

## Commentary

# Is it time for implementation of tight glycaemia control by intensive insulin therapy in every ICU?

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Published: 21 March 2006

This article is online at <http://ccforum.com/content/10/2/130>

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*Critical Care* 2006, **10**:130 (doi:10.1186/cc4871)

## Abstract

The second study on tight glycaemia control by intensive insulin therapy (IIT) confirmed in medical intensive care unit patients the decrease in hospital mortality reported by the same team in the first IIT trial in surgical patients. However, methodological concerns, the high rate of hypoglycaemia in spite of the infusion of large doses of parenteral glucose and the frequent use of steroids presently preclude considering these results as recommendations in other intensive care units, but rather argue for the need for large-scale assessment of the IIT approach by multi-centre studies to confirm the efficacy and safety of this therapeutic modality.

In a recent issue of the *New England Journal of Medicine*, Greet Van den Berghe and co-workers [1] published a confirmation of the life-saving effects of tight glycaemia control by intensive insulin therapy (IIT) in medical intensive care unit (ICU) patients. This second study intended to answer some of the questions and criticisms raised by the landmark Leuven study of 2001, which reported a 4% decrease in mortality in a surgical ICU population [2-7]. Hopefully, these questions will be answered by the multi-centre assessments of the effects of IIT, the NICE-SUGAR and GLUCONTROL trials, currently underway in Australia and Europe, respectively [8]. Before the completion of these two indispensable studies, Greet Van den Berghe and colleagues wanted to confirm the life-saving effects of IIT in medical ICU patients in order to answer specific criticisms related to the type of patients, mostly surgical with two-thirds being post-cardiac surgery patients, in the first Leuven study [2]. Indeed, patients with myocardial ischaemia could particularly benefit from a combination of a high amount of glucose and insulin, as reviewed recently [9]. Interestingly, Krinsley [10] reported a similar reduction in mortality in a mixed population of medical and surgical ICU patients.

Greet Van den Berghe and colleagues succeeded but, as in most major contributions, their study raised more questions, which further argue for the importance of multi-centre trials

[3,7]. Our concerns regarding the second Leuven study [1] follow.

Strictly speaking, this study cannot be considered to be positive, as the long-stayers in whom a survival benefit was found were actually not randomised. The sample of long-stayer patients ( $n = 767$ ) was smaller than the calculated sample size of 1,200 patients that was required to test the working hypothesis (a 7% reduction of the absolute risk of death) with an alpha level of less than 0.05 and a beta level of 0.2. In the entire set of patients, the intent-to-treat analysis indicated that there was actually no benefit related to IIT. Moreover, mortality in the patients in whom the stay was shorter than anticipated (less than 3 days) was higher in the IIT group (26.8%; 56/209) than in the conventional treatment group (18.8%; 42/224). This increase was found to be significant when analysed by the chi square test, but not by uncorrected proportional-hazards analysis, even after correcting for the difference in baseline risk factors.

Compared to the first Leuven study [2], some of the recorded secondary end points that could be considered as surrogate markers of severity (ICU and 28-day mortality, requirement for dialysis, incidence of bacteraemia, requirement for prolonged antibiotic therapy, incidence of hyperbilirubinaemia and 'hyperinflammation') were not influenced as hospital mortality was.

As already underlined [7], the mortality rate of the medical patients was high. Other local factors could also have influenced the results, thereby questioning the applicability of the findings to patients managed in other ICUs. The mean amount of parenteral glucose infused (a mean of more than 220 g/day in long-stayers) was probably higher than in most other ICUs, and parenteral steroids were used in more than half of the patients. Unequivocally, these two factors reduce the risk of hypoglycaemia and the duration of episodes of hypoglycaemia, a major side effect of IIT. Nonetheless, the

ICU = intensive care unit; IIT = intensive insulin therapy.

risk of hypoglycaemia was substantial, with 25.1% of the patients in the IIT group experiencing a blood glucose level below 2.2 mmol/l (40 mg/dl) at least once, compared to only 3.9% in the conventional group. The safety monitoring board of the German multi-centre study VISEP considered a similar increase in the incidence of hypoglycaemia important enough to stop this trial [11]. The mortality among these patients was higher than in the entire set. Clearly, the safety of IIT needs to be assessed in patients with significant risk of hypoglycaemia [12].

The target ranges of glycaemia were 4.4 to 6.1 mmol/l (80 to 110 mg/dl) and 10 to 11 mmol/l (180 to 200 mg/dl), implying that there was no assessment of an intermediary blood glucose value, which is often used [13]. Greet Van den Berghe and colleagues already answered this question by analysing the data of the first study and concluded that there was a dose-response effect, with the largest improvement found in patients with the lowest blood glucose level [14]. This hypothesis was found retrospectively, however, and clearly requires confirmation from prospective trials.

The use of IIT in Leuven is probably easier than in other institutions with a lower nurse-to-patient ratio. For an IIT approach, the accuracy of capillary samples from some of the patients is also questionable [15].

Lastly, insulin exerts many effects other than a decrease in blood glucose [16], which could possibly be beneficial or deleterious in different subsets of patients; these effects can not easily be assessed and monitored in the presently available trials.

In summary, questions about the efficiency and safety of IIT in different ICUs around the world are far from answered and much work has still to be done to answer the new questions raised by the second Leuven study.

## Competing interests

The authors declare that they have no competing interests.

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