Designing An Intervention Program To Control Glucose Level In Intensive Care Unit (ICU) In King Hussein Medical Center, Royal Medical Services

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Abstract

Controlling blood glucose level in ICU is one of the main priorities in ICU to decrease mortality rates and morbidity rates and to decrease the healthcare cost. The main objective of the present study is design and implement an intervention protocol in ICU. The method involved a suggested intervention protocol which was applied for 25 ICU patients and their findings were compared with 25 ICU patients in control group. Study findings showed that the intervention protocol was able to reduce mortality rates, positive blood cultures, decreased morning glucose level in the intervention group compared with control group. As a conclusion, controlling blood glucose level in ICU is considered an appropriate approach and leads to better outcome of the patients

Keywords: ICU, intervention, control, glucose, blood glucose level

Introduction

The present study is methodological in its nature and puts focus in designing an intervention to be implemented in the intensive care unit (ICU) to control glucose level.

Common clinical interventions

Patients in ICU are predisposed to elevated blood glucose levels because of common clinical interventions, such as the use of corticosteroids, vasopressors, glucose-containing intravenous fluids used for drug or fluid administration, enteral or parenteral nutrition, and dialysis (Krinsley *et al*., 2005).

Controlling hyperglycemia in ICU patients

Although extensive research efforts during the last decade focused on strategies to prevent or reverse the potentially lethal multiple organ failure, only few of them revealed positive results. One of these strategies is blood glucose control with insulin (Berghe., 2004). Another way for controlling hyperglycemia is by controlling the exogenous nutritional inputs (Chase *et al*., 2006).

Mechanisms of blood glucose control with insulin therapy in the ICU

Several mechanisms are involved and interrelated in explaining the clinical benefits of normoglycemic control; including metabolic and non-metabolic insulin effects, anti-inflammatory effects, prevention of glucose toxicity, and other direct insulin actions on several cell and organ systems. The relative contribution of those different mechanisms, however, is presently unknown (Derde *et al*., 2009).

Lowering blood glucose levels

Critically ill patients suffer from both hepatic and skeletal muscle insulin resistance. The increased metabolic insulin signal was observed in postmortem skeletal muscle, but not in liver biopsies of insulin-treated patients. This suggests that in critically ill patients exogenous insulin does not affect hepatic insulin resistance and lowers blood glucose levels mainly through stimulation of skeletal muscle glucose uptake (Langouche *et al*., 2007).

Insulin therapy also attenuated the cortisol (counter regulatory hormone) response to critical illness, without involvement of altered cortisol-binding activity, also suppress indirectly the synthesis and production of TNF and IL-2 which play a role in increased gluconeogenesis (Vanhorebeek *et al*., 2006).

Blood glucose control with nutritional inputs

Tighter glycemic control is possible by controlling the exogenous nutritional inputs exacerbating the original problem. Clinical studies that intentionally lowered carbohydrate nutrition have significantly reduced average blood glucose levels without added insulin. It was found that feeding 33% to about 66% of the amount recommended by the American College of Chest Physicians (ACCP) guidelines minimized the mortality and hyperglycaemia, also the enteral nutrition was preferred over the total parental nutrition since the later one causes higher plasma glucose levels (Chase *et al*., 2006).

Insulin infusion pumps

In a prospective study of 2500 diabetic patients who underwent cardiac surgery, the impact of sliding scale insulin compared with continuous insulin infusions titrated to maintain BG concentrations at 150–200 mg/dL was evaluated. A significant reduction in the incidence of deep sternal wound infections (0.8% versus 2%; p =0.01) was observed in the continuous infusion group. Subcutaneous sliding scale insulin alone may be inadequate to maintain glycemic control in older critically ill injured patients and in patients with greater physiologic insult (Gale *et al*., 2007).

Insulin protocols in the ICU

A lack of information about the importance of normoglycemia in critically ill patients is widespread in ICUs (Holzinger *et al*., 2009). However, achieving normoglycemia requires designing and implementing insulin protocols which include timing and frequency of glucose measurements, insulin infusion rates, and target glucose values. This will need education and efforts from the medical staff, including frequent glucose monitoring and adjustment of insulin dose.

Less stringent glucose level protocols

The benefit of glucose and insulin therapy has been studied in diabetic patients experiencing an MI. In the Diabetes Insulin–Glucose in Acute Myocardial Infarction (DIGAMI) trial, 620 diabetic patients were randomized to receive insulin and glucose infusion until the BG level was 128–199 mg/dL. Subcutaneous injections of insulin were continued for 3 months. Results at one year showed a statistically significant reduction in mortality from 26.1% in the conventional treatment group to 18.6% in the insulin group (p= 0.027) (Malmberg *et al*., 1995).

The most pronounced reduction in mortality was in diabetic patients with a low cardiac risk profile who had received no previous insulin administration (Malmberg *et al*., 1995). Furnary *et al* (1999) showed that the

use of an insulin infusion to maintain glucose levels between 150 and 200 mg/dL decreased the risk of sternal wound infection after coronary artery bypass graft surgery in diabetic patients by 58%.

In a later study Furnary *et al* (2003) showed that when the target blood glucose level was decreased to less than 150 mg/dl in a cohort of 2612 patients with diabetes who were undergoing coronary artery bypass grafting, compared with historical controls, the absolute mortality was reduced (57%). In a prospective, observational study, Finney *et al* (2003) found that a target blood glucose level of less than 145 mg/dl (8.0 mmol/L) may be adequate. This target was likely associated with less risk of inadvertent hypoglycemia.

Krinsley *et al* (2005) showed that intermediate blood glucose level decrease (<140 mg/dL), and a somewhat less strict level, which was chosen primarily for safety of patients and designed to avoid inadvertent hypoglycemia, was associated with a 29% reduced in-hospital mortality, decreased new organ failure, fewer blood transfusions, and shorter ICU stay compared with the historical control group, while the rate of hypoglycemia did not increase. The lowest hospital mortality (9.6%) occurred in patients with mean glucose concentrations between 80 and 99 mg/dL.

Tight glycemic control protocols (TGC)

Some institutions use tight glycemic control (TGC) protocols in their intensive care units. TGC protocols became standard of care after the initial, very promising, studies demonstrating that it improved patient outcomes (Mackenzie *et al*., 2005). Hyperglycemia and glucose variability in intensive care unit (ICU) patients had some clinical experts calling for routine administration of intensive insulin therapy to normalize glucose levels in hyperglycemic patients (Chase *et al*., 2007). Typical TGC protocols consist of placing postoperative and critically ill patients on a continuous intravenous insulin infusion, checking their blood glucose concentrations on an hourly basis (or other schedule), and giving a bolus of insulin and/or changing the infusion rate of insulin based on the glucose concentration, with a goal of maintaining glucose between 4.4 and 6.1 mmol/L (80 and 110 mg/dL) (Lonergan *et al*., 2006).

Most of the clinical benefits of intensive insulin therapy appear to be related to prevention of hyperglycemia, which has been demonstrated to adversely affect outcome (Berghe *et al*., 2006). Intensive blood glucose control is achievable using a nurse-directed nomogram. This improved control was achieved without substantially increasing resource use (Chant *et al*., 2005).

A new range of glycemic control protocol

A Joint Statement from the American Diabetes Association and American Association of Clinical Endocrinologist (2009) announced that this study should NOT lead to an abandonment of the concept of good glucose management in the hospital setting. The statement also emphasizes that; clinicians should strive for a reasonable control (i.e., glucose levels in the mid-100s) in such critically ill patients. The optimal target range for blood glucose in critically ill patients remains unclear.

Study objectives

The main objective of the present study is to design an intervention protocol to control glucose level in ICU.

Methodology

We designed an intervention protocol to be implemented in ICU.

Outcomes measured

The following measuring variables were taken into consideration for appropriate implementation of intervention protocol:

- Length of ICU stay.
- Mortality in ICU patients, after 28 days, and 60 days from randomization.
- Length of hospital stay.
- The need for organ support (inotropes, renal replacement therapy and positive pressure ventilation).
- Incidence of blood stream infections.
- Use of antibiotics for more than 10 days.
- Incidence and severity of hypoglycemia.
- Need for blood transfusion.
- The presence or absence of hyperbilirubinemia.
- New kidney injury during ei either a level of serum creatinine twice that present on admission to the ICU or a peak level of serum creatinine of >2.5 mg per deciliter [220 Xmol per liter]).
- Hemoglobin A1C that would provide insight in the hyperglycemic exposure of ICU patients.
- Total dose of insulin given in each protocol.
- Mean blood glucose level mg/dL for the two groups.

Hyperglycemia management

Management of hyperglycemia in the intervention group was with an insulin infusion pump protocol, to maintain blood glucose level (BGL) within range of 120-160 mg/dL, for ICU patients in general; and within

range of 160-180 mg/dL, for septic patients. This is in comparison with the control group who was managed by conventional insulin regimen to maintain blood glucose level less than 200 mg/dL in a target range of 180-200 mg/dL.

Insulin protocol ranges for intervention group:

Blood glucose ranges were defined as severely hypoglycemic (44 mg/dL), hypoglycemic (60 mg/dL), low (60–80 mg/dL), acceptable (80–119 mg/dL) target (120-160 mg/dL), hyperglycemic (161–250 mg/dL), and severely hyperglycemic (>250 mg/dL). For septic patients the target range was (160-180 mg/dL) and hyperglycemic range was (181–250 mg/dL). Insulin protocol for the intervention group was designed by the study members; the target range was set higher than the range of TGC protocols to decrease the risk of hypoglycemia. Insulin protocol used in the intervention group is shown in Table 1.

Table 1: Insulin protocol used in the intervention group

Current blood glucose level, mg/dL	Action
<45	Give 20 ml dextrose 50%
45-59	Give 10 ml dextrose 50%
60-119	No insulin
120-160	No insulin
161-199	Give insulin 2 units /hr
200-300	Give insulin 3 units /hr
>300	Give insulin 4 units /hr

Blood glucose ranges were defined as severely hypoglycemic (44 mg/dL), hypoglycemic (60 mg/dL), low (60–80 mg/dL), acceptable (80–179 mg/dL) target (180-200mg/dL), hyperglycemic (>200 mg/dlL, and severely hyperglycemic (>290 mg/dL). The insulin protocol for the control group was designed by the ICU clinicians, and it has been used as the conventional treatment for hyperglycemia in the ICU. Insulin protocol used in the control group is shown in Table 2.

Table 2: Insulin protocol used in the control group

Current blood glucose level, mg/dL	Action
<45	Give 20 ml dextrose 50%
45-59	Give 10 ml dextrose 50%
60-159	No insulin
160-200	No insulin
201-250	Give insulin 2 units /hr
251 -300	Give insulin 3 units /hr
>300	Give insulin 4 units / hr

Implementation of the intervention protocol

Two groups of ICU patients were randomly assigned into two groups intervention group (N=25) and control group (N=25). ICU patients were

from King Hussein Medical Center, the Royal Medical Services. A randomized controlled trial was conducted.

Study findings

As shown in table 3, variables associated with intervention protocol are described. In intervention group, 96% of patients were treated with insulin compared with 72% in control group, this variation in insulin treatment was statistically significant (p=0.021). Patients in intervention group received more insulin (28.32 IU) compared with those in control group (14.62 IU), and the difference of insulin dose was statistically significant (p=0.002). The results also showed that morning blood glucose in intervention group (139 mg/dl) was significantly (p=0.001) less than that in control group (174 mg/dl).

Corticosteroid treatment was higher in intervention group compared with control group, but not statistically significant (0.568). Mortality rates were lower in intervention group at day 28, and day 60, but this was not statistically significant (p=0.370, p=0.555). Renal replacement therapy was 8% in intervention group and this was less than that in intervention group 12%, but this was not statistically significant (p=0.139). Positive blood cultures were 8% in intervention group, and 36% in control group, but this was not statistically significant (p=0.068).

Table 3: Variables associated with intervention protocol in ICU

Variable	Intervention group	Control group	p value
Treated with insulin (%)	96%	72%	0.021
Insulin dose, units/day (M±SD)	28.32± 16.38	14.62± 12.26	0.002
Morning blood glucose (M±SD)	139± 17.09	174± 16.69	0.001
Corticosteroid treatment	48%	40%	0.568
Death, (%) at day 60	32%	40%	0.555
Death, (%) at day 28	28%	40%	0.37
Renal replacement therapy	8%	12%	0.139
positive blood cultures	8%	36%	0.068

Discussion

Hyperglycemia and glucose variability in intensive care unit (ICU) patients made some experts call for routine administration of intensive insulin therapy to normalize glucose levels in hyperglycemic patients on the assumption that treatment aiming at normoglycemia will benefit patients. Others, however, have raised concerns over the optimal glucose level, the accuracy of measurements, the resources required to attain tight glycemic control (TGC), and the impact of TGC across the heterogeneous ICU population.

A reasonable goal insulin protocol

The apparent contradiction between the adverse effects of hyperglycemia and increased administration of insulin provokes debate over the most appropriate target for glucose control. Controlling hyperglycemia without being too tight will result in the most benefit without increasing the risk for severe hypoglycemia (Bochicchio et al., 2008). A Joint Statement From the American Diabetes Association and American Association of Clinical Endocrinologists (2009) announced that it is important to consider that the severely ill patients in NICE-SUGAR trial -that reported an increase in mortality rate, and episodes of severe hypoglycemia with tight glycemic control- were treated intensively with intravenous insulin to very tight targets (target glucose level was 81–108 mg/dL) compared to a control group whose glucose control was good (average glucose 144 mg/dL). This study should NOT lead to an abandonment of the concept of good glucose management in the hospital setting. In light of the recently published NICE-SUGAR data, a systematic review and a new meta-analysis provide an updated estimate of the effect of such therapy on the risk of hypoglycemia and death. It has suggested that TGC protocols offer limited if any benefits in critically ill adults and revealed that these protocols resulted in a 3- to 5-fold increased risk of hypoglycemia. The meta-analysis examined 29 randomized controlled trials that met the predefined inclusion criteria with strict glycemic goals. Of the 27 trials that examined mortality as an endpoint, 16 favored TGC and 11 favored usual care, but the reductions in relative risk were statistically significant (95% confidence) in only 2 of the 16 favoring TGC and in none of the 11 favoring usual care. The only outcome for which TGC demonstrated a significantly reduced risk was the development of septicemia. This was seen in surgical intensive care patients but not in medical ICU which cannot exclude the possibility that some patients may benefit from intensive insulin therapy (Donald et al., 2009).

In our study a new range of glucose level was set to control hyperglycemia with an insulin infusion pump protocol used in the intervention group. A goal was to maintain blood glucose level within range of 120-160 mg/dL, for ICU patients in general in the intervention group, and the range of 160-180 mg/dL was set for septic patients, to prevent hypoglycemia, which is risky in this particular ICU population. While conventional treatment with an insulin infusion pump was maintained in the control group; that is to maintain blood glucose level less than 200 mg/dL for ICU patients in a target range of 180-200 mg/dL. The above ranges for the intervention group were higher than the TGC protocol since negative outcomes reported in the NICE-SUGAR study increased the need to target safer blood glucose level at the same time controlling hyperglycemia and preventing bad outcomes; a glucose levels in the mid-100s. Our goal was set

before the recommendations by ADA and AACE were declared (Moghissi et al., 2009).

The management of blood glucose levels was standardized. Nearly all patients received their assigned treatment. The mean blood glucose levels differed significantly between the two treatment groups during the study period (143.70±12.78 versus 175.56±14.07 mg/dL, p<0.001). When insulin resistance decreased, lower insulin rates were able to maintain better blood glucose levels. In this randomized controlled trial involving adults in the mixed ICU we found that a new target of blood glucose control that was used in the intervention group, as compared with a conventional glucose control in the control group, did not increase the absolute risk of death at 28 days and at 60 days.

The difference in mortality remained not significant after adjustment for potential confounders at 28 days (p=0.370), and at 60 days (p=0.555), between two groups in our study. This finding agrees with the result of a meta-analysis stating that the different targets of intensive insulin therapy (glucose level [6.1 mmol/L versus [8.3 mmol/L) did not influence either mortality (Fahey *et al*., 2009). It was noticed by secondary subgroup analysis for the primary outcome that the percentage of death was significantly higher in medical ICU patients than surgical ICU patients (p= 0.015), indicating that surgical patients may benefit more from insulin treatment. As found in previous studies (Berghe *et al*., 2001, He *et al*., 2007) and a meta-analysis (Donald *et al*., 2009).

In our study the rate of positive blood cultures was lower in the intervention group than that in the control group; (8% and 32% respectively) (p=0.068), which reflects reduction in the risk of septicemia. This finding was reported previously by other studies (Berghe, *et al*., 2001; Grey, *et al*., 2004; Cromphaut, *et al*., 2007).

Conclusion

Designing and implementation of intervention protocol in ICU led to positive impacts in reducing mortality rate, morning glucose level, positive blood cultures, and renal replacement therapy among intervention group compared with control group.

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