

Intensive insulin therapy in septic shock

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The 2004 Surviving Sepsis Campaign (SSC) guidelines recommend: "Following initial stabilisation of patients with severe sepsis, maintain blood glucose < 8.3 mmol/L", in the management of patients with severe sepsis and septic shock.¹ Van den Berghe et al recommend the use of intensive insulin therapy (IIT) aiming for a blood glucose range of 4.4 to 6.0 mmol/L in critically ill patients.^{2,3} In patients with severe sepsis, the clinical intensivist must decide whether to implement the guidelines as suggested by the SSC, to practice IIT, or to continue with permissive hyperglycaemia.

The Leuven trials

In critically ill patients, the benefits of preventing hyperglycaemia have become the focus of international attention following the two studies conducted by Van den Berghe et al in Leuven, Belgium.^{2,3} The first Leuven study reported reduced mortality and morbidity in critically ill patients treated with IIT to keep blood glucose in the range 4.4–6.1 mmol/L, compared with conventional therapy to maintain blood glucose in the range 10.0–11.1 mmol/L, in 1548 patients in a surgical intensive care unit. IIT was associated with a reduced overall in-hospital mortality of 34%, and significant reductions in the incidence of bloodstream infections, acute renal failure requiring haemofiltration, critical illness polyneuropathy, requirement for prolonged inotropic support, hyperbilirubinaemia, raised C-reactive protein level, number of blood transfusions, and length of stay (LOS) for patients with a duration of stay greater than 5 days. The improvement in outcomes was entirely attributable to effects on patients with an ICU LOS greater than 5 days. Insulin use, assessed both as the percentage of patients receiving insulin and actual dose, was increased with IIT, as were the episodes of hypoglycaemia.²

Analysis of the cost of implementing IIT showed a reduction in average total cost of health-care resource utilisation of 2638 euros (approximately A\$4448) per patient with IIT. This represented an increase in average cost of insulin delivery from 72 euros (A\$121) to 144 euros (A\$243) with IIT, combined with a decrease in average cost of resources used for ventilation, vasopressor support, dialysis, antibiotics and LOS from 10 569 euros (A\$17 820) to 7931 euros (A\$13 371) for IIT.⁴

The second Leuven trial again compared IIT to conventional therapy, but in 1200 critically ill medical ICU patients

ABSTRACT

The use of intensive insulin therapy (IIT) to maintain blood glucose level below 8.3 mmol/L is recommended for management of severe sepsis by the Surviving Sepsis guidelines. The recent trials reporting reduced morbidity and mortality in critically ill patients treated with IIT require careful examination, including the subsequent post-hoc analyses. An understanding of the molecular and metabolic mechanisms by which IIT may be beneficial and the evidence that it benefits patients with severe sepsis, and a review of the risks of hypoglycaemia are also necessary when deciding whether to implement IIT in severe sepsis. Patients with severe sepsis are likely to benefit from IIT based on metabolic effects and their prolonged stays in the intensive care unit. The current evidence suggests IIT should be implemented, aiming for the lowest glycaemic range that can be safely achieved while avoiding hypoglycaemia.

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who were assumed to require at least 3 days ICU care. A pre-hoc subgroup analysis was planned for patients who spent a third day in the ICU. Overall, IIT was associated with no difference in mortality; a reduction in the incidence of newly acquired kidney injury; earlier weaning from ventilation; and decreased ICU and hospital LOS. In the predefined group with an ICU LOS of 3 days or greater, IIT was associated with reduced ICU and hospital mortality; earlier weaning from mechanical ventilation; decreased ICU and hospital LOS; reduction in the incidence of newly acquired kidney injury, hyperbilirubinaemia and hyperinflammation; and reduction in cumulative scores on the therapeutic intervention scoring system (TISS-28). The authors recently presented further analysis of outcomes showing a significant reduction in critical illness polyneuropathy in the IIT group (39% versus 50%, $P=0.02$).⁵ In contrast to the first study, there was no reduction in bacteraemia in the IIT group, with the authors postulating that the increase in patients with sepsis on admission was a contributing factor.³

Although these studies have become landmarks in the critical care literature, and demonstrate mortality, morbidity, and cost benefits with IIT in critically ill patients, concerns about the widespread application of IIT remain. These include the single-centre design, the higher than

expected baseline mortality in the surgical ICU study, the less effective results in the medical ICU study, and the high incidence of hypoglycaemia in both studies. To address these concerns, further exploration of the effects of IIT, its potential for harm, and its application in sepsis are necessary.

Insulin and glucose in critical illness

In critical illness and severe sepsis, the changes in glucose-handling are complex. Increased cortisol, catecholamine, glucagon, growth hormone and cytokine secretion are associated with hepatic and peripheral insulin resistance, increased hepatic gluconeogenesis, suppressed insulin production, and impaired activity of glucose transporters.^{6,7} Hyperglycaemia has powerful effects on immune, coagulation, and vascular systems. These include increased generation of reactive oxygen species by polymorphonuclear leukocytes and mononuclear cells, impaired neutrophil phagocytic activity and response to inflammatory mediators, impaired endothelial production of nitric oxide, increased endothelial adherence of neutrophils and subsequent reduction of circulating neutrophils, and elevated levels of plasminogen-activator inhibitor, factor VII and factor XII.⁸ Alterations in serum lipid profile include increased triglyceride levels secondary to increased very low-density lipoproteins (VLDL), and decreased levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Hepatic triglyceride production is increased, and VLDL clearance of cholesterol is inhibited.⁹

Metabolic effects of IIT: The effect of IIT on the metabolic derangements in critical illness was investigated as part of the first Leuven study. The blood glucose-lowering effect of insulin in critical illness coincided with an increase in skeletal muscle glucose-transporter gene expression, with no alteration in hepatic glycogen-kinase gene expression, providing evidence that increased peripheral uptake rather than suppressed hepatic production was the dominant effect. Hepatic mitochondrial ultrastructure abnormalities on electron microscopy showed IIT was associated with the prevention or reversal of damage seen with conventional therapy, suggesting a protective effect of insulin.¹⁰ IIT was associated with beneficial effects on lipid profile, including a significant decrease in serum triglyceride levels, a smaller reduction in HDL, and normalisation of cholesterol levels. A multivariate logistic regression model suggested that the effect of IIT on serum LDL and HDL levels, but not triglyceride levels, was associated with reduced mortality.⁹

Insulin has also been shown to have antithrombotic, fibrinolytic, and anti-inflammatory effects that counteract

hyperglycaemia-induced immune and vascular modulation.¹¹ Evidence that this is associated with a reduction in nuclear factor kappaB, a nuclear transcription factor involved in the regulation of many genes related to inflammation, supports the hypothesis that this factor may be a therapeutic target for insulin.^{7,12}

Effect of glucose control versus insulin: These molecular and metabolic effects of hyperglycaemia and insulin provide a rationale for the benefit of IIT, but do not separate the individual effect of glucose control from that of insulin administration. This is an important distinction clinically, as the two important variables that can be manipulated in IIT are glycaemic range and insulin dose. Fortunately, clinical and laboratory data go some way to distinguishing the effects.

A post-hoc multivariate regression analysis performed following the first Leuven trial analysed univariate determinants of outcome to assess the impact of actual glycaemic control versus amount of infused insulin on morbidity and mortality. For ICU mortality, both insulin dose and mean level of blood glucose were independent risk factors. For critical illness polyneuropathy, bacteraemia and need for red cell transfusion, only mean level of blood glucose seemed to be an independent risk factor. For acute renal failure requiring haemofiltration, only insulin dose was an independent negative predictor. The authors concluded that there is a gradual decrease in risk of death with reducing blood glucose levels, without an identifiable lower threshold for risk.¹³

This conclusion is supported by recently reported animal studies designed to separate the effects of insulin and glucose. In a model of prolonged critical illness, rabbits were treated with combinations of high insulin (HI) and normal insulin (NI) infusion, and hyperglycaemia (HG) and normoglycaemia (NG). In both hyperglycaemic arms (HGHI and HGNI), hepatic and cardiac mitochondrial function were more severely affected than in the normoglycaemic arms, with HGHI showing more severe damage than HGNI.^{14,15} This suggests that the beneficial effect of IIT is the avoidance of hyperglycaemia, not the administration of insulin, and that failure to control glucose with increasing doses of insulin may increase harm more than hyperglycaemia alone.

Safety and harm

Inadvertent hypoglycaemia that may be undetected in the unconscious critically ill patient is an ongoing barrier to implementing IIT. The interpretation of hypoglycaemia in the critically ill patient is difficult and poorly defined. In conscious patients, hypoglycaemia is defined by the triad of low blood glucose level, associated signs and symptoms,

and their relief when blood glucose level is elevated.¹⁶ In the critically ill patient with altered conscious state, only blood glucose level may be assessable. A plasma glucose level of 2.5–2.8 mmol/L is often quoted as the range below which symptoms of hypoglycaemia occur. If whole blood glucose levels are used (which have values 15%–20% lower than plasma glucose levels),¹⁶ then 2.2 mmol/L can be defined as the limit for hypoglycaemia. However, the symptoms of neuroglycopenia may not be predicted by plasma glucose levels alone, and can be influenced by factors such as recent glucose control, fasting and insulin resistance.^{16–18} In animal models of hypoglycaemia, neuronal damage occurs only after electroencephalographic isoelectricity is achieved, with the density of neuronal necrosis related to cerebral isoelectricity rather than blood glucose level.¹⁹ In one study of adult-onset insulin-dependent diabetes mellitus, a history of one or more hypoglycaemic coma episodes in 55 patients was not associated with any difference in cognitive function when compared with 53 patients with no history of hypoglycaemic coma.²⁰

In the first Leuven study, hypoglycaemia (defined as blood glucose level <2.2 mmol/L) occurred in 39 of 765 patients with IIT compared with 6 of 783 in the conventional arm. Two patients in the IIT group were reported as symptomatic with sweating and agitation, but no long-term sequelae.² The second study reported hypoglycaemic episodes in 11 of 595 patients with IIT compared with 19 of 605 patients in the conventional arm. The mean blood glucose level during hypoglycaemia was 1.8 mmol/L. No adverse events were recorded for any episode of hypoglycaemia, leading the authors to conclude that IIT is a safe therapy.

Of special interest are the outcomes of patients who had an episode of hypoglycaemia in the second Leuven study. Although mortality did not differ significantly between the IIT and conventional arms, hypoglycaemia was identified by logistic regression analysis as an independent predictor of death. In patients with an ICU LOS less than 3 days, 56 in the IIT group, and 42 in the conventional group died. Statistical significance of this result varied depending on the analytical approach, complicating interpretation but raising the possibility of harm. The authors offer as explanation an increase in patients withdrawn in the first 72 hours because of futility in the IIT group.³

A study of the effects of IIT compared with conventional therapy using microdialysis in traumatic brain injury reported an increase in cerebral injury markers and a decrease in cerebral extracellular glucose, with no decrease in cerebral glucose utilisation in IIT. This suggests that there may be potential harm with the use of IIT in traumatic brain injury.²¹ In contrast, a pre-planned sub-

group analysis of central and peripheral nervous system effects of IIT in the first Leuven study reported a decrease in intracranial pressure and incidence of seizures and diabetes insipidus, and improved 12-month rehabilitation in patients with isolated brain injury in the IIT group.²²

We are left with no clear idea of what level and duration of hypoglycaemia is harmful, the effect of different patient diseases and glycaemic history, and how to measure potential harm.

Intensive insulin therapy in severe sepsis

The direct clinical evidence for IIT in severe sepsis is limited. There is to date only one randomised, prospective trial on the effect of IIT in severe sepsis, the VISEP trial, a 17-centre, two-phase trial comparing the effects of IIT and colloid administration in severe sepsis. The trial was stopped by the international review board after enrolment of 537 patients, because of a high incidence of hypoglycaemia in the IIT group (12.1% versus 2.1%; $P < 0.001$). At the time of stopping, there was no difference in mortality or morbidity between the IIT and conventional treatment arms.²³ The contribution of this trial to the current literature is limited, as the incidence of hypoglycaemia was similar to the Leuven trials, and the failure to detect benefit in the IIT group occurred with inadequate recruitment. It does bring attention to the difficulties encountered with the implementation of IIT.

With the VISEP trial failing to resolve the issue of IIT in sepsis, the decision to implement IIT in patients with sepsis must be made on indirect evidence. It seems logical that preventing hyperglycaemia and administering exogenous insulin will have favourable effects on sepsis-induced alterations to immune, endothelial, coagulation and hepatic function, and to lipid profiles. Clinically, IIT reduced the development of septic complications in longer-stay surgical ICU patients, but these findings were not reproduced in medical ICU patients.^{2,3} At best, this represents evidence of a role for IIT in preventing sepsis, not treating it.

A more compelling case for the use of IIT may be based on the epidemiological features of patients with severe sepsis. Both the Leuven studies showed that the benefits of IIT appear to occur in patients with an ICU stay greater than 3 days. In Victoria, analysis of a hospital database over 4 years reported a median ICU LOS of 5 days in patients with sepsis.²⁴ A 6-month inception cohort study conducted in 21 Australian and New Zealand hospitals reported 691 cases of severe sepsis from 5878 ICU admissions. The severe-sepsis patients had a median LOS of 6 days with an ICU mortality of 26.5%, compared with 3 days and 15.8% for all screened patients.²⁵ International

epidemiological studies of sepsis show a similar pattern of prolonged ICU stay in severe sepsis. A French prospective study of 206 ICUs reported a median ICU LOS of 11 days, with a 30-day mortality of 35%, in severe sepsis.²⁶ In the United States, a database study of 847 hospitals over 12 months reported 192 980 cases of severe sepsis with a median ICU LOS of 7 days, and a hospital mortality of 28.6%.²⁷ Finally, in the United Kingdom, a database review of 91 hospitals over 5 years reported 15 362 cases of severe sepsis on ICU admission, with a median ICU LOS of 3.59 days and a hospital mortality of 47.3%.²⁸ These studies all provide evidence that patients with severe sepsis are epidemiologically an ideal population to benefit from IIT based on ICU LOS.

Intensive insulin therapy in practice

Traditionally in the critical care setting, insulin has been administered to avoid hyperglycaemia, as either a bolus dose or a continuous infusion, when blood glucose level exceeds an arbitrary limit, typically between 10 and 11 mmol/L. This tolerance of mild hyperglycaemia during critical illness, or “permissive hyperglycaemia”, is based on the avoidance of hypoglycaemia and acceptance of elevated blood glucose levels as part of the stress response.

A “halfway” approach to IIT is to aim for a range of mild hyperglycaemia (eg, 8–10 mmol/L) in an effort to improve glycaemic control and to avoid a high incidence of potentially harmful hypoglycaemic episodes. However, it is important to observe that, although the Leuven trials aimed for glycaemic ranges of 4.4–6.0 mmol/L and 10–12 mmol/L, the mean blood glucose levels achieved were 5.4 (IIT) versus 8.7 (conventional) mmol/L and 5.8 (IIT) versus 8.9 (conventional) mmol/L in the surgical and medical studies, respectively. This suggests that allowing even mild hyperglycaemia may prevent the benefits of IIT. The NICE-SUGAR study, a large joint Australian and Canadian multicentre randomised trial in progress, comparing IIT (blood glucose levels in the range, 4.5–6.0 mmol/L) and conventional therapy (blood glucose levels in the range, 8.0–10 mmol/L), should address this issue.

We have previously reported the implementation of a tight glycaemic control protocol with a modified target range, aiming for blood glucose levels of 4.4–7.0 mmol/L in a tertiary adult ICU. In 148 patients receiving a total of 526 days or 5603 blood glucose measurements, with a mean LOS of 6.4 days, mean APACHE II score of 19 (SD, 5), and hospital mortality of 14.2%, the mean blood glucose level on IIT was 6.5 mmol/L. Hypoglycaemic episodes were uncommon, with blood glucose levels less

than 2.2 mmol/L on four occasions, and in the range 2.2–3.0 mmol/L on 43 occasions, with one symptomatic episode of hypoglycaemia.²⁹ This suggests that tight glycaemic control can be achieved safely and effectively.

Conclusion

Hyperglycaemia and insulin resistance are common and deleterious in critically ill patients, and IIT improves outcomes in patients with prolonged ICU LOS. Patients with severe sepsis are a population likely to benefit from IIT based on metabolic effects and their prolonged ICU LOS. The current evidence suggests IIT should be implemented, aiming for the lowest glycaemic range that can be safely achieved while avoiding hypoglycaemia. The potential risks of hypoglycaemia remain an ongoing concern, with the risk of harm in critically ill patients not clearly understood.

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