

Insulin Therapy for Hyperglycemia Management in Critically Ill Patients

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Abstract

Hyperglycemia is associated with increased morbidity and mortality in critically ill patients and requires treatment; however, hypoglycemia is also detrimental to patients and must be avoided. Maintaining blood glucose between 140 - 180 mg/dL for critically ill patients improves outcomes. Very frequent glucose monitoring and adjustment of intravenous insulin infusion remains the standard of care to reach blood glucose goals but is also labor intensive. Emerging technology for continuous glucose monitoring that may include notifications or automated communication with an insulin delivery system may improve the maintenance of blood glucose in range and avoid hypoglycemia and hyperglycemia.

Keywords

Insulin, Critical Care, Critically Ill, Hyperglycemia, Continuous Glucose Monitoring

1. Introduction

Hyperglycemia is a common condition among critically ill patients. Persistent hyperglycemia, defined by steady periods of blood glucose levels above 180 mg/dL, is the recommended point at which insulin therapy should be started in hospitalized patients [1] [2] [3]. Clinicians in critical care settings are often challenged by the onset and treatment of hyperglycemia due to its association with increased risk of adverse patient outcomes, such as lengthened recovery periods, impaired wound healing, and immunosuppression [4]. Stress hyperglycemia, often onset due to acute physical trauma, is also related to other complications. Patients who present with acute hyperglycemia after an ischemic stroke are at an increased risk for congestive heart failure [5]. Hyperglycemia in patients recovering from a cerebral aneurysm is associated with poorer cognitive recovery

and decreased neurological function compared to normoglycemic patients [6]. Additionally, hyperglycemia increases the risk for patients to exhibit clinical manifestations of critical illness polyneuropathy, such as prolonged stays in intensive care and lengthened use of mechanical ventilation [7]. Furthermore, hyperglycemia is correlated to increased in-patient mortality [8] [9]. In patients who have experienced myocardial infarction, hyperglycemia is associated with increased troponin I levels and increased tissue damage, leading to a higher risk of mortality [10]. Presentation of acute hyperglycemia after ischemic or hemorrhagic strokes is also shown to increase mortality [11]. Recently, hyperglycemia has been found to increase the risk of mortality and the likelihood of requiring mechanical ventilation in critically ill patients infected with COVID-19 [12].

Several studies have shown that hyperglycemia increases the prevalence of adverse effects in patients with and without previously diagnosed diabetes; however, acute hyperglycemia has been observed to have a greater risk of mortality in patients without any history of chronic hyperglycemia than those with an existing diabetes diagnosis [7] [10] [11]. Without considering any previous diagnoses of hyperglycemia, acute physical stress increases the release of cortisol and counter-regulatory hormones, which work to increase gluconeogenesis and insulin resistance, respectively [13]. On top of physiological stressors, exogenous promoters of hyperglycemia may include catecholamine or corticosteroid use, parenteral nutrition, intravenous medication in dextrose solution, or infusion of blood products preserved with glucose [4].

Following the publication of the NICE-SUGAR study in 2009, the American Association of Clinical Endocrinologists and the American Diabetes Association (ADA) issued joint guidelines with adjusted blood glucose target goals for treating hyperglycemia in hospitalized patients [6]. The recommendation continues to be to begin insulin therapy when blood glucose levels exceed 180 mg/dL and to maintain levels between 140 - 180 mg/dL [14] [15]. Comparatively, the Society of Critical Care Medicine maintains slightly more strict guidelines, recommending initiation of insulin therapy when blood glucose levels exceed 150 mg/dL and to maintain levels below that threshold value [16]. While the majority of critical care clinicians will adhere to the less stringent glucose targets, certain patients may be treated to maintain blood glucose levels between 110 - 140 mg/dL if there is minimal risk of hypoglycemia [15]. Treating hyperglycemia with insulin therapy and the importance of glycemic maintenance in critically ill patients are universally accepted.

Several studies have concluded that basal-bolus insulin is the safest way to maintain glycemic control in the acute care setting while minimizing the risk of hypoglycemia [17] [18] [19]. However, use of a continuous intravenous insulin infusion is the recommended course of action when treating hyperglycemia for meeting adjusted glycemic targets in critically ill patients [3] [20] [21]. Furthermore, critically ill patients are at high risk for fluctuating blood glucose levels,

and short-acting insulin has a faster onset and a much shorter half-life to limit rebound hypoglycemia and carryover hyperglycemia once the insulin infusion is stopped [20]. In critically ill patients, blood glucose levels should be checked at least every two hours via arterial or venous blood sampling to prevent hypoglycemia [16].

This review will examine the current evidence supporting optimal glucose control in critically ill patients, as well as consider clinical applications for clinicians who practice in this setting.

2. Literature Review

2.1. Blood Glucose Goals

Hyperglycemia management has evolved significantly in the past twenty years. Throughout the early 2000s, the general consensus was that glucose control in the intensive care unit was best managed with a goal glucose range between 80 and 110 mg/dL to improve outcomes [22] [23] [24]. In 2009 and throughout the following months and years, new research was released, including a set of articles from the study group Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR). From the NICE-SUGAR study, there have been three separate publications highlighted in **Table 1**.

In March 2009, original data from NICE-SUGAR was published [25]. The study's aim was to identify the optimal blood glucose target range for patients who were critically ill. This parallel-group, multi-national, randomized control trial was divided into intensive treatment control (between 81 and 108 mg/dL) and conventional control (less than or equal to 180 mg/dL), with the primary outcome of death from any cause at 90 days after randomization. Patients were well balanced based on SOFA and APACHE II scores, and intention to treat analysis was performed. Beyond the primary outcome, a safety outcome of severe hypoglycemia (a glucose level less than or equal to 40 mg/dL) was also assessed. In contrast to previous landmark trials, NICE-SUGAR demonstrated an increased risk of death at ninety days in the intensive glucose control group, with a number needed to harm of 38. In addition, there was a statistically significant increase in the frequency of severe hypoglycemia at 6.8% versus 0.5% in the intensive versus conventional glucose control, ($p < 0.001$).

The subsequent sub-analysis from the NICE-SUGAR group was published in 2012 [27]. The study's aim was to determine if death could be attributed to hypoglycemia in the critically ill. The data were reviewed for occurrences of severe hypoglycemia (a glucose level less than or equal to 40 mg/dL) and moderate hypoglycemia (a glucose level of 41 - 70 mg/dL). In reviewing the results, patients who experienced severe or moderate hypoglycemia had more prolonged ICU and hospital stays than those without hypoglycemic events, although no difference was seen in mortality in each group based on hypoglycemia status. Within the study population, 3089 patients did not experience hypoglycemia, 2714 had moderate hypoglycemia, and 223 had severe hypoglycemia. There was a 23.5%,

Table 1. Literature review on blood glucose targets for critically ill patients.

Trial	Study Design	Patients	Comparator Groups	Findings	Comments
NICE-SUGAR study investigators. [25]	Randomized post-hoc analysis	Critically-ill patients in intensive care units (N = 6026)	<u>Intensive glucose control:</u> BG range 81 - 108 mg/dL <u>Conventional glucose control:</u> Target 180 mg/dL or less	<u>Mortality:</u> No difference between groups <u>Morbidity:</u> Moderate/severe hypoglycemia correlated with longer ICU stays	Mortality increased in moderate/severe hypoglycemia, regardless of treatment group
Griesdale, DEG; <i>et al.</i> [26]	Meta-analysis of 26 trials	Critically-ill patients in intensive care units	--	Intensive glucose control had no effect on the overall mortality rate	Intensive insulin therapy may be beneficial to patients admitted to a surgical ICU
NICE-SUGAR study investigators. [27]	Randomized post-hoc analysis	Critically-ill patients in intensive care units (N = 6026)	<u>Moderate hypoglycemia:</u> BG range 41 - 70 mg/dL <u>Severe hypoglycemia:</u> BG range 40 mg/dL or less	<u>Length of Stay:</u> Increased for those experiencing moderate or severe hypoglycemia <u>Mortality:</u> No difference between groups	No causal relationship could be established, but an association was found between hypoglycemic events and death.
NICE-SUGAR study investigators. [28]	International randomized-controlled trial subgroup follow-up analysis	Traumatic brain injury (TBI) patients in intensive care units (N = 391)	<u>Intensive glucose control:</u> BG range 81 - 108 mg/dL <u>Conventional glucose control:</u> Target 180 mg/dL or less	<u>Mortality:</u> No difference between groups <u>Morbidity:</u> Glasgow outcomes score unchanged between groups	Follow-up of TBI patients who participated in the NICE-SUGAR study.
Krinsley, JS. [29]	Literature review of observational cohort studies	Critically-ill patients in intensive care units	--	Hypoglycemia, hyperglycemia, and more glucose variability are each associated with increased risk of death. Time in range >80% for nondiabetics is strongly and independently associated with survival.	Limiting glucose variability and improving the time within the goal range may be the key target to improving outcomes.
Perez, A; <i>et al.</i> [18]	Meta-analysis	Hospitalized patients, both critically and non-critically ill	--	Extremes of blood glucose led to poor outcomes. A target glucose range of 110 - 180 mg/dL is most appropriate for critically ill and noncritically ill patients.	Continuous intravenous insulin infusion is preferred for critically ill patients and scheduled basal-bolus-correction insulin is preferred in noncritically ill patients.

28.5%, and 35.4% death rate in each population. Although statistical significance was not reached, the hypoglycemia rate within each treatment group may be

more clinically significant within the intensive treatment group (74.2% moderate hypoglycemia and 6.9% severe hypoglycemia) than the conventional group (15.8% moderate and 0.5% severe hypoglycemia). The study authors noted that no causal relationship could be fully established, but an association appeared to be present based on the instance of hypoglycemia.

A further sub-group analysis was published in 2015 reviewing traumatic brain injury patients (TBI) [28]. A total of 391 TBI study patients were identified. This population split into 51.9% in the intensive control group and 48.1% in the conventional control group. This review did not demonstrate any differences in the outcome of death between either intervention group at 90 days or two years post-randomization. The only statistically significant difference was in the occurrence of severe hypoglycemia (4.9% versus 0%, $p = 0.003$) and moderate hypoglycemia (79.2% versus 9%, $p < 0.0001$) in the intensive and conventional control groups.

2.2. Blood Glucose Monitoring

Blood glucose monitoring is an essential component of hyperglycemia management. Hospitalized patients' glucose is commonly monitored using capillary blood from a fingerstick and a glucometer [15]. For patients who are critically ill and receiving insulin therapy via intravenous infusion, frequent monitoring every 30 minutes to two hours is standard.

While significant research has been conducted on determining the proper glucose target range, investigators are also focusing on how to achieve these desired glucose ranges. Continuous glucose monitoring systems (CGMs), which automatically provide glucose values every few minutes, may theoretically increase the effectiveness of glucose control, as well as minimize the risk of hypoglycemic events by detecting the rate of change and giving a timelier alert to make adjustments. In addition to potentially improving glycemic control, further benefits may include reducing the number of blood samples and blood loss, nursing workload, and costs. CGM sensors can be invasive (intravascular blood sampling or sensing devices that remove blood), minimally invasive (subcutaneous placement of a sensor), or noninvasive (transdermal), and since they measure different compartments, it can lead to differing values [30]. Although invasive CGMs are the only FDA approved option for ICU patients, several disadvantages exist that limit their use: they are invasive and thus associated with vascular complications such as thrombosis and catheter occlusion, they require a higher implementation resource and care burden, and finally they are only reserved for ICU settings and cannot be used when patient transfer to other levels of care [30]. As of this publication, subcutaneous CGMs have not been FDA-approved for use in hospitalized patients. However, it is postulated that since they allow for more frequent monitoring, they would consequently offer additional capability to identify glucose changes and to maintain glucose in range. A randomized controlled study of 144 patients evaluated whether CGMs in critically ill patients

could improve glucose management compared with standard point-of-care (POC) glucose monitoring [31]. The CGMs were programmed to alarm if glucose was outside goal range and were utilized every fifteen minutes to two hours per protocol. Time in range was significantly improved with the use of CGMs, while mean glucose and proportion of hypoglycemic events were similar [31]. In a similar randomized controlled trial, CGMs were found to be as effective as POC glucose monitoring in maintaining blood glucose in range while reducing nursing workload and daily care costs [32]. More research is required before CGMs will be able to replace point of care blood glucose testing, but this technology is very promising.

2.3. Insulin Therapy

Insulin infusion therapy (IIT) has long been the standard treatment for critically ill patients with hyperglycemia [ADA 2021 Guidelines]. IIT must be managed through a protocol that accounts for current glucose levels as well as direction and magnitude of change in levels. IIT has a quick onset and is readily titrated, which makes it ideal for achieving glycemic targets in critically ill patients. However, IIT is labor-intensive for the care team, often requiring very frequent blood glucose monitoring, dedicated intravenous access, dose change calculations, and dosing double-checks. Paper-based or computerized protocols have been shown to achieve and maintain blood glucose targets and minimize hypoglycemia [33] [34]. However, a standardized protocol does not exist, and extensive variation exists among institutions.

The future may see technology continue to advance to where closed-loop systems may be utilized that continuously monitor glucose levels and automatically communicate with the insulin distribution system and adapt to changing insulin requirements. Preliminary studies have demonstrated the ability to achieve and maintain blood glucose goals safely [35]. Larger studies in critical care populations may be needed to assess the utility and economic feasibility of these technologies.

As patients stabilize in the critical care setting, transitioning from intravenous to subcutaneous insulin will need to occur to allow the patient to transfer out of the critical care setting. The Endocrine Society recommends starting subcutaneous insulin one to two hours before discontinuing the intravenous insulin and point of care monitoring for insulin adjustments after that [36]. Similarly, the ADA guidelines recommend development of an institution-specific transition protocol to calculate basal insulin doses based on the last six hours of a stable insulin infusion and to give basal insulin two hours before stopping the insulin infusion [15].

There have been a limited number of studies evaluating the transition from intravenous to subcutaneous insulin. Avanzini *et al.* evaluated a standardized protocol in patients after acute coronary syndrome. This study calculated total daily insulin needs based on the average insulin infusion rate from the preceding twelve hours, divided as 50% basal and 50% bolus insulin. The results demon-

strated that 70.8% of patients were in the range of 80 to 160 mg/dL (80 - 200 mcg/dL post-prandial), and 26.8% of patients experienced hypoglycemia (<70 mg/dL) in the three days after changing to the basal-bolus regimen [37]. Another study in 2016 retrospectively looked at patients who converted from an insulin infusion to subcutaneous insulin. The groups in the study were based on the percent (less than 50%, 50% - 59%, 60% - 69%, 70% - 79%, and 80% or higher) of subcutaneous basal insulin given compared to a calculated 24-hour insulin need based upon the six hours before the transition. The results showed the 50% - 59% group had the highest occurrence of glucose levels between 70 - 150 mg/dL, with 68% of the readings in this range. The <50% group had the least effective achievement of 70 - 150 mg/dL with only 46% of the readings in that range. Hypoglycemia occurred in every group except the 50% - 59% and 60% - 69% groups. Although there are many confounders, the authors concluded that utilizing basal insulin at 50% - 59% of the 24-hour insulin need may be safe [38].

Based on the information available, utilization of stable, recent (six to twelve hours) insulin requirements to calculate a daily insulin need and initiating basal insulin two hours before stopping the insulin infusion appear to be best practices. It may be reasonable to consider using 50% of the 24-hour insulin needed as basal insulin. Furthermore, clinicians must balance all the variables (nutrition, steroid use, fluids, diabetes status, etc.) that can impact insulin requirements when transitioning to subcutaneous insulin regimens.

3. Conclusion

Hyperglycemia has long been recognized as detrimental to patients who are critically ill. Ongoing research has demonstrated benefits to blood glucose targets that are less intensive and consequently may be less prone to hypoglycemia. Utilization of insulin via intravenous infusion is the most responsive to the acute needs of critically ill patients and is the most widely supported by literature. However, appropriate adjustment of insulin infusion requires frequent blood glucose monitoring. Newer technologies for glucose monitoring and insulin delivery may further improve glycemic management while decreasing caregiver workload.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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