGL], 5.4 mmol/L) to the Leuven trials (IIT mean morning BGL M-ICU, 6.2 mmol/L; S-ICU, 5.7 mmol/L), although with much lower insulin requirements (36 IU/day versus 59 IU/day M-ICU; 71 IU/day S-ICU). This may be attributable to a difference in insulin resistance between trial populations, but is more likely to reflect differences in nutritional practices between Australia, New Zealand and the Leuven trials.

Is intensive insulin therapy safe? The incidence of hypoglycaemia (BGL < 2.2 mmol/L) is reported as 14.3% by Mitchell et al — similar to the Leuven trials (M-ICU, 18.7%; S-ICU, 5.1%). Although this may appear high, eight episodes of biochemical hypoglycaemia in 3411 BGL measurements at an average of 16 measurements per day represents one episode of hypoglycaemia every 26.6 patient days receiving IIT. However, the German Sep-Net committee interpreted a similar incidence (12.1%) as evidence of unacceptable risk in their multicentre, randomised controlled trial of IIT in severe sepsis, and stopped the trial early.[4]

The significance of transient biochemical hypoglycaemia remains a major stumbling block for the acceptance of IIT, even if the beneficial effects of IIT are confirmed by trials such as NICE-SUGAR. It is unclear what importance factors such as the absolute level of BGL, the duration of hypoglycaemia, the rate and amplitude of the fall, the glycaemic control history, and the interaction of the effects of glucose and insulin play in determining harm. The fear of undiagnosed, unmonitored episodes in unconscious patients is a concern, which may not be adequately addressed until continuous BGL monitoring becomes available.

The possibility that IIT is associated with worse outcomes in short-term ICU patients, and that mortality rates are increased for patients who have hypoglycaemic episodes,[2] raises questions about hypoglycaemia as a marker for "sicker" patients, and the potential harm of unknown mechanisms associated with this therapy.

In summary, there are many unanswered questions regarding the role of IIT in critically ill patients. The report by Mitchell et al[1] confirms that the NICE-SUGAR trial protocol is effective and arguably safe, and will help address these questions in a way that broadly reflects Australian and New Zealand feeding and glycaemic control practices.

Author details

Neil Orford, Intensive Care Specialist
The Geelong Hospital, Geelong, VIC.
Correspondence: neilo@barwonhealth.org.au

References

1 Mitchell I, Knight E, Gissane J, et al. A phase II randomised controlled trial of intensive insulin therapy in general intensive care patients. *Crit Care Resusc* 2006; 8: 289-293.
2 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.
3 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345: 1359-67.
4 Brunkhorst FM, Kuhnt E, Engel C, et al. Intensive insulin therapy in patient with severe sepsis and septic shock is associated with an increased rate of hypoglycemia — results from a randomized multicenter study (VISEP) [abstract]. *Infection* 2005; 33 Suppl 1: 19-20. ❑