Tight glycaemic control in the critically ill: losing its grip?

Tight glycaemic control in the critically ill is achieved by administering insulin to target a blood sugar concentration of 4.4–6.1 mmol/litre. This is a valid but controversial target: the Surviving Sepsis campaign currently supports a target of <8.3 mmol/litre. Proof of concept was originally demonstrated by Van den Berghe et al (2001) who recruited 1548 ventilated patients, two thirds post-cardiothoracic surgery, and found tight control reduced mortality from 8.0% to 4.6% (*P*<0.04), compared to conventional control (<11.9 mmol/litre). There was a 5% incidence of hypoglycaemia (blood glucose <2.2 mmol/litre) in the treatment group. However, subsequent studies, including a second by the same group in medical intensive care patients (Van den Berghe et al, 2006), have failed to replicate these impressive results. Some were terminated early owing to increased mortality and hypoglycaemic episodes (Brunkhorst et al, 2008; Wiener et al, 2008). A meta-analysis by Wiener et al (2008) failed to demonstrate any benefit. NICE-SUGAR, the largest single study performed to date, concluded that tight glucose control may increase mortality (Finfer et al, 2009).

Wiener et al's (2008) meta-analysis identified 1358 studies, of which 29 met inclusion criteria, totalling 8432 patients and 1869 deaths. The primary end point, a reduction in hospital mortality, was rejected. The relative risk of death was 0.93 (95% confidence interval 0.85–1.03). This meta-analysis was methodologically strong and used a widely accepted quality assessment tool (Jadad), although a consistently limiting factor was the single centre nature of many included trials. Critics have argued that it is inappropriate to pool trials which estimate glycaemic control differently (there is no agreed gold standard) or use different protocols for insulin delivery.

A number of secondary end points were also investigated. There was a significant reduction in septicaemia but not mortality among the subgroup of surgical patients, a finding heavily influenced by the first Van den Berghe study. The incidence of hypoglycaemic episodes in the treatment groups was 13.7%, compared to 2.5% in the control (relative risk 5.13, 95% confidence interval 4.09–6.43). Whether hypoglycaemic episodes contribute directly to death or indicate disease severity is unclear. There was no evidence that more liberal control (<8.3 mmol/litre), as suggested by Finney et al (2003), is of benefit. They used regression analysis to identify a blood glucose level that could minimize the risk of hypoglycaemia. The liberal treatment group was heavily influenced by a study comprised solely of stroke patients that was terminated early owing to slow recruitment.

NICE-SUGAR enrolled 6104 patients who were expected to stay in the intensive care unit for more than 3 days, across 42 sites over 4 years (Finfer et al, 2009), and randomized them to tight (4.5–6.0 mmol/litre) or conventional control (<10.0 mmol/litre). The primary end point, 90-day mortality, was significantly greater in the treatment (27.5%) than the control group (24.9%) (*P*=0.02). There was no difference in length of stay or organ dysfunction scoring. Hypoglycaemia occurred in 6.8% and 0.5% of patients respectively. There was no difference among secondary end points, nor any evidence that surgical patients may specifically benefit. Tight control was abandoned in favour of conventional control in 10% of patients, but patients were classified on an intention-to-treat basis. Corticosteroid therapy was slightly over-represented in the tight control group.

Is there a mortality benefit?

How can the mortality benefit seen by Van den Berghe et al (2001) be explained? Perhaps the atypical high calorie parenteral feeding regimen (9 g glucose/hour) worked in tandem to provide benefit or possibly contributed to the unexpectedly high mortality rate in the control group. Maybe cardiothoracic patients gain particular benefit – insulin-potassium-dextrose infusions are of recognized benefit in this group. Wiener's study and NICE-SUGAR did not analyse cardiothoracic patients per se. The low incidence of hypoglycaemic episodes was partly explained by the use of highly accurate arterial blood glucose, and is partly supported by the NICE-SUGAR data. Most other studies used less accurate capillary blood glucose, which provides no information about other parameters. Van den Berghe's unit had a dedicated glucose control nurse for each patient. The original study censored follow up after discharge – the benefits may only be short term – and was terminated early after a third interim analysis, so there is an increased risk the findings were simply the result of chance.

Conclusions

The ready occurrence of hypoglycaemia under the close attention of several clinical trials coupled with the increased mortality found by NICE-SUGAR is concerning. The latter investigators cautiously state that they cannot exclude that a subgroup of patients may benefit, but the blanket application of tight control seems another example where the pursuit of physiological normality in the critically ill may ultimately cause more harm than good. **BJHM**

The author would like to thank Dr R Schoub, Barnet Hospital, for his help with compiling this article.

Brunkhorst FM, Engel C, Bloos F et al (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis (VISEP). *N Engl J Med* **358**(2): 125–39

Finney SJ, Zekveld C, Elia A et al (2003) Glucose control and mortality in critically ill patients. *JAMA* **290(15):** 2041–7

Finfer S, Chittock DR, Su SY et al (2009) Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* **360**(13): 1283–97

Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in critically ill patients. *N Engl J Med* **345**(19): 1359–67

Van den Berghe G, Wilmer A, Hermans G et al (2006) Intensive insulin therapy in the medical ICU. *N Engl J Med* **354**(5): 449–61

Wiener RS, Wiener DC, Larson RJ (2008) Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* **300**(8): 933–44

Dr David Cain *is Speciality Registrar in Anaesthetics at The Royal Free Hospital, London NW3 2QG*

Anaesthetic and critical care dilemmas are coordinated by Dr Pervez Sultan and Dr Kate Adams, Specialist Registrars in Anaesthetics, University College Hospital London

Ideas for future dilemmas can be sent to Rebecca Linssen bjhm@markallengroup.com