ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 November 6; 10(31): 11214-11664

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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PUBLICATION DATE
November 6, 2022

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World J Clin Cases 2022 November 6; 10(31): 11260-11272

DOI: 10.12998/wjcc.v10.i31.11260

ISSN 2307-8960 (online)

MINIREVIEWS

Clinical challenges of glycemic control in the intensive care unit: A narrative review

Roshni Sreedharan, Adriana Martini, Gyan Das, Nida Aftab, Sandeep Khanna, Kurt Ruetzler

Specialty type: Anesthesiology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Ewers A, Austria; Iglesias J, United States

Received: May 22, 2022
Peer-review started: May 22, 2022
First decision: June 27, 2022
Revised: July 15, 2022
Accepted: September 27, 2022
Article in press: September 27, 2022
Published online: November 6, 2022

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Abstract

Glucose control in patient admitted to the intensive care unit has been a topic of much debate over the past 20 years. The harmful effects of uncontrolled hyperglycemia and hypoglycemia in critically ill patients is well established. Although a large clinical trial in 2001 demonstrated significant mortality and morbidity benefits with tight glucose control in this patient population, the results could not be replicated by other investigators. The "Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation" trial in 2009 established that tight glucose control was not only of no benefit, but in fact harmful due to the significant risk of hypoglycemia. The current guidelines suggest a moderate approach with the initiation of intravenous insulin therapy in critically ill patients when the blood glucose level is above 180 mg/dL. The most important factor that underpins glycemic management in intensive care unit patients is the consequent prevention of hypoglycemia. Robust glucose monitoring strategies and insulin protocols need to be implemented in order to achieve this goal.

Key Words: Diabetes management; Intensive care unit; Anesthesiology

Core Tip: Diabetes management in postsurgical patients admitted to intensive care unit is of utmost importance. Maintenance of normoglycemia (140-180 mg/dL), and strict avoidance of hypo- and hyperglycemia are the clinical goals.

Citation: Sreedharan R, Martini A, Das G, Aftab N, Khanna S, Ruetzler K. Clinical challenges of glycemic control in the intensive care unit: A narrative review. *World J Clin Cases* 2022; 10(31): 11260-11272
URL: https://www.wjgnet.com/2307-8960/full/v10/i31/11260.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i31.11260

INTRODUCTION

Dysglycemia is common in patients admitted to the intensive care unit (ICU). Research over the past decades has established a multitude of adverse effects of altered glycemic control in patients having surgery and admitted to ICU[1]. From targeting euglycemia or tight glucose control in the early 2000's, the focus has shifted to preventing hypoglycemia while maintaining moderate glycemic control. It has been recognized that both hyper- and hypoglycemia are independently associated with increased mortality in critically ill patients[2]. The past decade has seen more research focused on the impact of preexisting diabetes, various glycemic domains and glycemic variability on glycemic targets, control, and outcomes in critically ill patients. Taking a step closer to embracing the concept of "one size doesn't fit all". This review provides a historical perspective and current evidence-based approach to glycemic control in the ICU.

HYPERGLYCEMIA

Hyperglycemic critical ill patients are categorized into 3 separate categories[3]: (1) Known diabetes mellitus; (2) Undiagnosed diabetes mellitus; and (3) New onset hyperglycemia/stress hyperglycemia.

Known diabetes mellitus

According to the National Diabetes Statistics report 2022, 11.3% of the United States population is affected by Diabetes Mellitus (DM) and 38% of the adult United States population is prediabetic[4]. The American Diabetes Association (ADA) has set specific criteria for the diagnosis of DM, which includes [5]: (1) Fasting plasma glucose ≥ 126 mg/dL (7 mmol/L); (2) Postprandial plasma glucose ≥ 200 mg/dL (11.1 mmol/L) after 2 h of a 75 g oral glucose load; (3) HbA1C ≥ 6.5% (48 mmol/mol); and (4) Classic symptoms of hyperglycemic crises with random glucose ≥ 200 mg/dL (11.1 mmol/L).

Undiagnosed diabetes mellitus

The National Diabetes Statistics report in 2022 estimates that about 8.5 million people in the United States (23% United States adult population) are undiagnosed diabetics[4]. The ADA recommends testing HbA1C in any in-patient with a blood glucose over 140 mg/dL to establish diabetes mellitus and differentiate it from stress hyperglycemia[6]. Specifically in patients admitted to the ICU without a prior diagnosis of DM an admission HbA1C greater than 6.5% is associated with increased mortality[7].

New onset/stress induced hyperglycemia

Stress hyperglycemia is an elevation in serum glucose levels that occurs during an acute illness, which is expected to resolve spontaneously when the stress of illness or inflammation subsides[2]. The release of intrinsic hormones related to stress, as well as extrinsically administered catecholamines, steroids and nutrition, coupled with insulin resistance results in stress hyperglycemia[3,8,9]. Enhanced lipolysis and release of free fatty acids due to insulin resistance creates a milieu of lipotoxicity in addition to the glucotoxicity induced by unregulated glycogenolysis and gluconeogenesis[8]. A retrospective study evaluating the impact of New Onset Hyperglycemia (NOH) on in-hospital mortality noted a higher likelihood of ICU admission (9% *vs* 29%) and higher in-hospital mortality (1.7% *vs* 16%) in patients with NOH as compared to patients who were normoglycemic (ICU admission 9%, in-hospital mortality 1.7%) and those with a known history of diabetes (ICU admission 14%, in-hospital mortality 3%). Patients in the ICU with NOH were noted to have 3-fold higher mortality (31%) than normoglycemic patients (11.3%) or those with a known diagnosis of diabetes (10%). Although considered an adaptive survival response, stress induced, or NOH is linked to higher mortality and morbidity in both ICU and non-ICU patients[10]. Stress hyperglycemia Ratio (SHR) (Admission glucose divided by the mean blood glucose from HbA1C) and Glycemic Gap (difference between admission glucose and mean blood glucose from HbA1C) function as markers of stress hyperglycemia and could be predictors of adverse outcomes in critically ill patients. A recent prospective study evaluated the association of various glycemic parameters, including glycemic gap and SHR with outcomes in critically ill patients, with and without diabetes. Although not consistently associated with increased mortality, it was noted that a glycemic gap greater than 80 mg/dL was associated with an increased need for Renal Replacement Therapy [RR 1.949 (1.077-3.527)] and occurrence of shock [RR 2.02 (1.141- 3.576)]. On the other hand, a SHR greater than 1.1 was associated with an increased likelihood for the need for mechanical ventilation [RR 1.77

(1.194-2.627)] in critically ill patients[2].

GLYCEMIC GOALS IN THE ICU

Historical perspective

Glycemic targets for critically ill patients have shifted over time based on a litany of studies comparing intensive insulin therapy (IIT) to conventional glucose management over the last two decades (Table 1) [11-17]. Strategies and targets for glycemic control in critically ill patients were variable before the early 2000s. A study done by van den Berghe *et al*[16] in 2001, often referred to as the Leuven I study, brought glycemic management to the forefront of critical care. The investigators randomized 1548 surgical patients, to intensive insulin therapy [80-100 mg/dL (4.4-5.5 mmol/L)] or conventional glucose management [180-200 mg/dL (10-11.1 mmol/L)]. The results of this study were astounding. In patients randomized to IIT, they noted a significant decrease in ICU (risk reduction of 42%) and hospital mortality (risk reduction 34%) in addition to a decrease critical illness polyneuropathy (risk reduction 44%), blood stream infections (risk reduction 46%), and renal replacement needs (risk reduction 41%). 39 patients in the IIT group and 6 patients in the conventional treatment group had a documented blood glucose < 40 mg/dL (< 2.2 mmol/L) noting a trend towards hypoglycemic events in the IIT group[16]. However, result of this single center study was limited by the inclusion of mostly postsurgical patients and other research groups were unable to reproduce the results using similar study protocols[12,14,15]. With the hope of replicating their earlier results in non-surgical patients, the Leuven team trialed a similar protocol on medical ICU patients, often referred to as the Leuven II study[17]. Although no in-hospital mortality benefit was seen (IIT 37.3% *vs* conventional 40% $P = 0.33$), they noted a significant reduction in morbidity with IIT in these patients. Patients in the IIT group were discharged earlier from the ICU [hazard ratio (HR) 1.15, $P = 0.04$] and from the hospital (HR 1.16, $P = 0.05$), had a reduction in the incidence of new acute kidney injury (8.9% to 5.9% $P = 0.04$) and were weaned earlier from mechanical ventilation (HR 1.21, $P = 0.03$) as compared to patients in the conventional group. However, yet again, they noticed a higher likelihood of hypoglycemia in patients in the IIT group (18.7% *vs* 3.1% $P < 0.001$)[17]. In 2008, a German multicenter trial of 537 patients evaluated the impact of conventional and IIT in ICU patients with severe sepsis or septic shock. They found no significant difference in 28-d mortality between the groups (IIT 24.7%, conventional 26% $P = 0.74$). They did however find a significantly higher incidence of severe hypoglycemia (blood glucose < 40 mg/dL) (IIT 17%, conventional 4.1% $P < 0.001$) and serious adverse events (IIT 10.9%, conventional 5.2% $P = 0.01$) in the IIT group as compared to the conventional group which led to the trial being terminated early[12]. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR), a multinational randomized study done in 2009 attempted to answer the questions posed by the Leuven study and demonstrate generalizable results[18]. They randomized 6104 critically ill patients to intensive insulin therapy [81-108 mg/dL (4.5-6 mmol/L)] or a moderate glucose management strategy [less than 180 mg/dL (10 mmol/L)]. They found a significant increase in mortality despite adjustment for severity of illness and severe hypoglycemia in the IIT group. The 90-d mortality in the IIT group was 27.5% as compared to 24.9% with an odds ratio of 1.14 (1.02-1.18) for death in the IIT group. Yet again, they noted a significantly higher incidence of severe hypoglycemia (Blood glucose < 40 mg/dL) in the IIT group as compared to conventional management (IIT 6.8% conventional 0.5%, $P < 0.001$). The findings from this study underpin modern perioperative and critical care glycemic management[18]. In 2017, a meta-analysis of thirty-six randomized trials (17996 patients) confirmed the lack of mortality benefit and a 5-fold increase in the risk of hypoglycemia in patients on intensive insulin therapy *vs* moderate or conventional glucose management strategies[19]. Despite an overwhelming body of evidence suggesting the harm of intensive insulin therapy, an interesting question to ask is the impact of these studies on clinical glycemic management in critically ill patients. Niven and colleagues, in an analysis of 353464 adult patients admitted to 113 ICUs from 2001 to 2012, noted that pre-Leuven 1, about 40% of the ICU patients were hyperglycemic. After Leuven 1, which showed a benefit to IIT, they saw a significant reduction in hyperglycemia and an increase in tight glucose and hypoglycemia. Interestingly, after the publication of NICE-SUGAR, which showed that IIT was not only ineffective but also harmful, they did not note a change in tight glucose control or hyperglycemia[20]. This study highlights the challenges of de-adoption of implemented protocols even when there is substantial evidence in favor of the change. It is important for institutions to evaluate, implement and promote protocols and strategies based on the most current evidence for optimal patient care, which in the case of glycemic management of critically ill patients is to move away from IIT to a more moderate strategy.

Current recommendations

The current recommendation is to maintain a blood glucose level between 140-180 mg/dL (7.8-10.0 mmol/L) in both cardiac and non-cardiac ICU patients. Insulin infusion is initiated when the blood glucose level is over 180mg/dL (10 mmol/L). Once initiated, the infusion is titrated to maintain a goal of 140-180 mg/dL (7.8-10.0 mmol/L). This recommendation is supported by the ADA, American Association of Clinical Endocrinologists and the Society of Critical Care Medicine[21,22]. The Society of

Table 1 Landmark studies comparing intensive insulin therapy and conventional management

Study	Journal and year of publication	Study, location	Patient population	Glycemic target	Glucose measurement	Nutrition	Results	Conclusion	Comments
Intensive insulin therapy in critically ill patients[16]	*N Engl J Med*, 2001	Single institution Leuven, Belgium	1548 patients, mainly surgical patients	IIT 80-110 mg/dL (4.4-6.1 mmol/L) Conventional 180-200 mg/dL (10-11.1 mmol/L)	Arterial blood glucose using glucose analyzer	On admission-IV glucose 200-300 g/24 h Day 2- TPN, total enteral or combined enteral parenteral feeding started	ICU mortality IIT 4.6% Conventional 8% ($P < 0.04$) Risk reduction in IIT ICU mortality 42% (22%-62%) In hospital mortality 34% Blood stream infections 46% (25%-67%) Acute renal failure requiring RRT 41% RBC transfusion 50% Critical illness polyneuropathy 44%	IIT reduces mortality and morbidity in critically ill patients in the surgical ICU	
Intensive insulin therapy in the medical ICU [17]	*N Engl J Med*, 2006	Single institution Leuven, Belgium	1200 patients, medical ICU patients	IIT 80-110 mg/dL (4.4-6.1 mmol/L) Conventional 180-200 mg/dL (10-11.1 mmol/L)	Arterial or capillary using POC glucometer	Routine guidelines	In hospital mortality IIT 37.3% Conventional 40% ($P = 0.33$) Reduction in new kidney injury in IIT (8.9% to 5.9%, $P = 0.04$) Early weaning from mechanical ventilation in IIT group [HR 1.21 (1.02-1.44), $P = 0.03$] Early discharge from ICU in IIT [HR 1.15 (1.01-1.32), $P = 0.04$] Early hospital discharge in IIT [hazard ratio 1.16 (1-1.35) $P = 0.05$]	IIT significantly reduced morbidity but not mortality among all patients in the medical ICU	Risk of death and disease seems to be reduced in patients treated for three or more days in the ICU with IIT
Intensive versus conventional insulin	*Critical Care Med*, 2008	Single center	523, mixed medical and surgical	IIT 80-110 mg/dL (4.4-6.1 mmol/L)	Arterial or capillary using POC glucose analyzer	Routine institutional guideline	ICU mortality	No difference in mortality between IIT and conven-	

therapy: a randomized controlled trial in medical and surgical critically ill patients[11]				Conventional 180-200 mg/dL (10-11.1 mmol/L)			IIT 13.5% Conventional 17.1% $P = 0.3$ IIT and mortality Adjusted hazard ratio 1.09 (0.7-1.72) Hypoglycemia IIT 28.6% Conventional 3.1% $P < 0.0001$	tional insulin therapy Increased hypoglycemia in the IIT group
Strict glycemic control in patients hospitalized in a mixed medical and surgical intensive care unit: a randomized clinical trial [13]	*Crit Care*, 2008	Single center	504 mixed medical and surgical patients	IIT 80-110 mg/dL (4.4-6.1 mmol/L) Conventional 180-200 mg/dL (10-11.1 mmol/L)	Arterial or capillary using POC glucose analyzer	Combination of enteral and parenteral nutrition Nutrition was similar in both groups	28-d mortality IIT 36.6% Conventional 32.4% Relative risk 1.1 (0.85-1.42) ICU mortality IIT 33.1% Conventional 31.2% Relative risk 1.06 (0.82-1.36) Hypoglycemia IIT 8.5% Conventional 1.7% Relative risk 5.04 (1.2 -21.12) Conventional 26% ($P = 0.74$) Mean difference in SOFA score IIT 7.8 Conventional 7.7 ($P = 0.88$) Severe hypoglycemia (glucose < 40 mg/dL) IIT *vs* conventional group (17% *vs* 4.1% $P < 0.001$) Serious adverse events IIT group *vs* conventional	No difference in mortality between IIT and conventional insulin therapy Increased hypoglycemia in the IIT group

							group (10.9% *vs* 5.2%, $P = 0.01$)		
Intensive insulin and pentastarch resuscitation in severe sepsis, VISEP study[12]	*N Engl J Med*, 2008	Multicenter, multidisciplinary ICU, 18 academic tertiary hospitals in Germany	537 patients with severe sepsis/septic shock	IIT 80-110 mg/dL (4.4-6.1 mmol/L) Conventional 180-200 mg/dL (10-11.1 mmol/L)	Arterial or capillary using POC glucometer	Routine guidelines	28-d mortality IIT 24.7%	The use of IIT placed critically ill patients with sepsis at increased risk of serious adverse events related to hypoglycemia	Trial stopped early due to safety reasons
A prospective randomized multicenter controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: The Glucontrol study[14]	*Intensive Care Med*, 2009	Multi Center 21 medical surgical ICU's	1101 patients	Group 1 7.8-10 mmol/L Group 2 4.4-6.1 mmol/L	Arterial, central venous or capillary using blood gas analyzer or glucometer	Routine guidelines	ICU mortality Group 1 15.3% Group 2 17.2% $P = 0.4$ 28-d mortality Group 1 15.3% Group 2 18.7% $P = 0.1438$ Hypoglycemia (blood glucose < 2.2 mmol/L) Group 1 2.7% Group 2 8.7% $P < 0.0001$	Underpowered but showed a lack of clinical benefit of intensive insulin therapy (target 4.4-6.1 mmol/L) associated with a n increased incidence of hypoglycemia as compared to a 7.8-10 mmol/L target	Trial stopped early due to high rate of unintended protocol violations
Intensive versus conventional glucose control in critically ill patients	*N Engl J Med*, 2009	International	6104 patients, Both medical and surgical	IIT 81-108 mg/dL (4.5-6 mmol/L)	Arterial or capillary using POC, blood gas or laboratory analyzer	Discretion of treating physician	Mortality (90 d)	IIT increased mortality among adults in the ICU	
The NICE-SUGAR investigation [18]		42 hospitals (38 academic tertiary care hospitals, 4 community hospitals)		Conventional less than 180 mg/dL (10 mmol/L)			IIT 27.5% Conventional 24.9% [odds ratio for intensive control 1.14 (1.02-1.18)] Median survival time lower in IIT than in conventional group [hazard ration 1.11 (1.01-1.23) $P = 0.03$] Severe hypoglycemia < 40 mg/dL IIT 6.8% Conventional 0.5% ($P < 0.001$)	A blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81-108 mg/dL	
Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a	*JAMA*, 2010	Multicenter 11 ICUs, France	509 patients with septic shock and SOFA of 8 or more and received hydrocortisone	IIT 80-110 mg/dL (4.4-6.1 mmol/L) Conventional Physician discretion	Arterial blood using blood gas analyzer or laboratory analyzers.		Mortality IIT 45.9% Conventional	IIT did not improve in hospital mortality among patients treated with	

randomized controlled trial, COIITS trial[15]			therapy 42.9% (RR 1.07, P = 0.5) Severe hypoglycemia (blood glucose < 40 mg/dL) IIT 16.4% Conventional 7.8% (P = 0.003)	hydrocortisone for septic shock as compared to conventional insulin therapy

ICU: Intensive care unit; POC: Point of care; IIT: Intensive insulin therapy.

Thoracic Surgeons' recommend blood glucose levels less than or equal to 180 mg/dL for 24 h and maintenance between 140-180 mg/dL after cardiac surgery[23]. Tighter targets have not conferred a benefit in this subset of patients as well[24-26].

Given the heterogeneity in the ICU population, it is conceivable that for glycemic targets and outcomes, one size does not fit all. There is a significant body of work investigating glycemic domains and glucose management in diabetic *vs* non-diabetic patients. It has been noted that hyperglycemia is associated with worse outcomes in non-diabetic patients and hypoglycemia is associated with increased adverse outcomes in diabetic patients[27-30].

GLYCEMIC DOMAINS AND THE IMPACT OF PREMORBID DIABETIC STATUS

Hyperglycemia, hypoglycemia, and glycemic variability (GV) are the three domains of glycemic control. Each of these domains have been independently associated with increased mortality in ICU patients[2,28,31]. Research over the past two decades have highlighted the impact of hyperglycemia and hypoglycemia on the outcomes in critically ill patients[2,28,31-33]. A multicenter retrospective observational study in 2006 assessed the extent of variability of blood glucose levels from mean values during the ICU stay and its impact on mortality. SD of glucose was used to assess variability. There was a significant difference in SD of glucose between survivors (1.7 ± 1.3 mmol/L) and non-survivors (2.3 ± 1.6 mmol/L). They found that GV was a strong independent predictor of mortality both in-hospital as well as in the ICU. Furthermore, they noted GV to be a stronger predictor of ICU mortality than mean glucose concentration[32]. A retrospective review of 3252 prospectively evaluated patients further confirmed this effect of GV on mortality in ICU patients. This study also utilized standard deviation from mean as a surrogate for assessing glucose variability. They divided patients into quartiles based on GV. Mortality was 12.1% in the lowest quartile of GV increasing to 37.8% in the fourth quartile. In this study, the profound impact of GV on mortality remained, even after the exclusion of patients who had symptomatic hypoglycemia[33]. Oxidative stress and subsequent mitochondrial, endothelial and neuronal injury resulting from exposure to toxic glycemic levels with increased GV most likely influences its impact on mortality[33]. This impresses the importance of preventing GV while trying to achieve a glycemic target to optimize outcomes in critically ill patients.

The impact of these domains of glycemic control are variable in diabetic and non-diabetic patients. Yet, most large investigations assessing glycemic control protocols and targets in critically ill patients do not differentiate between diabetic and non-diabetic patients. A large multicenter retrospective study done in 2013 evaluated the impact of diabetic status on the association of hyperglycemia, hypoglycemia and GV on mortality[31]. While hypoglycemia (blood glucose < 70 mg/dL) was associated in increased mortality in both diabetic and non-diabetic patients, hyperglycemia and increased GV were associated with an increase in mortality only in non- diabetic patients. Furthermore, in diabetic patients with poor preadmission glycemic control, mortality seemed to be higher when they experienced relative hypoglycemia (lower blood glucose levels than their usual "normal" levels). In non-diabetic patients, maintenance of euglycemia was independently associated with reduced mortality[31]. Further studies are required to define optimal glycemic targets in ICU patients based on diabetic status.

GLUCOSE MONITORING IN THE ICU- CURRENT STRATEGIES

Common options used for frequent blood glucose monitoring in the ICU include- point of care (POC) glucometers (capillary, arterial or venous blood), traditional central laboratory devices (venous or arterial blood) or blood gas analyzers (arterial blood). POC glucometers tend to be the most used devices for blood glucose measurement and management in intensive care unit with their portability, ease of use and rapid result turnaround time. However, it is important to note that these devices were

designed for outpatient glycemic management. There is a substantial difference between outpatients and critically ill patients requiring close monitoring of their glycemic status. Peripheral edema, hypoxemia, acidosis, hypotension, hematocrit, hypertriglyceridemia, and hyperbilirubinemia are few of the several factors that confound POC blood glucose measurements in ICU patients[34,35]. The accuracy of these POC devices have been questioned as well. Per the standards set forth by the FDA, 99% of POC greater than 70 mg/dL are required to be within 10% of Central laboratory reference values and all readings less than 70 mg/dL should be withing 7 mg/dL[36]. Several hospital glucometers tend to not meet these requirements and are inaccurate for the monitoring and glycemic management of critically ill patients[37-39]. Central laboratory testing, although the gold standard for accuracy, is not practical in a critical care setting due to the prohibitive turnaround time[40]. Blood glucose levels on an arterial sample on a blood gas analyzer tends to be associated with fewer errors, close to laboratory standard and with the ability to provide quick results[35,40].

While using POC devices, capillary blood appears to be least accurate in reflecting the glycemic status. Kanji and colleagues evaluated three different blood glucose measurement methods [capillary sample with a glucometer, arterial sample with a glucometer and arterial blood gas analysis (BGA)] and comparted them to central laboratory values in ICU patients[38]. Less than 60% of the results from a capillary fingerstick were within a 20% error range of the central lab. This error appeared to be pronounced in the hypoglycemic range. Use of arterial blood in a glucometer fared better than capillary glucometer analysis but arterial BGA yielded the best agreement with central laboratory values (arterial glucometer 69.9%, arterial BGA 76.5%, capillary glucometer 56.8%; $P = 0.039$ and $P = 0.001$). Moreover, both arterial and capillary blood analyzed in a glucometer appear to overestimate blood glucose levels. This poses a significant challenge in the clinical environment and a risk for hypoglycemic events[38].

Overall, it is essential to periodically check the accuracy of POC blood glucose measurement devices. Arterial or venous samples are preferred over capillary samples. Arterial samples with blood gas analyzers are preferred for blood glucose monitoring when possible[40].

Continuous glucose monitoring

Continuous glucose monitor (CGM) devices help to consistently recognize and treat dysglycemic episodes in critically ill patients[41]. A CGM sensor can be placed either in the subcutaneous space to measure the glucose concentration in the Interstitial fluid compartment, or in a blood vessel to measure blood glucose levels. Intravascular sensors are seldom used given the risk of bleeding, infection, and thrombosis. Subcutaneous CGM devices have demonstrated accuracy and reliability in ICU patients in shock and on vasopressors[42]. Although utilization of CGM devices in critically Ill patients has not shown to improve overall glycemic control, it has been shown to reduce the occurrence of hypoglycemic events[43].

When considering accuracy in CGM, the degree of sensor drift should be quantified and accounted for. It represents the tendency of the device to report increasingly erroneous values due to change in sensor or patient conditions in the insertion site and may mask clinically important trends in glucose concentrations[44]. Automated closed loop glucose control systems can modulate delivery of insulin or dextrose based on the glucose measurements of the CGM device without nurse input. These closed loop systems when implemented well, have shown to maintain target glucose range for a longer duration without inducing episodes of hypoglycemia[45]. Although there is some evidence to support use of CGM devices in the ICU, more extensive evaluation in the clinical setting may facilitate their widespread utilization and adoption[44].

MANAGEMENT OF HYPERGLYCEMIA IN THE ICU

Continuous insulin infusion therapy is the treatment of choice in ICU patients with hyperglycemia. Insulin infusion is initiated for persistent hyperglycemia over 180 mg/dL (10 mmol/L). Once initiated, the infusion is titrated to maintain blood glucose levels between 140-180 mg/dL (7.8-10 mmol/L). The primary goal is to maintain moderate glycemic control while preventing the occurrence of hypoglycemia[21]. Validated algorithms for the titration of insulin infusion are essential to minimize adverse events, hypoglycemia, and glucose variability. Hypoglycemia prevention, recognition and treatment algorithm should be included in the insulin titration protocol[46]. The protocols should be descriptive with intervals for glucose checks, device used, sampling site *etc.* Once developed the ICU team should be educated and familiarized with the protocol.

When patients are ready to be transitioned to subcutaneous insulin from an insulin infusion, before their transfer out of the ICU, patients should receive the dose of subcutaneous insulin 2-4 h before discontinuation of intravenous insulin. Although practice is variable, utilizing 50%-70% of the 24-h insulin infusion requirement is a safe starting point to achieve target glucose levels[47]. The average amount of insulin infused during the preceding 12 h can help calculate the daily insulin requirement, which can be administered as a basal dose.

Generally, Oral antihyperglycemic agents (OHA) are not recommended for glycemic control in the inpatient setting. Nevertheless, it is not uncommon for patients to be on OHA's before their ICU

admission. The impact of the newer OHA, specifically SGLT2 inhibitors on the clinical course of the patients is worth mentioning.

Euglycemic diabetic ketoacidosis

Euglycemic diabetic ketoacidosis (EDKA) was initially described in 1973 while studying DKA, when a subgroup of patients presented with normal glycemic levels and ketoacidosis[48]. Most patients diagnosed with EDKA seem to have a glucose level less than 250 mg/dL, blood pH less than 7.3, increased anion gap and ketonemia. The underlying pathophysiology appears to be reduced glucose availability, an imbalance between insulin and glucagon, a relative deficiency of insulin and severe insulin resistance resulting in lipolysis and ketosis[49]. Overall, clinical situations such as starvation, postoperative NPO status, pregnancy, chronic liver disease or utilization of sodium-glucose co-transporter 2 (SGLT2) inhibitors could result in EDKA due to decreased availability of glucose, reduced insulin and increase in counter regulatory hormone secretion[48,49].

SGLT2 inhibitors such as canagliflozin, dapagliflozin and empagliflozin are utilized for the treatment of diabetes mellitus and have demonstrated efficacy in the reduction of serum glucose, HbA1C, blood pressure and body weight. However, these medications reduce ketone clearance, increase glycosuria, reduce availability of glucose substrate, and induce hypovolemia, increasing the risk of EDKA[49].

Once a diagnosis of EDKA is established, management is initiated with balanced fluid resuscitation. The crux of the management is timely initiation of insulin infusion to replenish the deficit and resolve ketoacidosis while preventing hypoglycemia, with simultaneous dextrose infusion. Serum potassium levels are monitored and repleted[49]. When recognized in a timely manner, most patients with EDKA recover uneventfully. A high index of suspicion in patients who are on SGLT2 inhibitors, and present to the ICU, aids in establishing a timely diagnosis.

HYPOGLYCEMIA

Like hyperglycemia, hypoglycemia is associated with poor outcomes and increased health care costs. An imbalance between glucose production and utilization, a relative or absolute excess of insulin, severe comorbidities (hepatic, renal or adrenal insufficiency) or occasional human errors are often the cause of hypoglycemia in the ICU[50]. Glucose is an essential substrate for the brain. The caudate nucleus, subiculum, hippocampus, and superficial layers of the cortex seem to be most susceptible to hypoglycemia[51,52]. Hypoglycemia results in functional brain failure and neuroglycopenic symptoms and when persistent can cause irreversible brain damage[50]. Although the heart predominantly utilized fatty acids as energy substrate, during conditions of ischemia and hypoxia, it tends to rely on glucose. Consequently, hypoglycemia can cause sinus, atrial and ventricular arrhythmias[50].

Diagnosis and recognition of hypoglycemia

The levels of hypoglycemia as endorsed by the ADA are as follows[53]: (1) Level 1- Glucose < 70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L); (2) Level 2- Glucose < 54 mg/dL (3.0 mmol/L); and (3) Level 3- Severe event. Altered mental or physical status requiring assistance from another individual for the treatment of hypoglycemia.

Neuroglycopenic symptoms tend to manifest when the blood glucose is less than 54 mg/dL. Even without clinical symptoms, a blood glucose level < 70 mg/dL is considered significant in critically ill patients and is associated with adverse outcomes[54]. Most studies looking at the impact of hypoglycemia on outcomes define severe hypoglycemia as a blood glucose level less than 40 mg/dL. Hypoglycemia can be difficult to diagnose in critically ill patients due to attenuation of as sympathoadrenal responses and neuroglycopenic symptoms can be attenuated in these patients[50]. Any sudden neurological change in an ICU patient should trigger a blood glucose check. Robust infusion algorithms, a high index of suspicion and close monitoring of blood glucose levels, for the prompt recognition and treatment of hypoglycemia is of paramount importance in high-risk patients and all patients on insulin therapy.

Prevalence and implications of hypoglycemia

A prospective study looking at the association of multiple glycemic parameters and clinical outcomes in critically ill patients, found an independent association of hypoglycemia with mortality [HR 1.68 (1.16-2.44) P = 0.006][2]. They noted that a single episode of hypoglycemia doubled the risk of death and tripled the need for renal replacement therapy and occurrence of shock. A post-hoc analysis of the NICE-SUGAR trial evaluated the association between hypoglycemia and death. Of the 6026 patients, 45% experienced moderate hypoglycemia (41-70 mg/dL) and 3.7% experienced severe hypoglycemia (< 40 mg/dL). When compared to patients who did not experience hypoglycemia, the adjusted HR for death was 1.41 (1.21-1.62; P < 0.001) and 2.10 (1.59-2.77; P < 0.001) in patients who experienced moderate and severe hypoglycemia respectively. Moderate hypoglycemia was associated with a 40% increase in adjusted mortality risk while the occurrence of severe hypoglycemia doubled that risk[54]. Interestingly, 82.4% of the patients who experienced moderate hypoglycemia and 93.3% of the patients who

experienced severe hypoglycemia were in the IIT group. While evaluating the impact of hypoglycemia on outcomes in critically ill patients Egi and colleagues noted that about 22.4% of all ICU admissions experienced at least one episode of hypoglycemia (< 81 mg/dL)[55]. These patients experienced a higher risk of in-hospital mortality as compared to non- hypoglycemic patients (36.6% *vs* 19.7%; P < 0.001). While the mortality rate increased with an increase in severity of hypoglycemia, the occurrence of even mild hypoglycemia (72-81 mg/dL) conferred a higher risk of mortality [odds ratio 1.42 (1.12-1.80); P = 0.004][55]. There is ample evidence suggesting that hypoglycemia is not only undesirable but also harmful. In fact, all our efforts in the management of hyperglycemia in the ICU are geared towards prevention of hypoglycemia while targeting moderate glycemic control.

Risk factors for hypoglycemia

A retrospective database of 102 adult ICU patients identified severity of illness, septic shock, mechanical ventilation, diabetes and IIT to be independent risk factors for the development of severe hypoglycemia in the ICU[56]. Continuous venovenous hemofiltration using bicarbonate substitution fluid, need for inotropic support and a decrease of nutrition without adjustment of insulin infusion also tend to be associated with hypoglycemia in critically ill patients[57].

Treatment of hypoglycemia

Once hypoglycemia is recognized, therapy is initiated based on the extent of neuroglycopenic symptoms. Glucose supplementation is provided orally for patients with mild to moderate symptoms. For those unable to take oral glucose, 25 g of 50% dextrose is given intravenously as an initial dose and repeated as needed. If hypoglycemia is refractory, glucagon 1 mg is administered either as an intravenous or subcutaneous dose. Once hypoglycemia is treated, the most important step is the evaluation of the cause of hypoglycemia to prevent recurrence. Various factors that need to be assessed in every patient who experiences hypoglycemia in an ICU include- the dose and timing of insulin or other antihyperglycemic therapy, interruption/alteration of nutrition and potential human errors.

CONCLUSION

Diabetes mellitus, both diagnosed and undiagnosed as well as stress hyperglycemia are associated with adverse outcomes in the ICU. Insulin infusion is the recommended pharmacological therapy for critically ill patients with hyperglycemia. The single most important goal in the management of hyperglycemia in the ICU, is the prevention of hypoglycemia. Insulin infusion algorithms and glucose monitoring strategies should be geared towards the prevention and prompt recognition of hypoglycemia while targeting moderate glycemic control.

FOOTNOTES

Author contributions: Sreedharan R, Martini A, Das G, Aftab N, Khanna S, and Ruetzler K designed the research project, wrote the manuscript, read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

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