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Review

In search of the perfect glucose concentration for hospitalized patients: A brief review of the meta-analyses

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ABSTRACT

In hospitalized patients, the optimal target blood glucose concentration is controversial. Numerous studies have examined clinical use of glucose control in various patient populations. In the present review, we briefly discuss corresponding meta-analyses. We electronically searched MEDLINE, EMBASE and CINAHL for meta-analyses relevant to the subject. Fifteen meta-analyses were identified that analyzed effects of a targeted glucose control. Twelve meta-analyses examined studies performed in critically ill patients. Included studies in this review varied in terms of the type of nutritional support, the efficacy of glucose control, the kind of glucose measurement, clinical end points (hospital or intensive care unit mortality, or 28-, 90- or 180-d mortality, or mortality 30 d after discharge), and the intensity of glucose control (moderate, tight, very tight). Four meta-analyses also including studies with a less stringent glucose control (glucose target <200 mg/dL) showed a beneficial effect on mortality. This effect disappeared when analyzing studies with a tighter glucose control (glucose target <150 mg/dL or <110/120 mg/dL, n = 5), with a very tight glucose control (glucose target <110/120 mg/dL, n = 2), or with a more precise definition of clinical endpoints (28-d mortality, n = 2). Eight meta-analyses showed that, despite the intensity of glucose control, the frequency of hypoglycemic episodes increased. The residual heterogeneity of individual studies incorporated into the various meta-analyses prevents a valid conclusion regarding potential benefits of a specific glucose target. A glucose concentration <200 mg/dL appears preferable.

Introduction

Hyperglycemia has been defined by the World Health Organization as blood glucose levels >7.0 mmol/L (126 mg/dL) when fasting, or blood glucose levels >11.0 mmol/L (200 mg/dL) 2 h after meals. Acutely, hyperglycemia can lead to serious conditions, including ketoacidosis (mostly in people with type 1 diabetes) and hyperglycemic hyperosmolar nonketotic syndrome (HHNS) in people with type 2 diabetes or in people at risk for type 2 diabetes. HHNS can lead to dehydration, potentially resulting in coma, seizures, and even death. Prolonged hyperglycemia in diabetes may increase the risk for infections, impair wound healing and vision, and may cause nerve damage. After injury or in infection, optimal glucose levels are usually different from levels intended or defined for otherwise normal individuals such as those with obesity or type 2 diabetes mellitus. There is ongoing debate on what should be the target blood glucose concentration in specific patient populations to avoid secondary complications in acute diseases. In the past, numerous studies evaluated the clinical benefits of a moderate (glucose target <200 mg/dL), tight (glucose target <150 mg/dL), or very tight (glucose target <110/120 mg/dL) glucose control. The very first study that addressed this issue with 1600 critically ill patients (studied mainly after cardiac surgery) from Leuven/Belgium (Leuven I study), showed that a very tight glucose control (target glucose concentration between 80 and 110 mg/dL) was superior to a conventional glucose control (target glucose concentration between 80 and 180–200 mg/dL) in terms of 28-d mortality and morbidity [1].

There are four reasons that this study rapidly became subject to severe criticism:

1. The study was terminated early because of an unexpectedly strong therapeutic effect (increasing the risk for false-positive results).
2. The magnitude, by which a lowering of morning blood glucose concentration by about 50 mg/dL improved mortality,

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has no biological explanation and has not yet been observed with any other therapeutic measure in critically ill patients.
3. Mortality of the control group was way above that of comparable cohorts treated in other tertiary hospitals.
4. Immediately after ICU admission, all postoperative patients received a daily amount of 200 g to 300 g parenteral glucose, or were fed parenterally (a concept that is not in line with modern therapeutic standards).

Subsequently, numerous other controlled studies were performed trying to reproduce the results of this initial monocentric study. When summarizing these studies, it is striking that only those follow-up studies, which had been executed in the same institution (Leuven II + III) on medical or pediatric patients, were able to reproduce benefits of a very tight glucose control [2,3].

Meta-analyses examining mortality in critically ill patients

To this date, 11 meta-analyses examined controlled studies that had searched for benefits (improved mortality) of a targeted glucose control in critically ill patients [4–14] (Table 1). Fou meta-analyses by Pittas et al., Pittas et al., Haga et al., and Gandhi et al. [4–7] showed that a moderate or very tight blood glucose control in the intervention group (glucose concentration <200 mg/dL or <110 mg/dL) was associated with a lower mortality. However, because the numbers of included patients were small or even very small [4], these studies bear a high risk for false-positive results. Furthermore, two of these meta-analyses [4,5] also included studies examining the use of an intraoperative insulin therapy in cardiac surgery patients (so-called glucose–insulin–potassium therapy), and do not allow safe conclusions concerning glucose control outside the operation room. Additionally, the meta-analysis by Gandhi et al. [5] suffers from inconsistent results (mortality improved although morbidity was unchanged), and from the fact that elimination of the Leuven I study [1] from the analysis also abolished beneficial effects of glucose control. Dominance of the Leuven I study also hampers interpretation of the meta-analyses by Pittas et al. [6,7].

Friedrich et al., Wiener et al., Griesdale et al., Kansagara et al., Zafar et al., and Marik et al. published other meta-analyses [8–13] that allow, due to their larger patient numbers or stricter selection criteria, a somewhat more reliable conclusion. The analyses by Friedrich et al., Wiener et al., Griesdale et al., Zafar et al., and Kansagara et al. [8–10,12,13] were unable to demonstrate that a tight or very tight blood glucose control in the intervention group (glucose concentration <150 mg/dL or <110 mg/dL) improved mortality or had a protective effect on long-term neurologic outcome after brain injury [13]. Simultaneously, however, the frequency of hypoglycemia increased. Nevertheless, intensive insulin therapy reduced the frequency of septicemia [9] and infections [13], and reduced mortality in a patient subgroup (critically ill surgical patients) according to Griesdale et al.'s analysis [10].

The latter meta-analyses also are subject to severe criticism [15–17]. In contrast to the Leuven I study [1], the meta-analyses by Friedrich et al. [12], Kansagara et al. [8], Wiener et al. [9], Griesdale et al. [10], and Zafar et al. [13] combined studies using variable target blood glucose levels in the intervention group (glucose concentration <150 mg/dL or <110 mg/dL). Additionally, the analyses by Friedrich et al. [12], Wiener et al. [9] Griesdale et al. [10], and Zafar et al. [13] examined studies with a variable clinical end point (28-, 90-, or 180-d mortality, or ICU or hospital mortality), which was not identical with that of the Leuven I study (28-d mortality) [1]. The latter critique was addressed by the meta-analysis of Kansagara et al. [8], who only included data from studies using 28-d mortality as end point, and by the meta-analysis of Shan et al. [14], who only analyzed data from studies using 120 mg/dL as target blood glucose level in critically ill neurologic patients. Nevertheless, intensive insulin therapy did not improve outcome.

Marik et al.'s meta-analysis [11] attempted to circumvent both points of criticism by an even more rigid study selection. However, even the exclusive analysis of data from studies using 28-d mortality as end point, and 110 mg/dL as target blood glucose level, did not reveal beneficial effects of intensive insulin therapy. The likelihood to survive, however, was increased in patients mainly receiving parenteral nutrition.

Even the latter meta-analysis (which combined data from studies closely imitating the design of the original Leuven I study), did not remain without critique. In the analysis by Marik et al. [11], more than 50% of the patients were retrieved from one single study (NICE-SUGAR [Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation], [18]) which, consequently, had a major effect on the quality of the results. The NICE-SUGAR study, however, is subject to intense criticism [16]. Table 2 presents the most important differences between the NICE-SUGAR and the Leuven I study [1]. A major criticism arises from the fact that the NICE-SUGAR study was clearly less efficient in terms of percentage of patients having had glucose concentrations in the target range. Furthermore, in NICE-SUGAR, a very tight blood glucose control may have been associated with a greater number of negative side effects (because of undetected variations of potassium concentration), and blood glucose measurement was based on less reliable laboratory methods (point-of-care measurements). Additionally, in the NICE-SUGAR study, initial nutritional support was possibly inadequate, and patients in the control group already had some kind of intensive insulin therapy to keep glucose concentration below 180 mg/dL.

It was argued that these limitations might have obscured a potentially beneficial effect of a very tight glucose control (glucose concentrations between 80 and 108 mg/dL) in the NICE-SUGAR study [18]. It should be noted, however, that these confounding mechanisms must have been quite strong if they were to interfere with beneficial insulin effects because in NICE-SUGAR, 90-d mortality of the intervention group (glucose concentrations between 80 and 108 mg/dL) was significantly greater than that of control patients (glucose concentrations between 80 and 180 mg/dL).

Other meta-analyses

Beyond the meta-analyses described here, four meta-analyses by Bellolio et al. [19], Murad et al. [20], Kao et al. [21], and Thomas et al. [22] were identified. These examined insulin effects on morbidity (disability, dependence, final neurologic deficit) or mortality in acute ischemic stroke [19], effects of glycemic control on morbidity (myocardial infarction, stroke) or mortality in non-critically ill hospitalized patients [20], effects of perioperative glycemic control on the rate of surgical site infection [21], or effects of a tight glucose control on the incidence of acute kidney injury in critically ill patients [22]. Except for one analysis [22], all results were negative. The value of these analyses, however, is very limited because authors also included studies without a specific glucose target [19] or purely observational studies [20,22], or because heterogeneity in the patient population, perioperative period, glycemic target, route of insulin administration, and definition of outcome measures prevented a reliable conclusion [21]. Furthermore, interpretation of