Glycemic control in acute illness

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Hyperglycemia is commonly observed in critical illness. A landmark large randomized controlled trial (RCT) reported that the incidence of hyperglycemia (blood glucose concentration > 108 mg/dl) was as high as 97.2% in critically ill patients. During the past two decades, a number of RCTs and several meta-analyses and network meta-analyses have been conducted to determine the optimal target for acute glycemic control. The results of those studies suggest that serum glucose concentration would be better to be maintained between 144 and 180 mg/dl. Although there have been studies showing an association of hypoglycemia with worsened clinical outcomes, a causal link has yet to be confirmed. Nonetheless, some researchers are of the view that the data suggest even mild hypoglycemia should be avoided in critically ill patients. Since acutely ill patients who receive insulin infusion are at a higher risk of hypoglycemia, a reliable devices for measuring blood glucose concentrations, such as an arterial blood gas analyzer, should be used frequently. Acute glycemic control in patients with premorbid hyperglycemia is a novel issue. Available literature suggests that blood glucose concentrations considered to be desirable and/or safe in non-diabetic critically ill patients might not be desirable in patients with diabetes. Moreover, the optimal target for acute blood glucose control may be higher in critically ill patients with premorbid hyperglycemia. Further study is required to assess optimal blood glucose control in acutely ill patients with premorbid hyperglycemia.

Key Words: Acute illness, Diabetes mellitus, Glucose, Glucose measurement, Hyperglycemia, Insulin.

Stress-induced Acute Hyperglycemia

Hyperglycemia is commonly observed in critical illness. It was reported that increased blood glucose concentrations of more than 108 mg/dl were observed in 97.2% of critically ill patients [1]. This trial also showed that blood glucose concentrations exceeded 180 mg/dl in 69.0% of the patients in this cohort.

Acute illness has been reported to be accompanied by a hypermetabolic state [2] due to the release of cytokines and counter-regulatory hormones [3]. A hypermetabolic state induces insulin resistance and increases hepatic glucose production (gluconeogenesis), resulting in acute hyperglycemia [4,5]. Acute hyperglycemia was reported to be more pronounced with the use of glucose-containing infusions [3], sympathomimetic drugs and corticosteroids [6]. Acute hyperglycemia was shown to be associated with poor outcomes and thus might be a marker of the severity of illness [7–12]. Two decades ago, it was believed that the blood glucose concentration would be better to be < 200 mg/dl to avoid adverse effects of hyperglycemia [13].

History of Intensive Insulin Therapy

The first randomized controlled trial (RCT) to assess the risks and benefits of intensive insulin therapy (IIT) (target blood glucose concentration: 80–110 mg/dl) compared with those of conventional insulin therapy (target blood glucose concentration: 180–200 mg/dl) was conducted by Van den Berghe et al. [14]. In that RCT, IIT significantly reduced the rate of hospital

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mortality (34% relative reduction). The second trial by the same investigators showed that mortality rate was not significantly reduced by IIT [15]. When the datasets of these two RCTs were combined, the mortality rates were 20.4% with IIT and 23.6% with conventional therapy [16].

More intensive glycemic control was widely recommended following those two studies [17]. However, a more cautious approach has also been recommended, and there are concerns about the widespread adoption of intensive glycemic control [13].

The GLUCONTROL trial, a multicenter RCT (1,078 patients from 21 intensive care unit [ICUs] in Europe) [18], was stopped early due to a high incidence of protocol violations. The GLUCONTROL trial showed that IIT increased the rate of hypoglycemia (IIT vs conventional: 8.7% vs 2.7%, P < 0.0001) with no significant difference in ICU mortality rates (17.2% vs 15.3%, P = 0.41). The VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) study was also a multicenter RCT (18 ICUs in Germany) conducted in patients with severe sepsis [19]. The VISEP trial was also stopped early because patients received IIT had a significantly higher risk of hypoglycemia without a beneficial effect on 90-days mortality (39.7% vs 35.4%, P = 0.31). In the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial conducted in 6104 critically ill patients, IIT significantly increased 90-day mortality compared with the effect of conventional treatment (IIT vs conventional: 27.5% vs 24.9%, P = 0.02) [1].

In 2010, Friedrich et al. [20] reported the results of a systematic review that showed no effect of IIT on mortality in critically ill patients (surgical cohort: risk ratio = 0.85, P = 0.11; medical cohort: risk ratio = 1.02, P = 0.61). Similarly, other meta-analyses [21–23] show that IIT may not reduce mortality and may increase the risk of hypoglycemia in acutely ill patients.

Optimal Target for Acute Glycemic Control

After the publications of NICE-SUGAR trial and subsequent meta-analyses, several clinical guidelines stopped recommending IIT, including the Surviving Sepsis Campaign [24]. However, the optimal target of acute glycemic control remains unclear, since there have been few RCTs to compare the target of blood glucose concentrations of 144–180 mg/dl with 110–144 mg/dl or > 180 mg/dl [25]. Accordingly, some guidelines recommend commencing insulin administration at a blood glucose concentrations of > 180 mg/dl [24], whereas other guidelines recommend starting insulin administration at a blood glucose concentrations of > 150 mg/dl [26].

Recently, we conducted a network meta-analysis (18,098 patients from 35 RCTs) to determine the optimal target in acute illness [25]. We showed that there were no significant differences in the risk of mortality and infection among four blood glucose ranges (< 110, 110–144, 144–180 and > 180 mg/dl). Blood glucose concentrations of < 110 mg/dl and 110–144 mg/dl were associated with greater risk of hypoglycemia than were blood glucose concentrations of 144–180 mg/dl and > 180 mg/dl. These findings were consistent with the results of a network meta-analysis by Yamada et al. [27].

Although not conclusive, the results of the network meta-analysis showed that a blood glucose target of 144–180 mg/dl might decrease the risk of hypoglycemia and death compared with a target of 110–144 mg/dl.

Impact of Hypoglycemia

The incidence of severe hypoglycemia (defined as a blood glucose concentration ≤ 40 mg/dl) was significantly higher in patients with IIT (relative risk = 13.7) in the NICE-SUGAR trial [1]. Although there have been studies showing a significant association of hypoglycemia with worsened outcomes, no study has confirmed a causal link between hypoglycemia due to IIT and increased mortality.

We conducted a retrospective observational study to determine whether mild or moderate hypoglycemia is independently associated with an increased risk of death in acutely ill patients [28]. Of the 4,946 patients studied, 1,109 (22.4%) had hypoglycemia; the hospital mortality rate of those patients was 36.6%, whereas it was 19.7% in patients without hypoglycemia (P < 0.001). Additionally, mortality increased significantly according to the severity of hypoglycemia (P < 0.001). Even after adjustment for possible confounders, hypoglycemia was independently associated with an increased risk of mortality including all-cause mortality, cardiovascular events related mortality and infectious disease related mortality.

Although the severity of hypoglycemia may be just a marker of the severity of illness [29], hypoglycemia itself might be harmful for acutely ill patients [13]. For example, hypoglycemia might be biologically toxic by inducing neuroglycopenia [30], increasing the systemic inflammatory response [31], causing cerebral vasodilatation [32], impairing sympathetic nervous system responsiveness [33], inhibiting the corticosteroid response to stress [34], or by mechanisms that have yet to be determined. Thus, the available literature may suggest that even mild hypoglycemia should be avoided in acutely ill patients [35].

Several studies have revealed risk factors for hypoglycemia including diabetes mellitus, septic shock, use of mechanical ventilation, use of inotropic support, renal insufficiency, high severity of illness, and use of insulin [36–38]. Therefore, we suggest that all acutely ill patients treated with insulin should be considered at risk for hypoglycemia.

Devices Used to Measure Blood Glucose

It is relevant to prevent hyperglycemia or hypoglycemia during acute illness. It is common to use an arterial blood gas (ABG) analyzers and glucometers to measure blood glucose concentrations in critically ill patients. We conducted a systematic review to compare blood glucose concentrations measured by using an ABG and a glucometers with those measured by a central laboratory machine in acutely ill adult patients [39]. In that systematic review, we found that blood glucose measurements of arterial blood using an ABG or a glucometer were significantly more accurate than measurements of capillary blood using a glucometer. Moreover, blood glucose measurements of arterial blood by an ABG tended to be more accurate than those by a glucometer. The risk of errors in measurement by these devices was also higher in the hypoglycemic range, when blood glucose concentration was < 81 mg/dl. Unstable hemodynamics (as evidenced by edema or the use of a vasopressor) combined with the administration of insulin was also associated with an increased risk of error in measurements using a glucometer [39].

Based on these findings, blood glucose monitoring of arterial or venous blood with a glucometer or ABG analyzer is superior to monitoring capillary blood with a glucometer. Nonetheless, we should note that there are large variations in accuracy among devices. Thus, measurement of blood glucose has not reached a sufficient reliability for providing IIT in critically ill patients [39].

Acute Glycemic Control in Critically Ill Diabetic Patients

The current criteria for the diagnosis of diabetes mellitus (DM) are based on methods certified by the National Glycohemoglobin Standardization Program. These criteria include a fasting plasma glucose concentration > 126 mg/dl, a random plasma glucose concentration ≥ 200 mg/dl, and a hemoglobin A1c (HbA1c) level ≥ 6.5% [40]. Since, because acute hyperglycemia is common in critically ill patients even without the presence of diabetes, measurement of HbA1c level at admission to the ICU may be useful for identifying undiagnosed diabetes [13,41].

We have reported that there is a significant interaction between the presence of DM and the association of hyperglycemia with adverse outcomes [42]. Patients with DM had a lower odds ratio of death at all levels of hyperglycemia than did non-diabetic patients, being consistent with results of other studies [43–47]. We have also demonstrated that there is a significant interaction between premorbid hyperglycemia (HbA1c level > 7%) and the association of hyperglycemia with risk of death [48]. A study by Plummer et al. [49] showed that hyperglycemia was associated with a higher mortality rate in non-diabetic patients with acute hyperglycemia and in diabetic patients with < 7% of HbA1c level. However, in diabetic patients with >7% of a HbA1c level, hyperglycemia was not associated with mortality. Furthermore, we conducted a multicenter observational study to assess the interaction between premorbid glycemic control and the association of acute hypoglycemia with subsequent hospital mortality in acutely ill patients [50]. In that study, chronic premorbid hyperglycemia increased the incidence of hypoglycemia and modified the relationship of acute hypoglycemia with mortality. Furthermore, the severity of premorbid hyperglycemia was directly proportional to hospital mortality in patients with acute hypoglycemia.

This phenomenon might be explained by the biological adjustment to pre-existing hyperglycemia and low glycemic variability. Thus, blood glucose concentrations that are considered to be desirable for non-diabetic ICU patients might be undesirable for ICU patients with diabetes. Moreover, the optimal blood glucose concentration might be higher in critically ill diabetic patients [13,41]. This hypothesis is supported by the results of a study by Van den Berghe et al. [16] showing that diabetic patients did not benefit from IIT. Further study is necessary to determine optimal blood glucose concentrations in acutely ill patients with premorbid hyperglycemia.

Conclusions

During the past two decades, a number of studies have been carried out to determine optimal acute glycemic control. The results of past studies suggest that blood glucose concentrations should be maintained between 144 and 180 mg/dl. The results also indicate that it is also necessary to avoid even mild hypoglycemia with careful monitoring. Because acutely ill patients receiving insulin infusion are at higher risk for hypoglycemia, reliable devices for measuring blood glucose concentrations, such as an ABG, should be used frequently. Moreover, acute glycemic control in patients with premorbid hyperglycemia is a novel issue for which further study is required.

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