



Evidence-Based Medicine Journal Club

EBM Journal Club Section Editor: Eric B. Milbrandt, MD, MPH

Journal club critique

Intensive insulin therapy in the medical ICU — not so sweet?

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Published online: 10th August 2007

This article is online at <http://ccforum.com/content/11/4/311>

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Critical Care 2007, 11: 311 (DOI 10.1186/cc5953)

Expanded Abstract

Citation

Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: Intensive insulin therapy in the medical ICU. *N.Engl.J.Med* 2006; 354: 449-61 [1].

Background

Intensive insulin therapy reduces morbidity and mortality in patients in surgical intensive care units (ICUs), but its role in patients in medical ICUs is unknown.

Methods

Objective: To investigate the efficacy of intensive insulin therapy in medical ICU patients.

Design: Prospective, randomized, controlled trial

Setting: Medical ICU in Leuven, Belgium.

Subjects: 1200 medical ICU patients anticipated to need intensive care for at least three days.

Intervention: On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) with the use of insulin infusion or to conventional therapy (insulin administered when the blood glucose level exceeded 215 mg per deciliter [12 mmol per liter], with the infusion tapered when the level fell below 180 mg per deciliter [10 mmol per liter]).

Measurements and main results: There was a history of diabetes in 16.9 percent of the patients. In the intention-to-treat analysis of 1200 patients, intensive insulin therapy 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, $P=0.33$). However, morbidity was significantly reduced by the prevention of newly acquired kidney injury,

accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. Although length of stay in the ICU could not be predicted on admission, among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy. In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent ($P=0.009$) and morbidity was also reduced.

Conclusion

Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy. Further studies are needed to confirm these preliminary data. (ClinicalTrials.gov number, NCT00115479).

Commentary

In 2001, Van den Berghe and colleagues published a seminal trial, which demonstrated that tight glycaemic control (blood glucose concentration between 80-110 mg/dL) resulted in absolute reductions in ICU and hospital mortality of 3.4% and 3.7%, respectively, for surgical ICU patients [2]. The results of this trial led to the integration of tight glycaemic control, also known as intensive insulin therapy (IIT), into various practice guidelines and quality of care indices. The results of this trial also prompted this obvious question: would implementation of the same protocol also improve outcome for medical ICU patients?

The current study by Van den Berghe and colleagues begins to address this question [1]. The authors randomized 1200 medical ICU patients to strict normalization of blood glucose levels (80 to 110 mg/dL) with the use of insulin infusion or to conventional therapy with a more liberal blood glucose target (180-200 mg/dL). The groups were equally

balanced with respect to age, sex, comorbid conditions, reasons for admissions and history of diabetes. The results of the study were surprising; there was no mortality benefit for IIT and there was a significantly greater occurrence of hypoglycemia in the IIT group (18.7% vs. 3.1%, $p < 0.001$). Those with hepatic or renal failure appeared to be at greatest risk of hypoglycemia. Countering these disappointing findings were improvements in several important secondary outcomes with IIT, including reductions in newly acquired kidney injury, earlier weaning from mechanical ventilation, and reduced ICU and hospital length of stay.

The study has several strengths including a randomized controlled design and an intention-to-treat analysis. Limitations include its unblinded nature and its single-center design. In the subgroup of patients who were in the ICU for fewer than three days, IIT appeared to result in a *higher* mortality rate (26.8% vs. 18.8%). The significance of this finding varied depending on the authors' statistical analysis; a Chi square test demonstrated a borderline statistically significant result ($p = 0.05$), whereas both uncorrected and corrected proportional hazards analyses were insignificant ($p = 0.35$ and $p = 0.41$, respectively). Notably, the subgroup with ICU stays of three or more days had significantly *lower* hospital mortality with IIT (43.0% vs. 52.5%, $p = 0.009$), although this group could not be reliably identified at study entry. As always, one must be cognizant of the dangers of subgroup analyses [3].

The results of this study differ significantly from those of the surgical ICU study [2]. Although it is tempting to compare the two trials, there are several differences between the study populations, most notably the severity of illness, which was much higher in the medical ICU study. There may be other reasons to account for the divergent results, including treatment differences between the two populations due to secular changes in intensive care practices, such as the use of steroids for relative adrenal insufficiency; the role of hyperglycemia in post-surgical infections; and the percentage of patients with hypoglycemia. In the current study, the authors identified hypoglycemia as an independent risk factor for death, though it did not appear to be directly responsible for the excess of deaths observed with IIT in those with ICU stays of less than three days. However, it remains plausible that the short-term benefits of IIT may be outweighed by the risks, death or otherwise, that hypoglycemia confers.

Two large ICU-based IIT trials, both of which were stopped early for lack of efficacy and safety concerns, highlight the issue of hypoglycemia with IIT. The German VISEP (Volume Substitution and Insulin Therapy in Severe Sepsis) study, a multicenter trial designed to examine the effects of colloid versus crystalloid volume resuscitation and an intensive insulin therapy regimen, was stopped after recruiting 488 out of a planned 600 subjects because of frequent hypoglycemia in the IIT arm (12.1% vs. 2.1%, $p < 0.001$) and no difference in mortality [4]. Similarly, the

GLUCONTROL (Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients) study, a multicenter, international study of IIT in mixed ICU populations, was stopped after recruiting 1101 of the planned 3500 subjects [5]. In this study, severe hypoglycemia (defined as blood glucose < 40 mg/dL) occurred more frequently in IIT subjects (8.6% vs. 2.4%, $p < 0.001$). Furthermore, there were no differences in mortality (17% vs. 15%, $p = \text{NS}$) or length of stay.

One additional trial of IIT in the ICU is ongoing. NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) is a multicenter, international study evaluating glucose management at two different levels (81-108 mg/dL vs. 144-180 mg/dL) in a heterogeneous group of critically ill patients in the ICU for at least one day [6]. The primary outcome is 90-day mortality. As of early 2007, 3000 of a planned 6100 subjects were enrolled. In August 2006, the study's Data and Safety Monitoring Board reviewed the interim results of the first 2000 patients, determining that the study should continue and that there was no reason for the interim analysis to be unblinded [7]. An additional interim analysis will be conducted when follow-up of 4000 patients is available, estimated to be mid-2007.

Recommendation

The best available evidence suggests that IIT may be an important treatment modality in certain critically ill patient populations, such as those who have undergone cardiac surgery [8] or other operative procedures [2]. We have reservations, however, in applying these same protocols to heterogeneous medical ICU populations given the negative results of this and other trials and the attendant risks of prolonged, unrecognized hypoglycemia. Clearly, real-time glucose monitoring systems have the potential to reduce this risk, but none are clinically available at this time. While awaiting the results of NICE-SUGAR, clinicians should carefully consider the potential risks and benefits when implementing IIT in medical ICU patients and may well be advised to avoid this treatment modality in those with hepatic or renal failure.

Competing interests

The authors declare no competing interests.

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