Glucose: the worst of all evils?

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Abstract

The acute phase response is associated with metabolic derangements, including hyperglycaemia. Hyperglycaemia is associated with adverse clinical outcomes, including increased morbidity and mortality in various patient populations. The obvious question is: does tight blood glucose control improve morbidity and mortality in critically ill patients? Tight glycaemic control (TGC) or intensive insulin therapy (IIT) has become a major area of research, debate and controversies. The belief that hyperglycaemia is a physiological response and intervention is only warranted when the renal threshold is exceeded rapidly changed to aggressive control and, currently, clinical practice is moving to a mid-point between the two.

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Introduction

Hyperglycaemia is common in critically ill patients.[1,2,3,4,5] The acute phase response is associated with the abundant production of pro- and anti-inflammatory mediators and counterregulatory hormones, causing pathologic metabolic derangements.[6,7] Hyperglycaemia occurs secondary to elevated levels of cortisol, epinephrine, norepinephrine, glucagon resulting in gluconeogenesis and glycogenolysis, as well as insulin resistance.[5,6]

Hyperglycaemia may cause harm through a direct toxic effect, increased intracellular oxidative stress due to higher mitochondrial peroxide production,[5] altered cytokine production and impaired phagocytosis.[6] Hyperglycaemia is a marker of severity of illness, and is associated with adverse outcomes, including increased morbidity and mortality in various patient populations.[2,3,5,6,8,9] The adverse consequences include increased infectious complications and higher mortality in trauma patients,[10,11,12] worse neurological outcome in a subset of traumatic brain injury (TBI) patients,[13] poor functional recovery and higher mortality in stroke patients,[14,15,16,17] and an increased morbidity and mortality after myocardial infarction[18,19] as well as higher morbidity and mortality in other critically ill patients.[20,21] In addition, hyperglycaemia during critical illness is associated with worse long-term outcomes such as degree of disability after a stroke[14] and risk for mortality and congestive heart failure one year after a myocardial infarction.[23]

The obvious question thus is: will intensive insulin therapy (IIT) improve morbidity and mortality in critically ill patients?

The past

When the first randomised clinical trials on blood glucose control in critically ill patients were first reported in 1995,[23] physicians did not place a high priority on blood glucose (BG) control.[23] Hyperglycaemia was considered part of the usual clinical course of critical illness and often not treated until levels exceeded the renal threshold of 12 mmol/L when it induced glucosuria and hypovolaemia.[24] Insulin was administered according to a sliding scale and few protocols tried to match insulin dose to nutritional intake and the effectiveness of these protocols were not assessed.[23]

Tight glucose control

One of the first randomised clinical trials on Tight Glucose Control (TGC), utilising intravenous insulin followed by multiple dose insulin therapy, was the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study. Mortality at one year was reduced by 26%.[22] It is, however, unclear whether this outcome was due to tight control during hospitalisation or due to better diabetes management after discharge.[1] The multicentre DIGAMI 2 trial could not reproduce these results and found no effect on morbidity or mortality after two years of follow up, possibly due to an inability to recruit an adequate number of patients[25,1] and the inability to achieve strict control.[26]

The landmark study by Van Den Berghe, et al (Leuven 1) was the first large randomised trial in critically ill patients in a surgical intensive care unit (SICU) (mainly coronary bypass surgery, 13% with diabetes) with hyperglycaemia and included both diabetic and non-diabetic patients.[27] Aggressive control, (BG 4.5–6.0 mmol/L) was associated with a significant reduction in ventilator support and

renal replacement therapy with a significant cost saving. The ICU mortality rate was reduced from 8% in the control group to 4.6% in the TGC group, and similarly, in-hospital mortality was reduced from 10.9% to 7.2%. The relative risk of in-hospital death was thus reduced by 33.9%. The benefit occurred in patients who remained in the ICU for > 5 days. The number of deaths in the first five days was similar in both groups.[27]

The results were very different when the same authors proceeded to apply the same protocol to medical ICU patients (MICU) (Leuven 2).[28] The mortality rate was lower in patients who stayed in ICU for ≥ 3 days, but higher in those that stayed < 3 days. The mortality reduction in the group who stayed longer in ICU was much smaller (6%) than the 42% reduction seen in the surgical ICU study.[28] From these two studies it seems that the beneficial effect was more pronounced in severely ill patients requiring prolonged ICU care.[5]

These studies led to the publication of guidelines for the management of severe sepsis and shock which recommended TGC as an important part of management[29] and was again included in the updated version of the guidelines in 2008.[30] It is surprising that TGC was widely adopted after the Leuven 1 study, since the authors stated that their patients were: 1) ventilated surgical patients, 2) admitted to ICU after predominantly cardiac surgery and 3) that the results can not be extrapolated to other groups of ICU patients. The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial applied the same protocol to septic patients and achieved lower BG concentrations, but no decrease in mortality.[31] Two studies did not find a decrease in mortality with TGC in mixed ICU populations.[3,32]

A large multi-centre trial, the NICE-SUGAR trial, compared patients whose blood glucose concentrations were maintained below 6.7 mmol/L (TGC) with those whose blood glucose was kept between 7.8–10.0 mmol/L in MICU and SICU patients in 42 hospitals. Although lower BG concentrations were achieved, TGC did not improve outcomes in terms of length of stay (LOS) in ICU or hospital, median number of days on mechanical ventilation or renal replacement therapy. Hypoglycaemia was recorded in 6.8% of the TGC group and 0.5% in the control group. Mortality was significantly higher in patients with tight control (27.5%–24.9%).[2]

Two recent meta-analyses have also evaluated TCG. The first one (done prior to the NICE-SUGAR study) found a significant decreased incidence in sepsis (subgroup analysis suggests that it was limited to SICU patients), no association with new need for dialysis, an increased risk for hypoglycaemia and no impact on mortality.[33] The second meta-analysis included the results from the NICE-SUGAR study confirmed these findings with regards to hypoglycaermia, but suggested that there is a mortality benefit with TGC surgical ICU patients.[9]

Methodological differences

The different outcomes between the Leuven 1[27] and the VISEP[31] trials were probably due to differences in design and study population. The VISEP trial was designed as a four arm study comparing two resuscitation fluids (10% pentastarch versus modified Ringer's lactate) as well as the efficacy and safety of TGC which may have had some influence on the outcomes. Furthermore, this study included patients with severe sepsis, known to be at a higher risk for hypoglycaemia,[1] while the Leuven 1 included mainly coronary bypass surgery patients. In addition, the fluid resuscitation arm of the study was also suspended due to an increased risk of organ failure (10%) in the pentastarch arm. This reiterates the point that the resuscitation fluid rather than the glucose control may have caused the higher mortality.

The VISEP trial, as well as the Glucontrol study,[34] was stopped due to high rates of hypoglycaemia (12.1/18.6% respectively), but there was no difference in mortality. An additional factor for the cessation of the Glucontrol study was a high rate of unintentional protocol violations.[35] It is also possible that the low number of patients per centre may have contributed to the lack of treatment effect.[5] The Glucontrol study was only released in abstract form, thus it is not possible to assess methodology fully.

The different outcomes in terms of mortality between the Leuven studies[27,28] and the two mixed ICU population studies[3,32] may possibly be explained by the different study designs, populations and the age difference in the study populations.[3,32] Another aspect that may indicate some difference in the study population is the high in-hospital mortality (10.9%) in the control group of the Leuven 1 study.[27] A subsequent study to investigate this point found an in-hospital mortality rate in similar patients in Australia to be only 3.8%, much lower than the mortality of both the treatment and control groups in the Leuven 1 trial.[36]

The NICE-SUGAR study and the Leuven 1 and 2 studies are most often compared in an effort to come to a conclusion with regards to TGC. However, various differences between these studies need to be pointed out. The Leuven studies were single centre trials while the NICE-SUGAR study was a multicentre trial. The accuracy of measuring tools at different centres and the experience of the nursing staff with TGC come into play.[1,24] Avoiding variable blood glucose and exact titration requires experience of the nursing staff[1,24] which may have been lacking in a multicentre trial.

It was also noted that the control group in the NICE-SUGAR study had an average BG of 7.8–10,0 mmol/L while it was 10.0–11.1 mmol/L in the Leuven studies.[2,27,28,37] This essentially means that the control group was already better controlled by targeting an intermediate blood glucose level, which makes a direct comparison between the studies difficult. It was speculated that the better control in the control group might have improved outcomes to such a degree that tighter control would not have resulted in a more significant benefit.[9,24,37] Van Den Berghe, et al (2009) agreed with this conclusion and suggested that an intermediate target range may be preferable in critically ill patients.[24]

In addition, the NICE-SUGAR (MICU and SICU) study is often compared to the Leuven 1 study, which was on SICU patients (predominantly cardiac surgery) only. In this regard, the NICE-SUGAR study results are more similar to that of the two mixed ICU studies.[3,32]

Furthermore, various other differences between the studies may have affected outcomes, such as early nutrition support and its mode of administration as well as energy content, and BMI status.[24,37] It is also important to note that some studies already described included both diabetic and stress induced hyperglycaemia patients, which is unfortunate, since recent data indicates that the two settings are different.[38] A comparison of outcomes in patients with known diabetes to those without diabetes after implementation of a moderate glycaemic control protocol (6.9 mmol/L) showed a significant reduction in mortality in non-diabetic patients, but not in those with known diabetes.[39] It is also unfortunate that the diabetic sub-sets were presented differently in the Leuven and NICE-SUGAR studies (type 1 and 2 versus on insulin or on oral medication/diet) making comparisons and conclusions even more difficult.

Other differences between the Van Den Berghe studies and subsequent studies, which are not comprehensively described herein, include: different target ranges for blood glucose control, differences in the definition of hypoglycaemia, duration of hyperglycaemia preceding the intervention and varying levels of expertise with the therapy among the ICU nurses and a high nurse to patient ratio in the Leuven studies,[1,9,24,38] APACHE scores, age of patients, the degree with which blood glucose levels fluctuated in an individual patient as well as quality of the glucose control process itself, the case mix, associated therapy (e.g. corticosteroids), the existing variability in the intervention evaluation, the timing of the initiation of IIT and the variability in outcomes measures.[4,9,35,36,40]

Mechanisms of potential beneficial effects of tight control

Irrespective of the limitations in comparing the described studies, the question still remains whether insulin therapy *per se* improved mortality directly through modulating the inflammatory response or indirectly through improving hyperglycaemia, and consequently metabolism (Table I). In this regard, insulin is an anabolic and anti-catabolic hormone. Insulin is also a regulator of the inflammatory and immune responses, which may contribute to the reduced mortality after IIT in some studies.[41] Furthermore, sub-maximal doses of insulin have been shown to enhance skeletal muscle protein anabolism in severely burned (> 60% TBSA) patients,[42] which may also contribute to reduced mortality in certain patients groups.

Hypoglycaemia

The major obstacle with TGC appears to be hypoglycaemia, which is possibly the major contributing factor to the poor outcomes documented in some studies. It thus appears that in order to benefit from TGC, hypoglycaemia needs to be avoided. The mechanism by which hypoglycaemia increases mortality in severe sepsis and shock has not been fully investigated. One possible mechanism is brain damage because of an energy deficit in the brain through hypglycaemia.[6] Many recent studies have reported significant rates of hypoglycaemia with TGC (defined as BG < 2.2 mmo/L). The incidence of hypoglycaemia in tight control groups varied from

Table I: Possible mechanisms of beneficial effects of insulin

Wade 2008[43]	Hyperglycaemia alters cytokine production and phagocytosis
Vanhorebeek et al, 2005[44]	Strict blood glucose control protects hepatocyte mitochondrial ultrastructure and function
Herman et al, 2007[45] Herman et al, 2009[46]	Intensive insulin therapy prevents critical polyneuropathy/myopathy
Dugo et al, 2006[47]	Insulin inhibits glycogen synthase kinase-3β, contributes to protective effect of insulin against organ injury/dysfunction caused by excessive systemic inflammation, independent from its effect on glucose
Bopp et al, 2008[48]	Tight glycaemic control may decrease AGE (advanced glycation end product) formation and thereby reduce the inflammatory response mediated through AGE and RAGE (receptor of advanced glycation end product) interaction
Jeschke et al, 2002[49] Jeschke et al, 2004[50]	Insulin decreases pro-inflammatory cytokines and proteins and increases the anti-inflammatory cascade in burned rats and children (BG between 6.6–10 mmol/IL).

Table II: Incidence of hypoglycaemia with TGC

STUDY	TGC	CONTROL
Leuven 1[27]	5.1%	0.8%
Leuven 2[28]	18.7	3.1%
Glucontrol[34]	9.8% (moderate) 41.1% (mild) 8.6%	2.7% (moderate) 9.6% (mild) 2.4%
NICE-SUGAR[2]	6.8%	0.5%
VISEP[31]	12.1%	2.1%
De La Rosa et al[32]	8.5%	1.7%

7–20% and was as low as 0.5% in control groups in ICU-based studies (Table II).[23]

Juneja et al (2009) found that the most common contributing cause for hypoglycaemia was measurement delay.[8] It is known that severe hypoglycaemia increases stress hormone levels in normal individuals, but adequacy of this response in critically ill patients with already increased stress hormone levels is not known.[23] Furthermore, the majority of hypoglycaemic episodes has been shown to occur during unplanned interruption of feeding.[51,52] From the Leuven studies it also appears that medical patients might be at a higher risk for hypoglycaemia, possibly due to higher necessity for treatments known to affect blood glucose control such as inotrope support, corticosteroid administration and renal replacement therapy. Liver failure and kidney failure, which increase the vulnerability to hypoglycaemia, may also partly explain this observation.

Another reason for the higher mortality with TGC may be due to the limitations in measuring glucose using the point-of-care devices (glucometers), since the glucose concentration obtained by these devices differs significantly from those obtained by conventional

laboratory methods.[53] In the NICE-SUGAR study only 60.1% of the hypoglycaemic episodes were confirmed by laboratory measurement.[2] A variety of glucometers were allowed in the NICE-SUGAR study. The accuracy of some types of glucometers has been shown to be poor in the ICU setting.[54] In addition, many critically ill patients are anaemic and it has been shown that a haematocrit of < 34% produces systematic errors in glucometer measurements.[55] Moreover, anaemia results in falsely elevated BG levels, while polycythaemia results in low values.[56] It is interesting in this regard that a correction formula has been developed which, when applied to device derived glucose concentrations, was associated with a 78% decrease in hypoglycaemia in the presence of TGC practices.[55]

Hirasawa et al (2009) used a novel approach to indicate "good" and "bad" responders to tight glycaemic control.[6] An interleukin-6 (IL-6) level of 1000 pg/ml can be used to diagnose systemic inflammatory response syndrome (SIRS) or hypercytokinaemia. Applying TGC (6.6–8.3 mmol/L) to patients with severe sepsis and septic shock resulted in a success rate of TGC was only 53%. When the researchers divided the patients into subgroups according to IL-6 levels on admission to ICU, they found that the success rate of TGC was relatively high in those with an IL-6 < 1000 mg/dl on admission, but very low in those with a level of > 10000 pg/ml.[6]

A protocol prescribing the control process may improve BG control.[4] TGC (4.4–4.6 mmol/L) in ICU patients, by using a computerised insulin dosing algorithm, resulted in hypoglycaemia in only 4.25% patients with 97.5% achieving target range and remained on target 73.4% of the time.[8] Unfortunately this study was not randomised, it was retrospective in nature and employed various BG sampling methods. The SPRINT protocol was applied in a general ICU to achieve TGC (4.4–6.1mmol/L). The implementation of the SPRINT protocol resulted in only 9.0% of all measurements being below 4.4 mmol/L, 3.8% below 4 mmol/L and 0.1% of measurements below 2.2 mmol/L. Hospital mortality was reduced for ≥ 3 (from 34.1% to 25.4%), ≥ 4 (from 34.3% to 23.5%) and ≥ 5 days (from 31.9% to 20.6%).[7]

Recommendations

Some recent recommendations for BG control targets (Table III) and safe recommendations for implementation of TGC (Table IV) are presented in the respective Tables.

Conclusion

Hyperglycaemia is associated with adverse effects in the critically ill patient. Studies investigating the effect of TGC, unfortunately, to date have not provided a definitive answer to the question whether TGC will improve mortality. The greatest risk in some studies on TGC has been shown to be hypoglycaemia. Future research needs to focus on blood glucose target for different populations and the design of effective tools to reach the targets safely. Furthermore, a distinction should be made between diabetic patients and other ICU patients, and the effect of nutrition support protocols and glucose variability should be assessed. In the meantime, it would be prudent to practice a moderate control target in the ICU, in general, with particular attention to settings that contribute to the precipitation of hypoglycaemia.

Table III: Recommemdations for BG targets in critically ill patients

STUDY	RECOMMENDATION
NICE-SUGAR[2]	< 10 mmol/L
Merz and Finfer, 2008[5]	Each ICU should define a blood glucose range which can be achieved without causing a significant increase in severe hypoglycaemia, and which fits within the constraints of their nursing and economic resources. Upper limit: 7.7–9.9 mmol/L
Reider et al, 2009[1]	7.7–9.9 mmol/L for the majority of critically ill patients; 6.05–7.7 mmol/L for surgical ICU patients
Preiser et al, 2007[35]	7.7–9.9 mmol/L
Americam Dietetic Aassociation[57]	7.7–9.9 mmol/L
ASPEN[58]	6.05–8.25 mmol/L

Table IV: Minimal safe requirements

- Close monitoring
- Frequent checks of blood glucose levels
- Systematic use of intravenous insulin infusion
- Validated protocols
- Training of staff
- Close collaboration between nursing and medical staff
- Appropriate and standardised means to measure blood glucose (preferably laboratory testing)
- Only arterial or venous samples
- Attention to nutrition support protocols
- Attention to feeding interruptions

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