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Editorial

Does strict glucose control improve outcome?

In 2001 and 2006, the *New England Journal of Medicine* published two single-centre studies which reported mortality benefits of tight glycaemic control in longer stay post-surgical critically ill adult patients.^{1 2} These papers created much debate with several repeat studies, meta-analyses, and, surprisingly, almost uniform early uptake by critical care practitioners.

Van den Berghe's first study¹ used an intensive regimen of insulin treatment (IIT) with the aim of keeping blood glucose concentrations at or below 6.1 mmol litre⁻¹ (110 mg dl⁻¹). A criticism of the study was that the patients were largely post-cardiac surgery and this therefore prompted the same workers to investigate the same approach in medical intensive care unit (ICU) patients, where a beneficial effect on in-hospital mortality was only seen in a subgroup of patients who stayed on the ICU for more than 3 days.² Subsequent studies conducted by others have not shown a mortality benefit and some even had safety issues associated with IIT.^{3 4} However, the practice of IIT still continues in most ICUs and a similar approach to the intra- and postoperative management of patients has been gaining momentum.

The SepNet trial reported last year investigated the use of IIT in patients with severe sepsis in multidisciplinary ICUs, since it had been argued that most of the mortality benefit reported in Van den Berghe's 2001 paper had been in such patients.³ However, the trial was stopped early on safety grounds, since the use of IIT placed critically ill patients with sepsis at increased risk for serious adverse events related to hypoglycaemia. Serious hypoglycaemia was roughly four times more common in the patients given IIT. In addition, neither 28 day mortality nor organ failure score was different between the two trial arms. However, this study was complicated by the concurrent use of two different fluid resuscitation regimes.³ Also published last year, a meta-analysis of 29 clinical trials of IIT involving

8432 critically ill adult patients showed that in-hospital mortality was similar in patients receiving IIT (21.6%) and usual care (23.3%) and episodes of hypoglycaemia were greater than five times more common with IIT.⁴ Despite this, Van den Berghe and colleagues⁵ still argue that IIT confers a mortality benefit when controlling blood glucose concentrations to normoglycaemia [below 6.1 mmol litre⁻¹ (110 mg dl⁻¹)] but agree on the need for more trials.

In April 2009, the NICE-SUGAR study was published,⁶ and data from this study were incorporated into a new meta-analysis.⁷ The NICE-SUGAR study recruited 6104 patients from 42 hospitals in Australia, New Zealand, and Canada. The groups of patients were assigned target blood glucose levels of either 4.5–6.0 mmol litre⁻¹ (IIT) or 8.0–10.0 mmol litre⁻¹ (conventional glucose control) and the main outcome measure was 90 day mortality.⁶ More patients in the IIT group died than in the conventional control group (27.5% vs 24.9%, $P=0.02$). The (predefined) groups of causes of death in the two groups were similar ($P=0.12$), although deaths from cardiovascular causes were more common in the IIT group (41.6% vs 35.8%, $P=0.02$). Severe hypoglycaemia (defined as a blood glucose of ≤ 2.2 mmol litre⁻¹) occurred in 6.8% of the IIT patients compared with only 0.5% of the conventional control patients ($P<0.001$), although there were no long-term sequelae in any patient. Interestingly, the two survival curves on the Kaplan–Meier graph only begin to diverge at around 20 days—which begs the question of how such an intervention can have an effect at this point, when the median duration of IIT treatment was only 4.2 days (range 1.9–8.7 days) in the IIT group and 4.3 days (range 2.0–9.0 days) in the conventional group. In addition, 90% of the patients who died were reported to have had potentially life-sustaining treatments withheld or withdrawn, perhaps illustrating the point that mortality is not a clear-cut endpoint after all.

The meta-analysis published hot on the heels of the NICE-SUGAR study, which included these results (as the authors were largely the same) inevitably came to similar conclusions as 6104 of the 13 567 patients included in the meta-analysis were from the NICE-SUGAR study.⁷ The pooled relative risk of death was 0.93, with significantly higher episodes of hypoglycaemia in the IIT group (relative risk, 6.0). However, the ICU setting was a factor in outcome with those in a surgical ICU having a better outcome with IIT: patients from a surgical ICU treated with IIT had a relative risk of death of 0.63 compared with 0.91 in patients from medical ICUs.

Another important study published in 2008 was the NIH NHLBI Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.⁸ This was a randomized trial of IIT in 10 251 patients with type 2 diabetes who had a median glycosylated haemoglobin level of 8.1%. Patients were assigned to receive IIT (target glycosylated haemoglobin level <6.0%) or standard therapy (target 7.0–7.9%). The primary outcome measure was a composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes. The patients were followed for 3.5 yr, but the trial was prematurely halted due to excess mortality in the IIT group (257 deaths compared with 203 deaths in the standard therapy group, $P=0.04$). Coupled with this, severe hypoglycaemia requiring intervention and weight gain of more than 10 kg were more common in the IIT group ($P<0.001$). Two previous studies had also failed to show beneficial effects of IIT on either cardiovascular events or mortality in patients with type 2 diabetes mellitus. The United Kingdom Prospective Diabetes Study (UKPDS) showed that although there was a significantly lower incidence of seven diabetes-related events in the IIT group, there was no significant effect of IIT on cardiovascular events or mortality.⁹ More than 10 yr ago, the Veterans Affairs Diabetes Feasibility Trial (VADT) showed that IIT did not affect mortality¹⁰ and a follow-up study was published this year.¹¹ Military veterans who had a suboptimal response to therapy for type 2 diabetes were randomized to receive either IIT or standard glucose control with a median follow-up of 5.6 yr.¹⁰ The goal in the IIT group was an absolute reduction of 1.5% in glycosylated haemoglobin. Median glycosylated haemoglobin was 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. There was no significant difference between the two groups in any component of the primary outcome, or in the number of deaths. Also, unlike the UK study, there were no differences in microvascular complications between the groups.

The enthusiastic adoption of IIT in critically ill patients has generated interest in its use in the perioperative period in both diabetic and non-diabetic patients. Indeed, in the USA, there has been a suggestion that this may be adopted as a quality indicator of care.¹² However, intraoperative IIT has not been shown to benefit death and morbidity rates. Reduced mortality was reported in patients who

have lower blood glucose concentrations after acute myocardial events (the DIGAMI study),¹³ and so it is logical that tight glycaemic control would be first studied in patients undergoing cardiac surgery. In 2007, one of the largest randomized trials reported the effect of IIT in adults with and without diabetes who were undergoing on-pump cardiac surgery.¹⁴ The primary outcome measure was a composite of death, sternal infections, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure, within 30 days of surgery. Patients received either continuous insulin infusion to maintain intraoperative glucose levels between 4.4 and 5.6 mmol litre⁻¹ (80–100 mg dl⁻¹) (IIT, $n=199$) or conventional treatment ($n=201$), where patients were not given insulin during surgery unless glucose levels were >11.1 mmol litre⁻¹ (>200 mg dl⁻¹). Both groups were treated with an insulin infusion to maintain normoglycaemia after surgery. Adverse events occurred in 82 of 185 patients (44%) in the IIT group and 86 of 186 patients (46%) in the conventional treatment group. There were more deaths in the IIT group (4 vs 0, $P=0.061$) and strokes (8 vs 1, $P=0.02$) than in the conventional treatment group. The authors concluded that IIT during cardiac surgery did not reduce the perioperative death or morbidity rates. However, they also stated that the increased incidence of death and stroke in the IIT group raises concern about the routine implementation of this intervention.

It is interesting to note that the DIGAMI-2 study¹⁵ of 1253 type 2 diabetic patients who had a myocardial infarction failed to show that acutely introduced, followed by subsequent long-term, IIT, improved survival compared with conventional management, or that IIT decreased the number of non-fatal myocardial re-infarctions and strokes. However, the target fasting blood glucose concentration of 5–7 mmol litre⁻¹ was never reached in any of the patient groups.

The potential for deleterious metabolic effects of insulin have been largely ignored. It is generally believed that the dangers of aggressive insulin administration are attributable solely to hypoglycaemic events, but changes in the metabolism of other substrates, such as plasma lipids, may also be important.¹⁶ Cardiac function, for example, is highly dependent on the myocardial energy source which is affected by substrate availability and concentrations of metabolic hormones such as insulin. Under normal circumstances, most of the energy needs of a healthy heart come from fatty acid oxidation. Glucose–insulin–potassium administration has been suggested to prevent hyperglycaemia and hyperlipidaemia during reperfusion after cardiac interventions and was also thought to reduce inflammatory responses. However, in patients undergoing coronary artery bypass surgery, high-dose insulin administration with a glucose infusion to maintain blood glucose levels within a target range of 4.0–5.5 mmol litre⁻¹, fatty acid concentrations decreased to very low levels. In fact, the concentrations were at a level which may be too low

to allow uptake by the heart. There was also no effect of the treatment on various inflammatory markers or lactate concentrations.^{17 18} These studies suggest that control of blood sugar by insulin may not be beneficial in the perioperative period.

What is the supposed mode of action of tight glycaemic control? The only proposed mechanism which has received any attention is that of glucose toxicity in the context of ischaemia–reperfusion. Glucose is transported into cells by several transporter systems called glucose transporters or GLUT but only GLUT4 is insulin-dependent. Van den Berghe¹⁹ has suggested that excess glucose is toxic to cells, particularly mitochondria, and that this occurs in cells that take up glucose in proportion to the circulating glucose concentration, independently of insulin. This may be related to GLUT4 transport in specific cells allowing glucose to be safely used as a fuel or converted to a storage medium rather than in other cells, where more potentially toxic pathways are utilized. In effect, exogenously administered insulin is decreasing circulating glucose and thus making less available for the glucose transporters that are concentration-dependent. Evidence for this statement is largely as a result of ultrastructural changes which were found in the mitochondria from liver biopsies of critically ill patients who died, with more pronounced changes observed in those with conventional glucose control than those receiving IIT.²⁰ This was coupled with changes in complexes I and IV activity. In contrast, there was no difference in the mitochondria from skeletal muscle (which expresses the GLUT4 insulin-dependent transporter). It is therefore argued that it is the excess glucose that is toxic and the insulin merely acts to lower the circulating concentrations of glucose. This hypothesis is also supported by studies which showed that hyperglycaemia can completely abolish anaesthesia-induced ischaemic pre-²¹ and post-conditioning²² in a rat model of myocardial infarction. However, GLUT1, which is the main transport protein for glucose into cells for their normal metabolic requirements and which is insulin-independent, is almost fully saturated at a concentration of around 4 mmol litre⁻¹ as it has a K_m of ~ 1.3 mmol litre⁻¹.²³ This renders highly improbable the suggestion that a reduction in circulating glucose to a concentration above 4 mmol litre⁻¹ is likely to have a beneficial effect on intracellular glucose concentrations. There are, however, other GLUT transporters; some of which are cell type specific, although most have a significantly lower transporting capacity than that of GLUT1. In addition, the total number of GLUT1 transporters could change during hyperglycaemia and this would have the effect of increasing glucose transport.

As an alternative, would it not be better to control circulating glucose concentrations by restricting carbohydrate intake? In the days before insulin, dietary carbohydrate restriction was recommended as the treatment for diabetes, with a total daily energy intake of around 1800 kcal, comprising 75% fat, 17% protein, 6% alcohol, and 2%

carbohydrate.²⁴ With the introduction of insulin and oral hypoglycaemic agents, it became possible to permit the reintroduction of carbohydrate into the diet since any peaks in blood glucose could easily be controlled. However, restricted carbohydrate intake is not associated with hypoglycaemic episodes and may potentially act in a similar way to IIT.

In conclusion, tight glucose control is probably not beneficial in the critically ill and may even be harmful, even less is known about any effect in patients undergoing surgery. Equally, the importance of the excessive use of insulin in this group of patients is unclear. Perhaps the time has come for an appraisal of what is the effect in Atkins approach to the management of hyperglycaemia. An investigation of the use of carbohydrate restriction to control circulating glucose concentrations in both the critically ill and the perioperative patients is the next logical step.

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