Blood glucose control within critical care – a review of literature influencing practice

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Article points

1. Hyperglycaemia is associated with increased morbidity and mortality in the critical care setting.
2. Intensive glucose regulation can reduce morbidity in people who are critically ill, although care must be taken to avoid hypoglycaemia.
3. A successful insulin administration protocol should be adaptable to all hospital units, be easy to implement and include a strategy to deal with any hypoglycaemic event.

Key words

- Blood glucose control
- Critical care
- Hyperglycaemia
- Hypoglycaemia

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The authors examine the literature to determine the effects of hyperglycaemia and hypoglycaemia within the critical care setting. They review the original evidence for the use of intensive glucose monitoring in critical and intensive care and critically discuss new evidence that the strict parameters are causing increased incidence of hypoglycaemic events. The commencement and duration of intensive glucose management as well as protocols to minimise glycaemic variability in critically ill individuals are also explored.

The effects of hyperglycaemia within critical care are profound, as critically ill individuals are in a hypermetabolic state as a result of either major surgery or acute illness. The causes of this metabolic response are the intense activation of the counter-regulatory hormones – cortisol, glucagon, epinephrine and growth hormone. These hormones increase blood glucose by stimulating the synthesis of glucose from amino acids (gluconeogenesis) and by breaking down glycogen into glucose (glycogenolysis; Bilous and Donnelly, 2010). These metabolic processes cause insulin resistance, where there is the appropriate level of insulin produced but the body is unable to use the insulin and is therefore unable to maintain normoglycaemia (Knieriem et al, 2007).

Hyperglycaemia in the critically ill person, also documented as "stress hyperglycaemia", was deemed a beneficial, adaptive response that provided essential glucose to vital organs such as the brain, skeletal muscles and heart during critical illness (Marik, 2009). In addition to the metabolic responses, hyperglycaemia may also be induced by some medical interventions, such as total parenteral nutrition (TPN), anaesthetic agents and dextrose supplements (McCowan et al, 2005). However, evidence suggests that stress hyperglycaemia may also be associated with increased mortality and morbidity in the intensive-care setting (Knieriem et al, 2007; Shultz et al, 2010).

Studies have shown that increased blood glucose circulation has detrimental effects, such as increased inflammation, immune system dysfunction, stimulation of coagulation and modulation of the endothelium (Knieriem et al, 2007). High blood glucose levels are also suggested to be acutely toxic – cellular glucose

overload damages the cells and becomes a further threat to already damaged organs (Shultz et al, 2010).

Blood glucose control in critical care

A randomised controlled trial (RCT) has been carried out to ascertain if normalising blood glucose in the critically ill adult admitted to surgical intensive care would improve the individual's prognosis (Van Den Berghe et al, 2001). The authors report:

> *"The critically ill patient with pronounced hyperglycaemia may lead to complications such as severe infection, polyneuropathy, multiple organ failure and death."*

A total of 1548 adults were randomised on admission to receive either intensive insulin therapy (to maintain blood glucose levels between 4.4 and 6.1 mmol/L) or conventional therapy (to treat with insulin if blood glucose levels exceeded 12 mmol/L). The trial was for 1 year and showed that intensive insulin treatment reduced mortality and morbidity from 8.0% to 4.6% in the critically ill adult admitted to surgical intensive care, regardless of diabetes history. Other findings showed that there was reduced morbidity with regard to organ failures, as a result of a reduction in time spent on mechanical ventilation, as well as a decrease in acute kidney failure, polyneuropathy and severe infection. This reduced morbidity may be linked to the reduction of circulating blood glucose levels that could have otherwise been toxic to the cells that were already exposed to stress. Overall, the study showed that intensive insulin treatment reduced mortality in intensive care by 42% and decreased hospital mortality by 34% (Van Den Berghe et al, 2001).

Krinsley (2003) conducted a retrospective review of a large database from a single university-affiliated hospital to explore the effect of hyperglycaemia on mortality in a heterogeneous population of critically ill adults. A total of 2098 adults were admitted to the intensive care unit with a range of surgical and medical prognoses. Krinsley found that even slight increases in glucose levels were associated with an increase in hospital mortality in a mixed medical/surgical intensive care unit.

Further to Van Den Berghe et al's (2001) RCT on blood glucose control in critically ill adults admitted to surgical intensive care, the research group performed an RCT of intensive blood glucose management in adults admitted to medical intensive care (Van Den Berghe et al, 2006). This second trial followed the same hypothesis as the first, but failed to show a reduction in mortality; however, it did show a reduction in morbidity (Van Den Berghe et al, 2006).

After Van Den Berghe et al's (2001) RCT, the "strict glycaemic control strategy" (Marik and Preiser, 2010) was adopted as the standard of care by several professional associations worldwide. Guidelines were produced for the management of hyperglycaemia within intensive care to prevent this condition from occurring (Angus and Abraham, 2005).

Hypoglycaemia

One of the major concerns with the introduction and implementation of a strict glucose regimen is the incidence of severe hypoglycaemia, defined as blood glucose levels <2.2 mmol/L (Egi and Bellomo, 2009); usually, outside of critical care situations, individuals with diabetes are considered to be experiencing hypoglycaemia when their blood glucose levels are ≤4 mmol/L (Bilous and Donnelly, 2010). In clinical practice, it is usual for individuals with diabetes to monitor more frequently if their blood glucose levels are ≤4 mmol/L.

Two intensive insulin therapy trials – the European Glucontrol Trial (Preiser et al, 2009) and the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial (Brunkhorst et al, 2005) – were stopped early as a result of the high prevalence of hypoglycaemic events; the severity of the hypoglycaemic events in the VISEP trial were considered to be life-threatening (Ellahham,

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1. In one study, a total of 1548 adults were randomised on admission to receive either intensive insulin therapy or conventional therapy (Van Den Berghe et al, 2001); the trial was for 1 year and showed that intensive insulin treatment reduced mortality and morbidity from 8.0% to 4.6% in the critically ill adult admitted to surgical intensive care, regardless of diabetes history.
2. In a follow-up trial (Van Den Berghe et al, 2006), results failed to show a reduction in mortality; however, it did show a reduction in morbidity.
3. One of the major concerns with the introduction and implementation of a strict glucose regimen is the incidence of severe hypoglycaemia, defined as blood glucose levels <2.2 mmol/L.

"Early clinical signs of hypoglycaemia in critically ill individuals who are receiving insulin therapy are often missed. This may be because of the severe condition that they are in, but early signs can also be masked by therapeutic interventions such as sedation, anaesthesia or vasopressin (Farah et al, 2007)."

2010). Two further single-centre, randomised studies have shown a trend towards a higher mortality in individuals receiving intensive glycaemic control (Arabi et al, 2008; De La Rosa Gdel et al, 2008).

The NICE-SUGAR Study Investigators (2009) performed a large, multicentre RCT (the NICE-SUGAR trial); they recruited 6022 individuals, and found they could not replicate the original findings of Van Den Berghe et al (2001). In fact, the NICE-SUGAR Study Investigators (2009) reported a 2.6% increase in mortality in those individuals randomised to the tight glycaemic control group. Reporting on these findings, Shultz et al (2010) found that the number of severe hypoglycaemic incident increased by five- to 10-fold in individuals in the tight glycaemic group compared with those in the conventional blood glucose control.

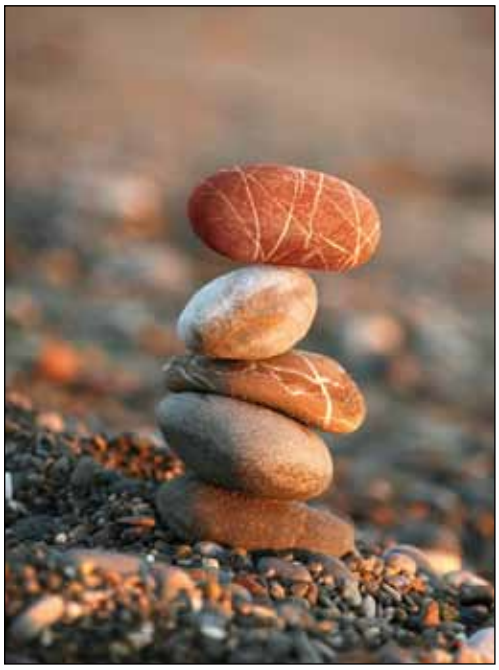
Early clinical signs of hypoglycaemia in critically ill individuals who are receiving insulin therapy are often missed. This may be because of the severe condition that they are in, but early signs can also be masked by therapeutic interventions such as sedation, anaesthesia or vasopressin (Farah et al, 2007). Hypoglycaemia is also a reported complication of sepsis, cardiac, hepatic or renal insufficiency by way of decreased hepatic gluconeogenesis, reduced insulin clearance and increased glucose uptake in the muscles, spleen and small intestine (Farah et al, 2007), and should therefore be taken into consideration when planning treatment for these conditions.

The brain is made up of glucose-dependant tissues (Knieriem et al, 2007), and during a time of critical illness the demand for energy increases. Vriesendorp et al (2006) reported that neuroglycopenia may cause some degree of cerebral damage, epileptic insults or possible coma; additionally, Oddo et al (2008) demonstrated that tight glycaemic control is associated with a greater risk of brain energy crisis and death.

In two retrospective studies by Bagshaw et al (2009) and Kinsley and Grover (2007), severe hypoglycaemia was identified as an independent predictor of mortality. Shultz et al (2010) analysed Van Den Berghe et al's (2006) RCT, and confirmed that severe hypoglycaemia was independently associated with increased mortality. Additionally, the National Diabetes Audit Mortality Analysis (National Information Centre, 2011) highlighted that the increased risk of death for individuals with type 1 diabetes was 2.6 times higher and for those with type 2 diabetes was 1.6 times higher than the general population, indicating that both hypoglycaemia and hyperglycaemia can increase mortality.

Glycaemic variability

The risks and benefits of following a strict glycaemic control protocol have many variables, including the population studied, disease severity, different protocols used, different glycaemic targets set, different definitions of hyperglycaemia and hypoglycaemia and length of hospital stay (Ellahham, 2010). Glycaemic variability may have a harmful biological effect in individuals who are critically ill (Egi and Bellomo, 2009).



Balancing blood glucose levels in the critically ill individual is essential to avoid hyperglycaemia or hypoglycaemia and resulting adverse effects.

Additionally, Al-Dorzi et al (2010) reported that wide glycaemic fluctuation was associated with higher mortality (22.2% versus 8.4% for narrow glycaemic fluctuation, $P<0.001$) as well as other poor outcomes in critically ill individuals.

Blood glucose levels in people who are critically ill swing markedly, even with the use of continuous feeding and insulin infusions (Egi and Bellomo, 2009). The association of glycaemic variability and worse outcomes may be explained by further study, as less glycaemic variability may be linked to less severe illness (Egi and Bellomo, 2009).

Timing of commencement of intensive insulin therapy

A question highlighted in some of the literature and in practice is whether the timing of intensive insulin treatments influences individuals' outcomes? The optimal time of starting insulin therapy is unknown; evidence suggests that maximal benefit is gained from administration on day one in intensive care, or even in the emergency department (Honiden et al, 2007). There is a need for an evidence-based protocol that all staff can follow, similar to the Joint British Diabetes Societies' guideline for the management of diabetic ketoacidosis (Savage et al, 2011), which can be implemented and which can potentially save lives.

When individuals first present with emergency conditions such as sepsis or acute respiratory syndrome, it is thought that maladaptive cellular pathways have already been established and that early insulin therapy may help to improve mortality (Honiden et al, 2007). The onset of hyperglycaemia from glycaemic control can be rapid; any delay in treatment may prevent the delay of toxicity and cause irreversible damage to the cells (Van Den Berghe et al, 2009).

In a single-centre prospective cohort study, Honiden et al (2007) investigated the timing of intensive insulin therapy. Their findings suggest that early therapy (within 48 hours) is associated with lower hospital mortality and improved outcomes such as shortened hospital stay. However, it may be the length of time that individuals receive intensive insulin therapy that is crucial, and not when it is commenced. Van Den Berghe et al (2001) found there was a marked benefit in mortality for individuals who stayed in intensive care for more than 5 days. They later reinforced these findings in their 2006 RCT, where individuals who stayed in intensive care for more than 3 days and received intensive insulin therapy had a significantly reduced morbidity and mortality. A higher number of deaths were recorded in the group who remained on intensive insulin therapy for 1–2 days (Van Den Beghe et al, 2006); however, these individuals might have been more ill, and therefore a higher mortality rate would be expected.

Hyperglycaemia

Individuals in the intensive and critical care setting require careful blood glucose monitoring as levels fluctuate with the state of their infection, type of feeding regimen and calorific intake (Farah et al, 2007). The marked difference in the findings from the Van Den Berghe et al RCTs (2001; 2006; 2009) may be attributed to the use of TPN, which is administered intravenously and is associated with hyperglycaemia. A report by Cheung et al (2005) demonstrated that blood glucose levels increased by the use of total parenteral nutrition (PNT) were associated with an increased risk of cardiac complications, infection, sepsis, acute renal failure and death. It would therefore seem counterintuitive to administer additional glucose to individuals with already raised blood glucose levels (Marik, 2009). Van Der Voortrekker et al (2006) reported that the mortality of the critically ill individual in intensive care could be independently related to the mean amount of glucose infused. This evidence suggests that TPN may have increased the mortality in the control arm of the Van Den Berghe et al RCTs (2001; 2006; 2009), as this would account for the noticeable benefit of tight glycaemic control (Marik, 2009).

In both the 2001 and 2006 Van Den Berghe et al RCTs, TPN provided an average of 1100 kcal/day to individuals; in contrast, the

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1. Although the optimal time of starting insulin therapy is unknown, evidence suggests that maximal benefit is gained from administration on day one in intensive care, or even in the emergency department (Honiden et al, 2007).
2. However, it may be the length of time that individuals receive intensive insulin therapy that is crucial, and not when it is commenced. Van Den Berghe et al (2001) found there was a marked benefit in mortality for individuals who stayed in intensive care for more than 5 days.
3. Individuals in the intensive and critical care setting require careful blood glucose monitoring as levels fluctuate with the state of their infection, type of feeding regimen and calorific intake.

"A successful insulin administration protocol should be adaptable to all hospital units, be easy to implement and include a strategy to deal with any hypoglycaemic event (Ellahham, 2010). Protocols designed to fit the needs of the multidisciplinary team are a common feature in the critical care setting, enabling consistency of care (Avanzini et al, 2009)."

NICE-SUGAR trial (NICE-SUGAR Study Investigators, 2009) provided an average of 880 kcal/day by way of enteral feeding. Both of these nutritional regimens provide less than the normal calorific requirements. However, the use of TPN may have increased the severity of the stress-induced hyperglycaemia (Van Den Berghe et al, 2001, 2006), while the NICE-SUGAR trial (NICE-SUGAR Study Investigators, 2009) had patients in a nutritionally deprived state that may have been harmful by evoking global substrate deficit via insulin-induced suppression of proteolysis, lipolysis, glycogenolysis and gluconeogenesis (Van Den Berghe et al, 2009). It is unknown which of these regimens is superior in the context of achieving normoglycaemia; however, there is a study in progress investigating this topic (Van Den Berghe et al, 2012).

Optimal blood glucose level monitoring

The optimum level as well as the optimal mode to enable normoglycaemia has yet to be defined (Shultz et al, 2010). The insulin protocol used within the authors' clinical setting is to maintain the individual's blood glucose between 4 and 10 mmol/L, regardless of diabetes status; only if the admission is diabetes-related, such as diabetic ketoacidosis, would a different protocol be followed, for example implementing the use of a sliding scale and titrating the rate of insulin according to the results of arterial or venous blood sampling. The use of peripheral glucometers is largely for ascertaining random blood glucose levels in individuals who are deemed to be ready for discharge to the general ward.

There is often a large deviation in results from venous and arterial blood glucose samples. When glucose diffuses through the capillaries and is used by the cells, the arterial glucose concentration (the capillaries' source) should be higher than the venous glucose concentration (the capillaries' drain) unless capillary diffusion or muscle glucose consumption has been stopped (Roe, 2012). However, it has been shown that in the fasting state the glucose levels in arterial, capillary and venous samples are practically the same (venous glucose is generally 0.01–0.27 mmol/L lower than fingerstick capillary or arterial blood glucose). Therefore, practitioners need to interpret the results obtained with caution and to record the source of the blood sample used to measure glucose (either arterial or venous) to accurately base decisions on these results. Vlasselaers et al (2008) reported that the accuracy of some glucometers in the critical care setting are extremely poor, making them unsuitable for use in implementing strict glucose control.

A successful insulin administration protocol should be adaptable to all hospital units, be easy to implement and include a strategy to deal with any hypoglycaemic event (Ellahham, 2010). Protocols designed to fit the needs of the multidisciplinary team are a common feature in the critical care setting, enabling consistency of care (Avanzini et al, 2009). Perhaps new technology that enables the continuous or near-continuous monitoring of blood glucose may help to reduce the incidence of severe hypoglycaemia and glycaemic variability (Shultz et al, 2010).

Conclusion

Hyperglycaemia induced by critical illness is associated with adverse outcomes as it is can be acutely toxic (McCowan et al, 2005); there is therefore a significant amount of evidence that supports the use of strict insulin therapy. Van Den Berghe et al (2001) showed that by implementing strict glycaemic control the mortality and morbidity of critically ill individuals was significantly decreased. However, further trials have failed to reproduce these findings, with one showing an actual increase in mortality (NICE-SUGAR Study Investigators, 2009).

An adaptation of Van Den Berghe et al's (2001) strict glycaemic control strategy is widely used (McCowan et al, 2005), but the use of protocols to maintain glucose levels <6.1 mmol/L remains controversial. This is largely because tight glycaemic control increases the incidence of hypoglycaemic events.

There is some evidence that supports the argument that hypoglycaemia has a harmful effect on the critically ill individual, but evidence for the use of insulin therapy appears to outweigh these concerns. However, there are many variables to consider with each of the trials, including feeding regimens, blood glucose variables, timing of initiating insulin, the length of hospital stay, patient population and using different blood glucose targets.

There remains some uncertainty as to what is the optimum level and optimal mode to reach the desired normoglycaemic range within the intensive care environment, which makes treatment decisions difficult. Perhaps the development of a protocol for insulin use and blood glucose control in critically ill patients, similar to the Joint British Diabetes Societies' guideline for the management of diabetic ketoacidosis (Savage et al, 2011), would be beneficial and potentially could save lives; further investigations are needed to achieve this. ■

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