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EDITORIAL

Glycemic control in critically ill patients: What to do post NICE-SUGAR?

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Abstract

Until recently, stress hyperglycemia was considered to be a beneficial adaptive response, with raised blood glucose providing a ready source of fuel for the brain, skeletal muscle, heart and other vital organs at a time of increased metabolic demand. Following the Leuven Intensive Insulin Therapy Trial in 2001, tight glycemic control became rapidly adopted as the standard of care in intensive care units (ICU's) throughout the world. However, four randomized controlled studies and the recently published NICE-SUGAR study have subsequently been unable to replicate the findings of the Leuven Intensive Insulin Therapy Trial. This paper offers an explanation for these discordant findings, and provides a practical approach to glucose control in the ICU.

Key words: Stress hyperglycemia; Intensive care; Critical care; Glucose; Insulin

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INTRODUCTION

Stress hyperglycemia is common in critically ill and injured patients and is a component of the "fight or flight" response. Excessive counter regulatory hormones, such as glucagon, growth hormone, catecholamines, and glucocorticoids, as well as cytokines, such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α), result in increased gluconeogenesis and insulin resistance, which are the major factors leading to stress hyperglycemia. Until recently, stress hyperglycemia was considered to be a beneficial adaptive response, with raised blood glucose providing a ready source of fuel for the brain, skeletal muscle, heart and other vital organs at a time of increased metabolic demand. However, retrospective studies in patients undergoing cardiac surgery have suggested that peri-operative hyperglycemia was associated with an increased risk of post-operative infections and increased mortality[1-3]. Furthermore, these studies suggested that control of blood glucose reduced these complications. Hyperglycemia increases oxidative injury, potentiates the pro-inflammatory response, promotes clotting, causes abnormal vascular reactivity and impairs leukocyte and mononuclear cell immune responsiveness[4,5].

GLYCEMIC CONTROL IN THE INTENSIVE CARE UNIT (ICU)

In 2001, van den Berghe and coworkers published a "landmark study" (the Leuven Intensive Insulin Therapy Trial) in which they demonstrated that tight glycemic control (blood glucose between 80-110 mg/dL) using

intensive insulin therapy improved the outcome of critically ill surgical patients[6]. Following this study, tight glycemic control was rapidly adopted as the standard of care in ICUs throughout the world and was endorsed by the Institute for Health Care Improvement and other national organizations in the USA and abroad. In 2006, van den Berghe and colleagues repeated the study design in medical ICU patients[7]. Although failing to reproduce improvement in survival in the entire set of patients, this study demonstrated a reduction in morbidity in the patients randomized to the tight glycemic group with a reduction in mortality in the subset of patients with an ICU stay of three days or more. Following this study, two multicenter, randomized European studies were prematurely discontinued due to an alarmingly high rate of hypoglycemia in the "tight glycemic control" arm with no mortality benefit[8,9]. Two additional single center, randomized studies showed a trend towards a higher mortality in the in the "tight glycemic control" arm[10,11]. Recently, a large (6022 patients) multicenter, randomized controlled study (the NICE-SUGAR study[12]), was published that was unable to confirm the findings of van den Berghe *et al*[6,7]. Indeed, this study demonstrated a 2.6% absolute increase in 90-d mortality in patients randomized to tight glucose control (P = 0.02). Summary data of these five studies (excluding the van den Berghe *et al*[6,7] studies) demonstrated that intensive insulin therapy is associated with an increased risk of death with mortality being significantly lower in the control group (OR 0.89; 95% CI 0.81-0.99, P = 0.04).

The explanation for the disparate findings between the van den Berghe *et al*[6,7] studies and subsequent studies probably lies with the high rate of use of parenteral nutrition (TPN) in the van den Berghe *et al*[6,7] studies. In both van den Berghe *et al*[6,7] studies, 87% of the calories were provided *via* the intravenous route[13]. TPN is associated with severe hyperglycemia. It would therefore appear counter intuitive to administer large amount of intravenous glucose to patients with stress hyperglycemia; this will only compound the degree of hyperglycemia. Van der Voort and colleagues have demonstrated that the ICU and hospital mortality of critically ill patients was independently related to the mean amount of infused glucose[14]. In a retrospective analysis of 111 hospitalized patients receiving TPN, Cheung and coworkers reported that hyperglycemia was independently associated with an increased risk of cardiac complications, sepsis, acute renal failure and death[15]. In this study, the mortality of subjects with blood glucose in the highest quartile was 10.9 times that of subjects in the lowest quartile. These data suggest that TPN may have increased mortality in the control arm of the van den Berghe *et al*[13] studies; and this may have accounted for the apparent benefit from tight glycemic control in those treated with insulin to achieve a blood glucose of between 80-110 mg/dL. Indeed, a mortality of 8% (control arm) in predominantly elective cardiac surgery patients (with a median APACHE Ⅱ score of 9), appears rather high.

Tight glycemic control in ICU patients is not benign and this may account for the higher mortality in the intensive insulin group in the NICE-SUGAR study. The "harm" of tight glycemic control may be due to the high rate of both absolute (blood glucose < 40 mg/dL) and relative hypoglycemia (blood glucose 40-80 mg/dL) in these patients[7]. Glucose is the sole source of energy for the brain with demand increasing during stress. Using cerebral microdialysis in patients following severe brain injury, Oddo and colleagues demonstrated that tight glycemic control is associated with a greater risk of brain energy crisis and death[16]. It would therefore appear that in critically ill patients, hyperglycemia (especially that induced by TPN) is not desired, but that "low" blood glucose is even less desired.

The results of the NICE-SUGAR study, as well as the additional four randomized controlled studies that have attempted to replicate the van den Berghe *et al*[6,7] studies, clearly demonstrate that tight glycemic control (70-110 mg/dL) has a limited role in the management of general ICU patients. However, the role of tight glycemic control in patients undergoing cardiac surgery remains unclear. In these patients, it is likely that both pre- and post-operative optimization of blood glucose may improve outcome, however, the optimal blood glucose target is unknown (probably between 100-140 mg/dL). In all other ICU patients, it appears reasonable to maintain the blood glucose concentration between 140-200 mg/dL. The optimal method for achieving this goal is unclear, however, a number of options are available. In the control arm of the NICE-SUGAR study, an insulin infusion was administered if the blood glucose level exceeded 180 mg/dL, insulin administration was subsequently reduced and then discontinued if the blood glucose level dropped below 144 mg/dL. In our practice, we avoid parenteral nutrition as there is no data suggesting this mode of nutritional support has any advantages over enteral nutrition[17,18]. Furthermore, we use an enteral formula with a high concentration of lipids (omega-3 fatty acids) and we avoided overfeeding[19]. Mesejo and colleagues demonstrated that ICU patients fed a "diabetic" tube feed had better glucose control than those fed a standard enteral formula[20]. In those patients whose blood glucose remained greater than 180 mg/dL, we used a twice daily regimen of intermediate acting insulin together with insulin amounts on a sliding scale to keep the blood glucose less than 180 mg/dL. We limited the NPH-intermediate insulin to a maximum of 20 units in 12 h. If this approach did not adequately control blood glucose (< 200 mg/dL), we then switched to an insulin infusion. Although the use of sliding scales for insulin administration in hospitalized patients (who are eating) is considered a"relic from the past" (and reactive rather than proactive) this approach does have some utility in ICU patients who are receiving continuous tube feeds[21]. Further, although the absorption of subcutaneous insulin may be impaired in the critically ill, absorption may be adequate for the control of blood glucose.

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