Review Article

The benefits of tight glycemic control in critical illness: Sweeter than assumed?

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Abstract

Hyperglycemia has long been observed amongst critically ill patients and associated with increased mortality and morbidity. Tight glycemic control (TGC) is the clinical practice of controlling blood glucose (BG) down to the "normal" 4.4–6.1 mmol/L range of a healthy adult, aiming to avoid any potential deleterious effects of hyperglycemia. The ground-breaking Leuven trials reported a mortality benefit of approximately 10% when using this technique, which led many to endorse its benefits. In stark contrast, the multi-center normoglycemia in intensive care evaluation–survival using glucose algorithm regulation (NICE-SUGAR) trial, not only failed to replicate this outcome, but showed TGC appeared to be harmful. This review attempts to re-analyze the current literature and suggests that hope for a benefit from TGC should not be so hastily abandoned. Inconsistencies in study design make a like-for-like comparison of the Leuven and NICE-SUGAR trials challenging. Inadequate measures preventing hypoglycemic events are likely to have contributed to the increased mortality observed in the NICE-SUGAR treatment group. New technologies, including predictive models, are being developed to improve the safety of TGC, primarily by minimizing hypoglycemia. Intensive Care Units which are unequipped in trained staff and monitoring capacity would be unwise to attempt TGC, especially considering its yet undefined benefit and the deleterious nature of hypoglycemia. International recommendations now advise clinicians to ensure critically ill patients maintain a BG of <10 mmol/L. Despite encouraging evidence, currently we can only speculate and remain optimistic that the benefit of TGC in clinical practice is sweeter than assumed.

Keywords: Critical care, glucose, monitoring, tight glycaemic control

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Introduction

Historically hyperglycemia was deemed a beneficial response to critical illness. More recently, a substantial body of evidence has associated it with adverse outcomes. This review aims to discuss if artificially controlling hyperglycemia to the blood glucose (BG) levels of healthy adults (4.4–6.1 mmol/L) is beneficial. This practice is often referred to as "tight glycemic control" (TGC). It will firstly discuss the evidence for the deleterious effect of hyperglycemia in critical illness. After, the outcomes of the most defining studies in the field, Leuven and normoglycemia in intensive care evaluation–survival using glucose algorithm regulation (NICE-SUGAR), will be analyzed. These studies produced significantly contrasting outcomes and to help explain why, their differences in protocol design will be compared; focusing on hypoglycemia as a major risk while using TGC. Finally, it will cover the new generation of predictive modeling, aimed at providing a safer and more accurate control of the inherent variability of glucose in the critically ill. It is hoped that TGC represents an exciting new revolution in intensive care research.[1]

The observation that hyperglycemia occurs in critical illness is first credited to Bernard and Lefèvre in 1855,[2] and subsequently Cruikshank who documented an unusually high prevalence of glycosuria among

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patients after a myocardial infarction (M.I).[3] It is now seen as phenomenon common amongst critically ill patients-those requiring Intensive Care Unit (ICU) admission.[1,4] It is referred to as "stress hyperglycemia," commonly defined as the "transient increase in BG concentration above the normal range during acute physiological illness" and is independent of the raised BG common in diabetes mellitus. It has been associated with an increased frequency of mortality and major complications, such as organ failure, sepsis,[5] acute kidney injury[6] and polyneuropathy. It is thought to contribute to the high mortality among ICU patients, approximately 20% worldwide.[7] In critical illness glucose is inherently variable due to complex hormonal and metabolic changes, making it difficult to control.[8] Studies adopting TGC in an attempt to control stress hyperglycemia have showed varied outcomes.[9-13]

Is Hyperglycemia Harmful?

To justify the premise of TGC it is important to establish whether stress hyperglycemia (in this review, commonly referred as simply "hyperglycemia") is directly contributing to mortality, or a simply a symptom of the very ill.[14] Amongst ICU admissions, patients with a higher BG are more likely to die.[5] Those who experience hyperglycemia are 20% more likely to require ICU admission,[15] 9 times more likely to die during their hospital stay and be admitted for twice as long.[1] The consistent association hyperglycemia has with an increased mortality frequency, regardless of length of stay and the type of ICU unit, suggests it is having a deleterious effect on health in critical illness and is therefore worthy of being controlled.[16]

Despite hyperglycemias association with poor outcome, little is understood as to how it is harmful. It's potentially deleterious physiological effects include causing intracellular and extracellular dehydration, electrolyte abnormalities and suppressing immune function.[1,7] In one rabbit model, hyperglycemia (>13 mmol/L) caused a 33–66% reduction in immune effectiveness (measured by impaired phagocytosis and oxidative killing).[17] *In vitro* data has also shown that leukocytes are less responsive to inflammation at high glucose concentrations.[18] If true in humans, a worse immune function could contribute to the vulnerability patients have to infection during critical illness. In addition, the over-production of superoxides and a direct toxic effect of glucose, may be contributing to end-organ damage.[19] A far better understanding of the physiological impact hyperglycemia has during critical illness is required, but until then research must rely on assessing the outcome from controlling it.

During physiological stress, hormones and acute-phase proteins are released in the body's attempt to control and prevent further damage. The production of excess cortisol, glucagon, catecholamines and growth hormone constitute an important part of this response. These are all counter-regulatory to insulin, the primary hormone which serves to control glucose levels.[14,20] Therefore, along with the increase in hepatic glucose production observed in critical illness, hyperglycemia partially arises from a relative insulin deficiency.[4] Increased production and lack of inhibition together lead to the "stressed" hyperglycemic state.

The Leuven Studies

In 2001 the field of TGC was ignited by a study by van den Berghe *et al*.[12] Previously, standard practice had been that the hyperglycemia observed in critical illness was treated using artificial insulin infusions (and dietary regulation) when BG reached the "renal threshold" (though variable, usually ≥12 mmol/L). This is the point at which glycosuria and hypovolemia start to occur, due to a saturated absorptive capacity and osmotic diuresis. Instead, they used a continuous central-line insulin infusion, "intensive insulin therapy" (IIT), in an attempt to keep patients in a normoglycemic range.[21] The study design is summarized in Table 1. Among a cohort of surgical ICU patients (primarily cardiac),

Table 1: Comparing the Leuven and NICE-SUGAR protocols, using data from Van den Berghe *et al*. (2009)

	Leuven	NICE-SUGAR
Number of patients	2748	6100
Setting and sample (center)	3×1	41
Sample of ICU admissions (%)	68-95	15
Control comparison group (mmol/L)	10-12	7.8-10
Intervention target† (mmol/L)	<6.1	<6.0
Blood sampling site	Arterial	Arterial/venous/ capillary
Glucose measuring device	Blood gas analyzer	No standardization: All allowed
Insulin infusion	Continuous (central line)	Continuous and bolus: All routes
Nurse instructions	Guideline and intuition	Strict "if-then" algorithm
Feeding route for week 1	Parenteral and enteral (fed)	Enteral only (hypocaloric)
Average kcal/day received (kcal/day)	1100	800
BG target reached (%)	70	<50
Intergroup overlap in the standard-deviation of BG measurements (%)	<10	>50
Hypoglycemic events	X6	X13
Morbidity	Less organ failure/infections	Negative
Mortality (%)	Lowered by absolute 3	Increased by absolute 3
Therapy withdrawal	Late	Early

†Normal for age. BG: Blood glucose; ICU: Intensive care unit

they found their intervention reduced ICU mortality by 3.4%. The greatest benefit was found for those staying longer than 5-day. Among these patients, the mortality incidence for those receiving IIT was only 10.6%, compared to 10.2% in the control group. These patients also had a reduced incidence of acute kidney injury.[6] polyneuropathy and severe infection.[12] These data provided much hope that TGC would radically reduce ICU mortality and morbidity.

When the Leuven study was repeated in a medical ICU, while TGC reduced the frequency of morbidities associated with critical illness (e.g. less newly acquired kidney injury and an earlier discharge), it did not significantly reduce the risk of overall mortality. However, for those staying ≥ 3 days mortality was reduced by 9.5% in long term follow-up.[11] The investigators hypothesized that the failure to replicate all the previously shown benefits was due to a larger fraction being admitted with established organ damage (prevention of which is thought to be a major benefit of TGC). A patients underlying condition will presumably effect the benefit they can gain from TGC and their vulnerability to hyperglycemia.[21] For example, the type of ICU is an independent risk for hyperglycemic associated mortality.[5] While this second Leuven study did not fully replicate the outcomes of the first, positive benefits were shown, which were likely affected by the cohort constituents.

Benefits from TGC have been observed elsewhere too. Reed *et al*. observed a reduction in mortality using TGC in postsurgical trauma intensive care, in addition to fewer intra-abdominal abscesses.[22] In a pediatric ICU setting, the use of age-adjusted TGC reduced the cumulPative mortality by 3.1%.[23] Previous concerns that targeting low BG levels was deleterious to the developing brain,[24] seemed to be unfounded.[25] A meta-analysis of seven trials identified an overall reduction in ICU mortality when using TGC protocols; the duration of stay and medical ventilation were also reduced.[26] Together these data represent important support for TGC, though identified that future studies required a large and representative sample of patients, motivating the NICE-SUGAR trial.

The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation Trial

Until NICE-SUGAR there were few multi-center analyses of TGC. Studies which had failed to reproduce the Leuven outcomes had been criticized as being too small and lacking statistical power.[9,27] NICE-SUGAR was the response to these concerns. Their results showed 90-day mortality was increased from 24.9% to 27.5%.[10] This shed further doubt on the validity of Leuven, and the concept of normoglycemia being desirable in critical illness. The increased mortality was primarily attributed to cardiovascular disease, however there were no differences in the frequency of organ failure between the treatment and control groups. Nor did investigators find TGC increased the length of ICU stay and the time patients were on mechanical ventilation or renal replacement therapy.[10] While disappointing, many were puzzled by the outcome and sought to find an explanation.

Previous studies have associated TGC with an increased risk of hypoglycemia.[13,28-30] Some have suggested hypoglycemia is part of the explanation behind the increased mortality observed in NICE-SUGAR.[31] A meta-analysis, including the NICE-SUGAR data, found a 6-fold increase in hypoglycemia among patients treated with IIT to achieve TGC.[32] Supporting this hypothesis, two major trials were stopped prematurely due to an unacceptable frequency of hypoglycemic events (≤4.4 mmol/L) - 12.1% in the VISEP trial,[33] and 8.7% in GLUCONTROL.[30] In comparison, GLUCONTROL's control group only had an incidence of 2.7%, 3 times fewer.[30] Similarly, TGC in a pediatric ICU caused a 25-fold increase in episodes of severe hypoglycemia (≤2.2 mmol/L).[23] In summary, these data point to a strong association between TGC protocols and an increased likelihood of hypoglycemic events.

Are the negative effects of hypoglycemia out-weighing the potential benefits from controlling hyperglycemia during critical illness? Severe and/or prolonged episodes of hypoglycemia are associated with arrhythmias, convulsions, brain damage and death.[34] They are a common occurrence in ICU; in one study 22.4% of patients had at least one episode of hypoglycemia. They also tended to have worse outcomes, with an in-hospital mortality 17% higher than those who never experienced hypoglycemia.[35] Elsewhere, hypoglycemia has been shown to be more than double the frequency of ICU mortality.[36] The NICE-SUGAR "TGC group" had 13.7 times the frequency of severe hypoglycemic episodes.[35] The potentially deleterious effects of hypoglycemia may have contributed to NICE-SUGAR's results. Identifying the elements of their protocol which predisposed to hypoglycemia will allow better studies to be designed.

Comparing Normoglycaemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation and Leuven

Leuven and NICE-SUGAR produced incredibly different outcomes, and understanding variations in their respective protocols can help explain why.

Firstly, they were designed to target very different glucose ranges. Unlike Leuven, which compared attempted normoglycemia versus "hands-off" (the renal threshold: ≥12 mmol/L), NICE-SUGAR's "conventional" (control) treatment targeted an intermediate range (8–10 mmol/L). This practice meant 70% of patients received insulin. Higher BG levels were considered medically, and presumably ethically, unacceptable. It is unsurprising, therefore, that while the patients constituting the NICE-SUGAR control and TGC treatment group had greatly overlapping BG readings, very little overlap was seen in the Leuven trial. This distinction meant NICE-SUGAR was not an accurate replication of the Leuven methodology, therefore a like-for-like comparison of them is impractical and inaccurate.[37] This may have significantly contributed to the lack of benefit they achieved using IIT.

Normoglycemia in intensive care evaluation–survival using glucose algorithm regulation, therefore, actually assessed whether further lowering BG below an intermediate range was desirable. It was designed, based on the Leuven data, to include 6100 patients so an absolute decrease in mortality of 3.8% could be detected (with 90% power), from a baseline ICU average mortality of 30%.[10,38] To produce a statistically significant benefit, a 3–4% reduction in mortality was required from a far smaller reduction in BG, compared to Leuven. Therefore, only the plateau of the BG level-mortality curve was observed.[5] This distinguishes it from Leuven, which aimed to challenge the previously-held assumption that uncontrolled hyperglycemia is a beneficial adaptation.[39]

Retrospective analysis of the Leuven studies showed that three quarters of the mortality benefit was reaped by lowering BG to an intermediate 8–10 mmol/L range.[21] Presumably both NICE-SUGAR's treatment and control groups benefitted from this effect, as both were treated at or under this threshold. This may explain why the mortality in the control group was 24.9% (substantially lower than the expected 30%). Therefore, a speculative and approximate 5.1% reduction in mortality had already been gained for the control patients, before further glycemic control was attempted in the treatment group. To detect the additional quarter of benefit predicted from reducing BG to normoglycemia (a 1–1.5% reduction in mortality) approximately 70,000 trial participants would have been required.[21,27] It is possible that any added benefit was outweighed by the increased risks from controlling BG close to the hypoglycemic-threshold.[5]

There were also elements of the study design which disadvantaged NICE-SUGAR [Table 1]. For example, only 15% of patients admitted to participating ICUs qualified for the study, inevitably limiting the clinical staffs' experience with the protocol. This differed dramatically from Leuven. Glucose sample sites and measurement tools also had no cross-center standardization and many have subsequently been criticized as imprecise, and therefore unsuitable.[40,41] Discrepancies between measurements may have masked hypoglycemic events, due to misguided insulin titration.[42] Comparatively, there was 7 times more instances of hypoglycemia using the NICE-SUGAR protocol compared to Leuven; investigators suggest the need for more accurate glucose measuring devices.[43] The sole use of arterial measurements, analyzed using central lab or blood gas instruments, now form the international recommendations for glucose control.[44] Such examples suggest elements of the NICE-SUGAR study design was flawed which may have contributed to its outcome.

The increase in 90-day mortality in NICE-SUGAR were attributed to cardiovascular causes, despite being accompanied with no indication of more frequent organ failure or documented arrhythmias and M.I. Insulin is known to cause an intracellular shift of potassium. By always using arterial blood samples the Leuven protocol regularly tested potassium levels, whereas this was not standardized in NICE-SUGAR. Hypokalemia predisposes to dangerous cardiac arrhythmias. A 6% increase in hypokalemic measurements from the Leuven IIT group, and 55% increase in the use of intravenous potassium supplementation, indicates a tendency for these patients to become hypokalemic.[23,39] Speculatively, hypokalemia may have contributed to the increase in cardiovascular attributed mortality.

Glucose Variability

Understanding glucose variability (GV) is necessary if accurate control of BG is required for successful TGC.[45,46] High GV, combined with hyperglycemia, is often associated with the highest mortality.[47] Patients with the lowest mean change-per-hour have the lowest.[48] In one study, the mortality of patients in the highest quartile of GV was 25.7% higher than the lowest, and a longer duration of ICU admission.[8] GV also increases the risk of hypoglycemia.[49] Overall, this suggests GV has a negative effect, and attempts should be made to minimize it.

Considering this, GV may be able to partly explain some of the contrasting outcomes of TGC studies. Leuven showed far less inter-group overlap in the standard-deviation of BG measurements between patients [<10%, Table 1]. Comparatively NICE-SUGAR

had far more (>50%), suggesting just as much GV in the treatment group as the control.[50] Indeed, significantly more patients in the Leuven protocol reached their BG target [70%, Table 1]. It is unclear to what extent GV is associated with poorer outcome because it serves as a surrogate marker for a predisposition to hypoglycemia, or a harmful nature of intrinsic variability itself. Greater variability correlates with less frequent glucose measurements[51] and mortality, irrespective of BG concentration.[52] It will be important to account for GV as a metric of well-regulated control in future study protocols.

Sensitivity to insulin increases over the length of ICU stay, most rapidly increasing over the first 24–48 h. This can be partly explained by an accompanying decline in insulin counter-regulatory hormones.[14,20] Speculatively, with low intrinsic sensitivity to insulin at the onset of critical illness, this could lead to the over-administration of insulin as a patient appears initially unresponsive. TGC protocols not taking this into account, especially with those without upper limits on dosing (e.g. GLUCONTROL), radically increase the risk of hypoglycemia as hormonal regulation changes.[14,30] This necessitates models which are easily able to adapt to the changing requirements of critically ill patients.

Modeling Glucose: The SPRINT Trial

Modeling is becoming an increasingly important element of TGC studies in an attempt to efficiently and safely achieve normoglycemia.[53,54] By controlling for the kinetics of glucose, and the endogenous production, clearance and absorption of insulin, modeling allows for more precise glucose control to be achieved. Computerization and accessible interfaces help reduce human measurement error.[55-57] Using this principle, the SPRINT trial improved BG control to a normoglycemic range by 19% (average measurement: 6.0 mmol/L). For patients admitted ≥ 5 day's ICU mortality was reduced by 11.3%, compared to a retrospective cohort.[20]

The SPRINT model also reduced the risk of hypoglycemia: Only 9% of patients experienced an event of ≤4.4 mmol/L. Only 2% of measurements were ≤2.2 mmol/L. In the most recent pilot, this was improved to 1.9% and 0% of measurements, respectively.[58] This dramatically compared to GLUCONTROL where 7.7% experienced ≤ 2.2 mmol/L.[30] Such data indicates SPRINT provides more accuracy and less variability.[59] The average duration of a patient's stay in ICU was reduced by 25% and BG was removed as a statistically significant risk factor in ICU mortality.[20] Retrospective analysis of SPRINT also showed organ failure resolving faster.[19] Therefore, modeling glucose appears to benefit mortality as well as the co-morbidities associated with ICU admission.

The Next Generation of Stochastic Modeling: The Stochastic Targeted Protocol

Stochastic Targeted (STAR) is one of the most recently developed TGC protocols and uses a stochastic model which can forecast the BG concentration from a given insulin intervention. This allows the inherent GV in critical illness to be better controlled, minimizing the chance of hypoglycemia.[60] Compared to previous models, STAR provides tighter and more dynamic control.

Data from the first two pilot studies shows hypoglycemic events were reduced by a further 2–3%, improving on the SPRINT protocol.[45,46] Put into perspective, 4.4% of the second STAR pilot measurements were <5.6 mmol/L, and 0% were <3.9 mmol/L.[45] Comparatively, NICE-SUGAR and GLUCONTROL recorded severe hypoglycemia (≤2.2 mmol/L) with a frequency of 6.8%[10] and 8.7%,[30] respectively. Future studies would benefit from recording and publishing data on recordings at standardized thresholds, to allow for more accurate comparisons. Nevertheless, a substantial reduction in the frequency of hypoglycemic events is implicated.

A major drawback of TGC protocols are their clinical burden. With 3-hourly measurement intervals, and instead targeting a BG range, the second pilot was able to reduce measurements by 30% whilst maintaining tight control. This minimizes the clinical burden of multiple glucose measurements, a significant drawback in other TGC protocols.[55,61,62] By nature, these pilot studies were brief and had very small sample sizes. These recent data suggest hypoglycemia, as a major deleterious risk while using TGC, can be minimized.

Conclusions

Until recently hyperglycemia was controlled only when it reached the renal threshold of 12.0 mmol/L. After Leuven, many reconsidered their practice, attempting to more vigorously control BG. The publication of NICE-SUGAR called TGC protocols into question, though the differences between the two studies designs may explain their differences in outcome. Certainly, stress hyperglycemia is not an innocent bystander and is associated with an increase in mortality. The Leuven studies should be viewed as a "proof-of-concept" with future work aiming to optimize and confirm their findings.[37]

It is likely a threshold exists above which hyperglycemia rapidly becomes increasingly harmful. Finney *et al*. hypothesized this is approximately 8–10 mmol/L.[7] A target of <10 mmol/L is now strongly suggested by international recommendations.[44] Whether benefits can be elicited from a further reduction deserves future research. Critically ill patients have high GV due to the complex and poorly understood interactions of hormones and metabolites. The increased risk of hypoglycemia from attempting TGC must be obviated before any benefit is likely to be consistently seen. Recently, stochastic models have been designed to improve the predictability of BG and the safety of TGC protocols.

Intensive Care Unit's that are unequipped in trained staff and monitoring capacity would be unwise to attempt TGC, especially considering it's yet undefined benefit and the deleterious nature of hypoglycemia. Instead, they should aim for the higher target of controlling BG to <10 mmol/L as per Ichai *et al*.'s (2010) recommendations.[29] While not focused on in this review, improvements to feeding regimes will also constitute an important part of glycemic control, and ICU treatment generally.[63,64] Better control using "software-guided" algorithms requires the accuracy of glucometers to improve, for which continuous monitoring may be the necessary conclusion – an advance which would make TGC far easier. Despite encouraging evidence, currently we can only speculate and remain optimistic for the future benefit that TGC might 1-day offer.

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