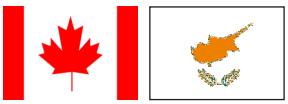
Blood glucose control in sepsis: a comprehensive narrative review



Aliza Kozyakovsky RN; BSN, MSN, Faculty of Nursing, Edmonton Clinic Health Academy, University of Alberta, Alberta, Canada
***Meropi D A Mpouzika RN; MSc, PhD,** Lecturer, Nursing Department, School of Health Sciences, Cyprus University of Technology, Limassol, Cyprus
Gerri Lasiuk RN; PhD, RPN, Associate Professor, College of Nursing, University of Saskatchewan, Canada
Colleen M Norris RN; PhD, Professor, Faculty of Nursing, University of Alberta, Alberta, Canada

Key Words: Glucose control ❖ hypoglycemia ❖ hyperglycemia ❖ intensive care unit ❖ intensive care unit ❖ mortality ❖ sepsis ❖

***E-mail:** meropi.mpouzika@cut.ac.cy

SUMMARY

- Sepsis and death due to sepsis continue to increase in intensive care units worldwide, affecting up to 30% of intensive care units' patients. Several measures have been proposed by the Surviving Sepsis Campaign in the last decade, one of which is maintaining a strict blood glucose control.
- The aim of this review was to comprehensively review the literature addressing intensive insulin therapy as an adjunct treatment for patients with sepsis.
- A comprehensive narrative review was undertaken. The electronic databases PubMed, CINAHL, and Embase were searched to identify studies for the literature review.
- The search identified 93 articles; 16 of which met the inclusion criteria. The literature review revealed that hyperglycemia is associated with increased mortality in septic patients and that intensive insulin therapy is not associated with improved survival compared to conservative insulin therapy in sepsis, but it is associated with a greater frequency of hypoglycemic events.
- It is concluded that unchecked stress-related hyperglycemia is associated with increased mortality, but intensive insulin therapy as an adjunctive treatment for sepsis has not been reported to improve survival outcomes when compared to conservative insulin therapy.

INTRODUCTION

Every year worldwide, millions of people become severely septic and the associated mortality rate is estimated at 25% (Dellinger et al., 2013). Sepsis and death due to sepsis continue to increase in intensive care units worldwide, affecting up to 30% of intensive care units' (ICU) patients (Martin, 2012). Given the aging population, a greater percentage of patients are at risk for developing sepsis due to higher rates of chronic disease, immunocompromised states, and multi-drug resistant infections (Dellinger et al., 2013).

The term sepsis refers to a life-threatening condition "caused by a dysregulated host response to infection" (Singer et al., 2016) (usually bacterial in nature). If untreated, it may progress to septic shock, which involves multi-system organ dysfunction and hypotension, which does not respond to fluid resuscitation, eventually leading to death (Hodgkin & Moss, 2008). The initial insult tends to be respiratory or genitourinary in origin (Dellinger et al., 2013). Sepsis is currently identified using the SOFA (Sequential Organ Failure Assessment) score (Vincent et al., 1996) and, especially, an acute increase of > 2 points from baseline.

It is clear that sepsis will become even more widespread and possibly result in higher rates of fatality in the future. As part of the 2013 Surviving Sepsis Campaign (Dellinger et al., 2013) and 2016 Surviving Sepsis Guidelines (Rhodes et al., 2017), a number of measures intended to improve mortality outcomes for patients who develop sepsis are outlined. One of these is maintaining blood glucose levels below 180 mg/dL (approximately 10.2 mmol/L).

Existing studies have shown that critically ill patients who are extremely hyperglycemic, have a much higher mortality rate than those who are normoglycemic (NICE-SUGAR Study Investigators, 2009). While there is broad agreement that extreme hyperglycemia increases mortality, there is controversy as to the optimal blood glucose target. The purpose of this literature review was to comprehensively review articles published since 2012 dealing with hyperglycemia and to evaluate them in order to determine if there is sufficient evidence to ascertain the optimal blood glucose level for patients with sepsis. Special emphasis was placed on randomized controlled trials (RCTs), cohort, retrospective observational and single site prospective studies. Although there is a recent review (Song et al., 2014) this synthesis of evidence was done from the perspective of nursing implications in the interest of informing nursing protocols.

METHODS

We carried out a narrative literature review based on a comprehensive literature search. The following inclusion criteria, that reflected the review purpose, were used to identify articles:

Inclusion criteria:

Research manuscripts published in the English language between 2000-2015 whose primary focus was:

- The effect of hyperglycemia on the mortality of patients with sepsis
- The effect of hypoglycemia on the mortality of patients with sepsis
- The effect of blood glucose control on mortality and morbidity of patients with sepsis.

Exclusion criteria:

- Non-English publications
- Research conducted with a non-human sample

Search for relevant studies: Electronic searches of PUBMED, CINAHL and Embase were performed using the following key words together and in different combinations: "sepsis", "severe sepsis", "septic shock", "blood glucose", "blood glucose control", "glycemic control", and "hyperglycemia". Article abstracts were retrieved and assessed for relevancy; the full text of articles that met the inclusion criteria were retrieved for review.

RESULTS

The electronic database search yielded 93 citations. The titles and abstracts of these articles were reviewed for relevancy based on the previously described exclusion and inclusion criteria. Thirteen articles were retrieved for full text review. Three additional articles were found through ancestry searches of reference lists in the retrieved articles. A total of 16 manuscripts were included in the full review. The type of study, number of participants, method, results and study recommendations are presented in Table 1.

Of the 16 studies reviewed, all took place in critical care settings. There were 9 randomized controlled trials (RCTs) (Arabi et al., 2008; Brunkhorst et al., 2008; Cappi et al., 2012; COIITSS Study Investigators, 2010; Jin & Guolong, 2009; NICE-SUGAR Study Investigators, 2009; Savioli et al., 2009; van den Berghe et al., 2001; van den Berghe et al., 2006), 3 cohort studies (Leonidou et al., 2008; Rusavy et al., 2004; Yu et al., 2003); 2 prospective observational studies (Gornik et al., 2010; Waeschele et al., 2008) and 2 retrospective observational studies (Park et al., 2012; Tiruvoipati et al., 2012).

Sample sizes

The largest study was the Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation [NICE-SUGAR Study Investigators (2009)] with 6500 patients, followed by the van den Berghe et al. study (2001) in surgical ICUs with 1548 participants and van den Berghe et al. study (2006) in medical ICUs with 1200 participants. There were eight studies with a sample size between 200 and 950 and five with sample size of less than 200.

Outcomes of stress hyperglycemia in patients in the ICU

The seminal study that ignited interest in the impact of stress hyperglycemia on patient mortality was the 2001 study by van den Berghe et al., which investigated the effect of exogenous insulin on the promotion of strict normoglycemia in critical care surgical intensive care unit patients. Compared with the control group, patients in the experimental group demonstrated a median 32% reduction in mortality (from 8.0 percent with conventional treatment to 4.6 percent [$p < 0.04$] in the experimental group); a decreased length of stay among patients who stayed more than five days (20.2% with conventional treatment compared to 10.6% with intensive insulin therapy; $p = 0.005$); and a 46% decrease (25% to 67%, 95% CI) in the number of patients who developed septicemia after surgery (van den Berghe et al., 2001). The results of this study provided strong evidence that intensive blood glucose control was an effective measure for decreasing the incidence of septicaemia and reducing mortality among critically ill patients in the surgical ICU. As a result of this study, the 2004 Surviving Sepsis Guidelines recommended strict blood glucose control as an adjunctive treatment for sepsis (Dellinger et al., 2004).

Interestingly, the follow-up study by the same authors in a medical ICU did not demonstrate a similar reduction in mortality in the experimental group compared to the control group (van de Berge et al., 2006). Although the patients in the conventional-treatment (control) group were slightly more likely to develop septicemia (37.6%) compared to the intensive-treatment group (31.9%; $p = 0.09$), overall few patients were septic and it was difficult to determine whether the strict glucose control in the experimental group was protective. For those patients whose ICU stays were less than three days, the mortality rate was slightly higher in the intensive insulin group (37.3%) versus 40.0% in the conventional-treatment group ($p = 0.33$).

The results of these studies demonstrated that the evidence related to blood glucose control and patients with sepsis was equivocal. However, these foundational studies did result in further studies regarding optimal blood glucose for patients in an intensive care setting, specifically those in septic shock.

Several years after these two studies (van den Berghe et al., 2001; van den Berghe et al., 2006), the NICE-SUGAR Study (NICE-SUGAR Study Investigators, 2009) was conducted with 6500 patients in both surgical and medical ICUs. After enrolment, patients were randomly assigned to the experimental group (n = 3054); intensive glucose control, with a target blood glucose range of 81 mg to 108 mg/dL (4.5 to 6.0 mmol/L)], or control group (n = 3050); conventional glucose control, with a target of ≤ 180 mg/dL (≤10.0 mmol/L). Patients in the intensive insulin treatment group had a slightly higher mortality, as well as a significantly higher number of hypoglycemic episodes. As the authors noted, however, their study was not powered to distinguish if the 2.6% higher mortality rate in the experimental group was due to the patient's blood glucose, excessive insulin intake, hypoglycemic episodes, or some other unknown cause.

Another international study performed by Arabi and colleagues (2008) found no significant improvement in mortality between critical care patients in medical-surgical ICU settings who received intensive insulin therapy (n = 523, target blood glucose 4.4 - 6.1 mmol/L) as compared to the conventional insulin therapy group (target blood glucose 10-11.1 mmol/L (13.5% versus 17.1%, $p = 0.30$). There were also significantly higher rates of hypoglycemic episodes in the intensive insulin therapy group compared with controls (28.6% versus 3.1%; $p < 0.0001$) (Arabi et al., 2008). Arabi and colleagues did not recommend intensive insulin therapy for critically ill patients based on their findings. While these large studies did not specifically address the association between sepsis and blood glucose, they did raise questions regarding strict blood glucose control as an effective clinical measure to decrease overall mortality in ICU patients and raised concern that strict control may increase co-morbidities such as hypoglycemic episodes.

Exogenous insulin to promote normoglycemia in septic patients

Studies of blood glucose control in the critical care setting are mixed regarding the optimal target glucose range for patients in the ICU. The evidence is also contradictory in studies that focused on septic patients specifically. The main outcomes addressed in these studies included mortality, severity of sepsis, hypoglycemic events, and other associated co-morbidities.

Hyperglycemia and mortality

Jin and Guolong (2009) conducted a multicentre randomized control trial in which critically ill septic patients were assigned to one of three groups. The first group was given a target blood glucose range of 4.4 - 6.2 mmol/L, the second a target range of < 10.1mmol/L and the third a conservative blood glucose range of 10.1 - 12 mmol/L. Patients received an exogenous insulin infusion to maintain their target blood glucose. The 30-day mortality for these patients was 20%, 21.8%, and 38.9% respectively ($p = 0.008$) (Jin & Guolong, 2009). There was no difference between groups in the length of stay in ICU (13.90 ± 1.70, 9.65 ± 1.21, 14.40 ± 1.54, $p = 0.7$). The authors

Authors, year	Type of study	Number of participants	Method	Results	Recommendations
Cappi et al., 2012	RCT	63	Compared conventional and strict blood glucose in their effects on lipid profile and other metabolic outcomes.	Free fatty acid levels were higher in the conservative group than in the intensive group after 4 hours.	Intensive glycemic therapy is associated with decreased levels of free fatty acids, which are highly toxic.
Park et al., 2012	Retrospective observational study	313	Patients admitted to ICU over a three-year period were enrolled retrospectively and assessed for mortality.	Mild hypoglycemia was independently associated with increased hospital mortality (odds ratio of 3.43). Mild hypoglycaemia was significantly associated with a lower 1-year survival rate among patients with sepsis ($p < 0.001$).	Mild hypoglycemia was associated with an increased risk of in-hospital and 1-year mortality. Practitioners need to recognize the importance of mild hypoglycemia in patients with sepsis.
Tiruvoipati et al., 2012	Retrospective observational study	297	Evaluate the effects of stress hyperglycemia in critically ill patients with sepsis admitted to ICU over a 5-year period (July 2004 and May 2009).	204 patients (68.7%) had stress hyperglycemia during the study period. Intensive care unit mortality was significantly lower in patients who had stress hyperglycemia. On logistic regression analysis, the presence of stress hyperglycemia was associated with reduced ICU mortality. Subgroup analysis revealed stress hyperglycemia to be protective in patients with septic shock.	Stress hyperglycemia may not be harmful in critically ill patients with sepsis. Patients with stress hyperglycemia had lower ICU mortality.
COIITSS Study Investigators, 2010	RCT	509	Compared four groups: continuous insulin with hydrocortisone, continuous insulin with hydrocortisone +fludrocortisone, conventional. insulin with hydrocortisone, and conventional insulin with hydrocortisone + fludrocortisone	Of the 255 patients treated with intensive insulin, 117 (45.9%) died, and 109 of 254 (42.9%) treated with conventional insulin therapy died.	Intensive insulin therapy did not improve in-hospital mortality among patients who were treated with hydrocortisone for septic shock.
Gornik et al., 2010	Single site prospective study	173	Patients divided into a hyperglycemic group (glucose > or = 7.8 mmol/L) and normoglycemic group. Assessed on severity of sepsis, survivors followed up in 5 years.	One hyperglycemic incident made patients 4x more likely to be diagnosed with type II diabetes in the next 5 years.	Hyperglycemic sepsis patients should be screened for diabetes in follow-up care.
Jin & Guolong, 2009	RCT	356	Compared mortality and morbidity in three groups: control, (10.1-12) strict blood glucose (4.4-6.2) and intermediate (6.2-10.1).	Mortality: 20%, 21%, and 38.9% for strict, intermediate, and convent. blood glucose. Hypoglycemia 8.5% vs.0.8% in strict vs. control.	Intensive insulin therapy provides significant benefits in patients with severe sepsis and septic shock in the ICU; on the other hand, it is associated with a higher rate of hypoglycemia.
NICE-Sugar Study Investigators, 2009	RCT	6500	Compared control group, with a blood glucose aim of less than 10, and the experimental group, with a blood glucose target of 4.4-6.2 for mortality and morbidity.	Mortality rate 27.5% in the intensive-control group and 24.9% in the conventional-control group (odds ratio: 1.14).	The intensive glucose control increased mortality among adults in the ICU.
Savioli et al., 2009	RCT	90	Compared tight glycemic control (treatment group, target glycemia, 80-110 mg/dL) to conventional glycemic control (180-200mg/dL) and compared fibrinolysis.	Significant, enhancement of fibrinolysis could be observed in the treatment group, as indicated by the time course of PAI-1 activity ($p < 0.001$), PAI-1 concentration ($p = 0.004$), and plasmin-antiplasmin complexes ($p < 0.001$). Morbidity, rated with the Sepsis-related Organ Failure Assessment score, was significantly lower ($p = 0.03$) in the treatment group.	Tight glycemic control reduced the fibrinolytic impairment and morbidity in sepsis.
Arabi et al., 2008	RCT	523	Compared the efficacy of a blood glucose range of 10.1-11.1 (control) to intensive insulin therapy (with a range of 4.4-6.1).	No significant difference in mortality between intensive insulin therapy and control groups (13.5% vs. 17.1%, $p = 0.30$).	Does not advocate universal application of intensive insulin therapy in intensive care unit patients.
Brunkhorst et al., 2008	RCT	537	Compared mortality and morbidity of septic patients with blood glucose target ranges of 4.4-6.2 and < 8.4.	Stopped at 1st safety juncture due to 5X more hypoglycemic events and 2X more adverse events in tighter glucose control group. No difference in mortality was observed.	Intensive insulin therapy placed critically ill patients with sepsis at increased risk for serious adverse events related to hypoglycemia.
Leonidou et al., 2008	Cohort study	265	Compared mortality and secondary outcomes between three groups on admission: hyperglycemic, diabetic, normoglycemic.	42.5% of septic patients with stress hyperglycemia died compared with 13.7% patients with normal glucose levels and 24.6% of diabetics.	Stress-induced hyperglycemia is related to a more severe disease and poorer prognosis.
Waeschele et al., 2008	Prospective observational study	191	Compared intensive insulin therapy to conventional and assessed for severity of sepsis.	Number of patients with hypoglycemia and hyperglycaemia was highly dependent on the severity of sepsis.	Patients with severe sepsis are at high risk for glycemic variability and hypoglycemic incidents.
Van den Berge et al., 2006	RCT	1200	Experimental group had a blood glucose target of 4.4-6 mmol/L, and the control group had a target of. 10.5-12mmol/L. Assessed mortality and morbidities.	Strict blood glucose control reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional-treatment group vs. 37.3 percent in the intensive-treatment group, $p = 0.33$).	Intensive insulin therapy significantly reduced morbidity but not mortality. Reduces mortality for patients in ICU > 3 days.
Rusavy et al., 2004	Cohort study	30	The goal of the study was to compare the effects of two levels of insulinemia on glucose metabolism and energy expenditure in septic patients and volunteers.	Differences in glucose uptake and storage were significantly less in septic patients. Baseline energy expenditure was significantly higher in septic patients.	High level of insulinemia in sepsis increases glucose uptake and oxidation significantly, but not increase energy expenditure, in comparison with volunteers.
Yu et al., 2003	Cohort Study	40	Compared control group and impaired glucose tolerance group to assess role of blood glucose in inflammatory responses.	IGT group, baseline plasma glucose, insulin, glucagon, cortisol, IL-6 and TNF-alpha levels were significantly higher ($p < 0.05$). Plasma cortisol levels were not significantly changed between the two groups. In control group, plasma IL-6 and TNF-alpha levels rose ($p < 0.01$) within 2 hours of the clamp and returned to basal values at 3 hours. In IGT group, increased levels of plasma cytokine lasted 3 hours vs 2 hours ($p < 0.05$) and the cytokine peaks of IGT group were higher ($p < 0.05$) as well.	Hyperglycemia may play a role in the modulation of immune and inflammatory responses.
Van den Berghe et al., 2001	RCT	1548	Experimental group: BG target of 4.4 - 6 mmol/L; control: 10.5 - 12mmol/L.	12 months post ICU, the experimental group had a 32% decrease in mortality and a 46 % decrease in post-op septicemia compared to controls.	Basis for 2004 surviving sepsis guidelines –Strict blood glucose control as recommended treatment for sepsis.

Table 1: Summary of identified studies. RCT: randomized controlled trials, ICU: intensive care unit

concluded that intensive insulin therapy provides significant benefits to patients with sepsis in the ICU.

Leonidou et al. (2008) conducted a prospective observational study across three hospitals to investigate the relationship between hyperglycemia in sepsis and mortality. Two hundred and sixty-five patients were divided into three groups at admission: those who had stress hyperglycemia, those who were normoglycemic, and those with a history of diabetes. Results indicated a sharp difference in survival rates, with a 42% mortality rate for patients who were hyperglycemic upon admission compared to 13% of those patients who were normoglycemic ($p < 0.05$) (Leonidou et al., 2008). These results were similar to the findings of NICE-SUGAR Study Investigators et al. (2009) who also reported associations between hyperglycemia in sepsis and increased mortality. In contrast, Tiruvoipati et al. (2012) conducted a five-year retrospective study and reported that stress hyperglycemia was not associated with increased mortality. Over the study period, 68.7% of the ICU patients had stress hyperglycemia. Patients with stress hyperglycemia who had cardiac and septic

comorbidities had a 14.8% rate of mortality, while patients with normoglycemia had a 26.9% mortality ($p < 0.013$) (Tiruvoipati et al., 2012). However, the investigators of this study defined hyperglycemia as blood glucose > 6.9mmol/L as per the American Diabetic Association, which is a stricter definition than used by other investigators (Leonidou et al., 2008, Tiruvoipati et al., 2012).

Hypoglycemic events

Strict normoglycemia targets have been associated with increased rates of hypoglycemic events (in which the patient's blood glucose drops to less than 2.2mmol/L). Brunkhorst et al. (2008) conducted a randomized control trial with 537 severely septic patients to assess the effect of intensive insulin therapy on mortality. The experimental group's target blood glucose range was between 4.4 - 6.2 mmol/L, and the control group's blood glucose was maintained at less than 8.4mmol/L. Most notably, the trial was stopped at the first safety juncture because the intensive insulin group had a five-fold higher rate of severe hypoglycemia and a two-fold higher rate of serious adverse events. Despite this large disparity in adverse events, there was no significant difference in mortality. In another RCT, Jin and Guolong (2009) also reported higher rates of hypoglycemia for those in the insulin intensive group (8.5%) as opposed to only 0.8% in the control group.

The negative impact of hypoglycemia was further evidenced in a three-year retrospective observational study in a critical care unit where the blood glucose target was 4.4 - 8mmol/L for septic patients. Mild hypoglycemia was associated with increased hospital mortality, increased ICU complications, and increased one-year mortality (Park et al., 2012). Even a single hypoglycemic event was associated with a three-fold increase in mortality. However, as the authors state, the causal relationship between hypoglycemia and mortality is not clear. It was suggested that the relationship between hypoglycemia and mortality may be the result of the body's physiological response to hypoglycemia, including increasing the systemic inflammatory response, or else may merely be a marker for severity of sepsis. The increased mortality may also have been due to cellular damage, as a consequence of the large concentrations of intravenous glucose.

A meta-analysis by Song and colleagues (2014) evaluated the effects of tight glycemic control (≤ 150mg/dL/8mmol/L) on mortality stratified into four subgroups (90-day and 28-day mortality and hospital and ICU mortality). The authors performed a meta-analysis of 12 RCTs involving 4100 adults with sepsis; 2,094 patients were assigned to the intensive insulin therapy (IIT) group and 2,006 were in the control group. There were 681/2,094 (32.5%) deaths in the IIT group and 661/2,006 (33%) in the control group. Overall, there was no reduction in mortality in subgroups that received IIT (28-day, 90-day, ICU or hospital mortality). However, intensive insulin therapy did significantly increase the frequency of hypoglycemic episodes. As the authors pointed out, one of the limitations of the review was that the glucose target ranges in most trials included in the meta-analysis were between 4.4 - 6.2mmol/L rather than their own trial target of < 8mmol/L. Furthermore, they speculated that had the RCTs used the current higher end blood glucose range (< 8 mmol/L versus 6.2 mmol/L) it is possible that there would have been fewer hypoglycemic events and perhaps a differentiation in mortality between the experimental and control groups.

Severity of sepsis

Waeschele et al., (2008) investigated the relationship between glycemic control and the severity of sepsis. In this study, 191 participants who were admitted to the ICU with sepsis were assigned a goal blood glucose range of 4.4 - 8mmol/L. The upper end goal of 8mmol/L was chosen instead of strict normoglycemia in order to decrease the incidence of hypoglycemic events. The objective of the study was to determine if there were any correlations between the severity of the sepsis and the number of hyperglycemic or hypoglycemic episodes. Patients were divided into three categories: those who were septic (i.e. met ≥ 2 SIRS criteria), those with severe sepsis (secondary organ failure), and those in septic shock (persistent hypotension requiring vasopressor therapy). The results indicated that patients with severe sepsis were significantly more likely to have critical hypoglycemic episodes and slightly more likely to have hyperglycemia. These results were supported by another single center prospective study that also found that patients with a greater severity of sepsis were more likely to be hyperglycemic (Gornik et al., 2010). While these studies provided useful information regarding the fluctuating blood glucose levels in patients with severe sepsis, the small sample sizes and lack of intervention or control group attenuate any conclusions that can be drawn. Further investigation is required to provide evidence regarding the association between sepsis severity and the fluctuation of blood glucose levels.

Secondary outcomes

Several studies in this review observed associations between intensive insulin therapy in septic patients and various secondary outcomes. For example, fibrinolysis is frequently inhibited in patients with sepsis, and this inhibition is associated with increased mortality and morbidity. Intensive blood glucose control is associated with improved fibrinolysis and significantly lower rates of morbidity (Savioli et al., 2009).

Hyperglycemia in sepsis may also be associated with developing type II diabetes later in life. Septic patients who had more than one instance of hyperglycemia while in critical care, were reported to be more than four times as likely to be diagnosed with type II diabetes within the next five years compared to those who were normoglycemic during their ICU stay (Gornik et al., 2010). However, it is unclear whether these hyperglycemic patients developed the hyperglycemia as a result of infection or rather due to pre-existing undiagnosed diabetes.

DISCUSSION

This comprehensive literature review was motivated by recognition of the discrepancy between standard blood glucose targets in ICU and the stricter blood glucose targets recommended in the 2004 Surviving Sepsis Guidelines. The review reveals that the optimal blood glucose target for septic patients remains unclear. Several studies show slightly decreased mortality with strict blood glucose control, while others demonstrate increased patient mortality, and still others demonstrate that the therapy has no apparent effectiveness. Some of these discrepancies may be attributed to differing protocols; different studies had different optimal blood glucose ranges as targets as well as different control groups, population sizes, and periods of time over which the studies commenced. Many of the studies were observational or quasi-experimental, and the available randomized control trials that focused specifically on septic patients rather than critical care patients in general also differed in the blood glucose targets that they used to compare their septic patient populations. Thus, it is not surprising that this heterogeneous group of studies would produce conflicting results.

RCTs that compared septic patients using strict blood glucose target ranges versus conventional management demonstrated no benefit for strict blood glucose management: rather, they demonstrated increased rates of adverse events due to hypoglycaemia (Arabi et al., 2008; Brunkhorst et al., 2008; COIITSS Study Investigators, 2010). However, one RCT that divided patients in three groups (strict blood glucose target, new guidelines and conventional management) showed a significant improvement in mortality for patients in the first two groups, though the first group had a significantly higher incidence

of hypoglycaemic events (Jin & Guolong, 2009). Another finding of note is that patients with more severe sepsis have greater blood glucose fluctuation and were more likely to have hyperglycaemic and hypoglycaemic events (Waeschele et al., 2008). The most recent meta-analysis, primarily using studies that compared groups using the stricter guidelines, concluded that there is no evidence that this practice benefits patient mortality.

The most important issue identified by this comprehensive review is that there is at present little evidence supporting the current recommendation to maintain blood glucose < 10mmol/L for septic patients. While there is consistent evidence that hyperglycemia is associated with increased mortality, and that the previous, narrower target of 4.4 - 6.2mmolL was associated with a higher incidence of hypoglycemic events, there is conflicting evidence as to whether the new blood glucose target should be used as an adjunctive therapy to decrease septic patients' mortality. Given the accumulating results on the hazards of hypoglycemia, ensuring that patients stay within the recommended range at both the lower and upper limits would help limit morbidity and mortality.

There are limitations to this comprehensive review, specifically regarding the paucity of RCTs that report on the use of intensive insulin therapy as adjunct therapy in septic patients using the new guidelines espoused by the Surviving Sepsis Campaign 2013. There are several studies using the older, strict blood glucose target guidelines, but without RCTs using the current guidelines, it is difficult to assess their efficacy. Furthermore, there is some evidence that blood glucose variability is associated with severity of illness, and thus there may be some benefit to determining whether it is necessary to have separate blood glucose targets for different levels of severity of sepsis. Lastly, most of the studies that focused specifically on patients with sepsis were observational or quasi-experimental.

CONCLUSIONS

While there have been a number of studies on the effect of strict blood glucose control on the mortality of both general and septic ICU patients, this comprehensive review has identified that the results of studies addressing this issue are contradictory. It is interesting to note that as a result of some of these studies, the 2013 Surviving Sepsis campaign targeted glucose levels between 140 and 180 mg/dL (Dellinger et al., 2013) and the 2016 Surviving Sepsis Guidelines (Rhodes et al., 2017) use an upper target blood glucose ≤ 180 mg/dL.

However, this guideline change was due in part to randomized control trials that indicated that the previous strict blood glucose control did not decrease mortality, and more importantly may have caused harm through hypoglycemic episodes.

Blood glucose control in the intensive care unit environments is largely under the purview of nurses. In critical care, it is common practice for physicians to order a target blood glucose range which nurses use to titrate an insulin infusion that maintains the prescribed range (Wilson et al., 2007). While guidelines have been established that encourage blood glucose control as an adjuvant treatment for patients with sepsis, it is important that guidelines are evidenced-based. This comprehensive literature review suggests that while unchecked stress hyperglycemia is associated with increased mortality, it has not been conclusively shown that intensive insulin therapy improves outcomes compared to conservative insulin therapy. It is important that critical care nurses continue to monitor and prevent both hypoglycemic and hyperglycemic episodes during the care of patient in the ICU. Moreover, this review provides nurses with data that suggests that the present evidence does not support strict glycemic control protocols as an adjunct treatment for sepsis.

REFERENCES

Arabi YM, Dabbagh OC, Tamim HM, et al. (2008). Intensive versus conventional insulin therapy: a randomized control trial in medically and surgical critically ill patients. Critical Care Medicine 36(12), 3190-3197.

Brunkhorst FM, Engel C, Bloos F, et al. (2008). Intensive insulin therapy and pentastarch resuscitation in severe Sepsis. The New England Journal of Medicine 358(2), 125–139.

Cappi SB, Noritomi DT, Velasco IT, Curi R, Loureiro TC, Soriano FG (2012). Dyslipidemia: a prospective controlled randomized trial of intensive glycemic control in sepsis. Intensive Care Medicine 38(4), 634-641.

COIITSS Study Investigators, Annane D, Cariou A, et al. (2010). Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA 303(4), 341-348.

Dellinger RP, Carlet JM, Masur H, et al. (2004). Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Critical Care Medicine 32(3), 858-73.

Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Medicine 39(2), 165-228.

Gornik I, Vujaklija A, Lukić E, Madzarac G, Gasparović V (2010). Hyperglycemia in sepsis is a risk factor for development of type II diabetes. Journal of Critical Care 25(2), 263-269.

Hodgkin KE, Moss M (2008). The epidemiology of sepsis. Current Pharmacological Design 14(19), 1833-1839.

Jin Y, Guolong C (2009). A multicentre study on intensive insulin therapy of severe sepsis and septic shock patients in ICU-collaborative group on IIT in Zhejiang Province, China. Intensive Care Medicine 35(1), 86.

Leonidou L, Michalaki M, Leonardou A, Polyzogopoulou E, Fouka K, Gerolymos M, Leonardos P, Psirogiannis A, Kyriazopoulou V, Gogos CA (2008). Stress-induced hyperglycemia in patients with severe sepsis: a compromising factor for survival. American Journal of the Medical Sciences 336(6), 467-471.

Martin GS (2012). Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Review of Anti-infective Therapy 10(6), 701-706.

NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. (2009). Intensive versus conventional glucose control in critically ill patients. The New England Journal of Medicine. 360(13), 1283-1297.

Park S, Kim DG, Suh GY, et al. (2012). Mild hypoglycemia is independently associated with increased risk of mortality in patients with sepsis: a 3-year retrospective observational study. Critical Care 16(5), R189.

Rhodes A, Evans LE, Alhazzani W, et al. (2017). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine 45(3), 486-552.

Rusavy Z, Sramek V, Lacigova S, Novak I, Tesinsky P, Macdonald IA (2004). Influence of insulin on glucose metabolism and energy expenditure in septic patients. Critical Care 8(4), R213-R220.

Savioli M, Cugno M, Polli F, et al. (2009). Tight glycemic control may favor fibrinolysis in patients with sepsis. Critical Care Medicine 37(2), 424-431.

Singer M, Deutschman CS, Seymour CW, et al. (2016). The Third International Consensus Definitions for sepsis and septic shock (Sepsis-3). JAMA 315(8), 801-810.

Song F, Zhong LJ, Han L, et al. (2014). Intensive insulin therapy for septic patients: A meta-analysis of randomized controlled trials. Biomed Research International 2014, 698265

Tiruvoipati R, Chiezey B, Lewis D, et al. (2012). Stress hyperglycemia may not be harmful in critically ill patients with sepsis. Journal of Critical Care 27(2), 153-158.

Van den Berghe G, Wouters P, Weekers F, et al. (2001). Intensive insulin therapy in critically ill patients. The New England Journal of Medicine 345(19), 1359-1367.

Van den Berghe G, Wilmer A, Hermans G, et al. (2006). Intensive insulin therapy in the medical ICU. New England Journal of Medicine 354(5), 449-461.

Vincent JL, Moreno R, Takala J, et al. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Medicine 22(7), 707-710.

Waeschle RM, Moerer O, Hilgers R, Herrmann P, Neumann P, Quintel M (2008). The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. Critical Care 12(5), R129.

Wilson M, Weinreb J, Hoo GW (2007). Intensive insulin therapy in critical care: a review of 12 protocols. Diabetes Care 30(4), 1005-1011.

Yu WK, Li WQ, Li N, Li JS (2003). Influence of acute hyperglycemia in human sepsis on inflammatory cytokine and counterregulatory hormone concentrations. World Journal of Gastroenterology 9(8), 1824-1827.