

# Severe hypoglycemia during intensive insulin therapy

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**Background:** Tight glycemic control reduces mortality in surgical intensive care patients and in long-term medical intensive care patients. A large study on intensive insulin therapy was prematurely discontinued due to safety issues. As the safety of intensive insulin therapy has been questioned, we screened all patients during a 17-month period to reveal the incidence of hypoglycemia and its effects on the outcome of the patients.

**Methods:** All patients treated between February 2005 and June 2006 in two intensive care units (ICUs) of a tertiary care teaching hospital were included in the study. A nurse-driven intensive insulin therapy with a target blood glucose level of 4–6 mmol/l had been introduced earlier. The patients were divided into two groups according to the presence of severe hypoglycemia ( $\leq 2.2$  mmol/l).

**Results:** One thousand two hundred and twenty-four patients (1124 treatment periods) were included. During the study period, 61,203 blood glucose measurements were

performed, 2.6% of which were below and 52.6% above the target range. Severe hypoglycemia (glucose  $\leq 2.2$  mmol/l) occurred in 25 patients (36 measurements). The incidence was 0.06% of the measurements and 2.3% of the patients. The median age, sex, Acute Physiology And Chronic Health Evaluation II, Simplified Acute Physiology Score II, diagnosis category, ICU or hospital length of stay did not differ between the groups. The hospital mortalities were 25% and 15% in patients with or without severe hypoglycemia, respectively ( $P = 0.16$ ).

**Conclusion:** Severe hypoglycemia during intensive insulin therapy is rare in clinical practice compared with previous clinical trials.

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TIGHT glycemic control has been shown to reduce mortality in surgical intensive care patients and in long-term medical intensive care patients.<sup>1,2</sup> In these studies, the incidence of severe hypoglycemia (defined as glucose  $\leq 2.2$  mmol/l) in the intensive treatment group was 5.1% and 18.7%. Recently, a large study on intensive insulin therapy was prematurely discontinued due to safety issues. The incidence of hypoglycemia was 17.0% in the intensive treatment group and the mortality among patients experiencing hypoglycemia was 18.6%.<sup>3</sup> As the safety of intensive insulin therapy has been of major concern, we screened all patients during a 17-month period to reveal the incidence of hypoglycemia in critically ill patients. The secondary aim was to evaluate the effect of severe hypoglycemia on the outcome of the patients.

## Methods

A retrospective study was performed in two closed ICUs of a tertiary care teaching hospital (one 8-bed general and one 10-bed surgical ICU). All patients

treated between 7 February 2005 and 30 June 2006 were included in the study. If a patient was readmitted or if the patient was transferred from one ICU to the other, this was considered as two treatment periods. The data were collected from the clinical data management system (Critical Care Manager, Picis, Wakefield, MA) and from the quality database (Intensium<sup>®</sup> Benchmarking database, Intensium Ltd, Kuopio, Finland).

Intensive insulin therapy with a target blood glucose level of 4.4–6.1 mmol/l had been introduced in 2002 in the surgical ICU with a written protocol and in 2003 in the mixed ICU without a written protocol for adjustments (carried out by the nurse). After the implementation of the clinical data management system in 2004, the blood glucose target of 4–6 mmol/l was automatically generated for each patient. If blood glucose was above the limit, the nurses could initiate insulin infusion without consulting the attending physician.

The blood glucose was determined in parallel with each arterial blood gas measurement. The

samples were analyzed by ABL800 Flex (Radiometer Ltd, Copenhagen, Denmark) in the general ICU and by ABL700 in the surgical ICU, and the results were automatically transferred to the hospital laboratory database and the clinical data management system. All blood glucose measurements performed during the ICU stay were collected for analysis. The patients were divided into two groups according to the lowest detected blood glucose value (lowest blood glucose  $\leq 2.2$  mmol/l or  $\geq 2.3$  mmol/l). In addition, the area under time–concentration curve AUC of severe hypoglycemia was calculated by using the linear trapezoidal rule. A  $P$ -value  $< 0.05$  was considered statistically significant.

Data are expressed as number (percentage) or median (interquartile range, IQR). Statistical differences between groups were compared by the Mann–Whitney  $U$  test, two-tailed Fisher’s exact test and Pearson’s  $\chi^2$  test as appropriate. Forward stepwise logistic regression analysis was used to find independent risk factors for mortality. All statistical analyses were performed by SPSS 13.0 for Windows (SPSS Inc, Chicago, IL).

## Results

During the study period, a total of 1054 patients were treated in the two ICUs. Thirty patients were excluded due to missing data. In the remaining 1024 patients, 1124 treatment periods were included in the study. Patient characteristics are presented in Table 1.

During these treatment periods, a total of 61,203 blood glucose measurements were performed; the average time between measurements was 2 h. Of all blood glucose measurements, 44.9% were within the target range. Hypoglycemia (glucose  $< 4.0$  mmol/l) was present in 1578 measurements (2.6%). Severe hypoglycemia (glucose  $\leq 2.2$  mmol/l) was present in 36 measurements in 25 patients. Hypoglycemia values ranged from 1.3 to 2.2 mmol/l. The incidence of severe hypoglycemia was 0.06% of the measurements and 2.3% of the patients.

The glucose measurements were above the target range (glucose  $\geq 6.1$  mmol/l) in 52.6% of the

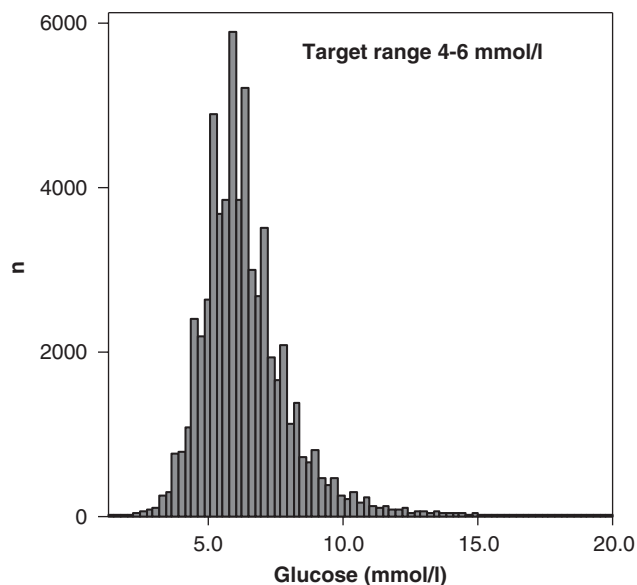


Fig. 1. Distribution of glucose measurements ( $n = 61,203$ ).

Table 1

Patient characteristics.	Hypoglycemia (glucose $\leq 2.2$ mmol/l) ( $n = 25$ )	No hypoglycemia ( $n = 1099$ )	$P$ -value
Age (median, range)	59 (23–87)	61 (16–96)	0.80
Male/female	16/9	761/338	0.58
APACHE II*	19 (15–24)	18 (12–22)	0.26
Operative/non-operative	12/13	657/442	0.24
Emergency/elective	22/3	838/261	0.23†
Diagnosis category $n$ (%)			0.16†
Cardiovascular	5 (20)	404 (36.7)	
Respiratory	7 (28)	167 (15.2)	
Gastrointestinal	9 (36)	379 (34.5)	
Renal and metabolic diseases	2 (8)	48 (4.4)	
Other	2 (8)	101 (9.1)	
Use of steroids ( $n$ )	28% (7)	13% (146)	
ICU length of stay (days)*	4.3 (1.8–10.6)	2.7 (1.2–5.7)	0.06
Hospital length of stay (days)*	18 (8.5–39.5)	13 (7–23)	0.08
ICU mortality ( $n$ )	12.0% (3)	7.8% (86)	0.44†
Hospital mortality ( $n$ )	24.0% (6)	14.7% (162)	0.16

\*Median (interquartile range).

†Fisher’s test.

APACHE II, Acute Physiology And Chronic Health Evaluation; ICU, intensive care unit.

measurements. Hyperglycemia (defined as glucose  $>8.3$  mmol/l) was present in 10% of the measurements. The distribution of measurements is shown in Fig. 1.

The ICU and hospital length of stays as well as ICU and hospital mortalities are presented in (Table 1). Age, sex, APACHE (Acute Physiology And Chronic Health Evaluation) II, diagnosis type or category did not differ between the groups.

In logistic regression analysis including age, sex and APACHE II as covariates, the presence of hypoglycemia or the AUC of hypoglycemia were not associated with death as independent risk factors.

## Discussion

In our study, the rate of severe hypoglycemia was relatively low even though intensive insulin therapy with a blood glucose target below 6.1 mmol/l was used. However, the success of the intensive insulin therapy was not optimal because only 44.9% of the blood glucose measurements were in the target range and 52.6% of the measurements were above the target.

Intensive insulin therapy was shown to reduce mortality and morbidity in a surgical ICU, but these effects were not confirmed in the following large trial in medical intensive care patients. In a subgroup analysis, though, mortality benefit was seen in patients treated longer than 3 days in the ICU.<sup>1,2</sup> The high incidence of hypoglycemia may override the potential beneficial effects of intensive insulin therapy. In the studies by Van den Berghe and colleagues, the proportion of patients experiencing severe hypoglycemia in the intensive treatment group was 5.1% in surgical, and 18.7% in medical patients, whereas in the conventionally treated group the incidences were 0.8% and 3.1%, respectively. A recent study in septic shock patients was prematurely discontinued, due to the high incidence of hypoglycemia in the intensive treatment group.<sup>3</sup> The incidence of hypoglycemic episodes in this study was similar to that in the second study by Van den Berghe and colleagues, and the same insulin titration protocol was used in both studies. In the recent literature, the fear of hypoglycemia has become an obstacle to implementation of intensive insulin therapy. Smaller studies have shown, however, that intensive insulin treatment can be carried out safely using special insulin titration protocols, resulting in an incidence of hypoglycemia of  $<1\%$ .<sup>4,5</sup> The total

number of patients exposed to intensive insulin therapy in these studies is considerably lower (179 and 70, respectively) than that in the studies by Van den Berghe and colleagues (765 and 595 patients). Recently, a retrospective study was presented in which severe hypoglycemia was present in 102 of the 5365 patients (1.9%).<sup>6</sup> All of these patients were not, however, treated with intensive insulin therapy. A large prospective randomized multicenter study comparing tight glucose control with higher glucose target values (Nice Sugar) is ongoing.<sup>7</sup> When completed, it will probably be of major guidance in determining the benefits of tight glucose control.

In our study, surgical patients represented 60% of the study population. In the Van den Berghe study,<sup>1</sup> 62% of the patients were cardiac surgery patients and at least 82% of the study population were surgical patients. This explains the relatively low APACHE II score of 9.<sup>1</sup> However, as there is a separate ICU for cardiac surgery patients in our hospital, only occasional cardiac surgery patients are admitted to the mixed ICU. In the Van den Berghe<sup>2</sup> study and Visep,<sup>3</sup> the mean APACHE II scores were 23 and 20, respectively, in patients receiving intensive insulin therapy. The study population in the Van den Berghe<sup>2</sup> study included medical ICU patients and only patients with severe sepsis were recruited in Visep. The APACHE II scores in our study population are considerably higher than those in the Van den Berghe 2001 study, but because of inclusion of patients with scheduled high-risk surgery (e.g. abdominal aortic reconstruction and esophageal resections), the median APACHE II score in our population is lower than that of medical ICU patients or patients with severe sepsis. The lower APACHE II score reflects lower ICU and hospital mortalities than in the Van den Berghe<sup>2</sup> and Visep studies.

Several predisposing factors for hypoglycemia have been identified by Vriesendorp et al.<sup>8</sup> in a heterogeneous group of critically ill patients. In the future, awareness of these factors may help to reduce the risk induced by the intensive insulin treatment. In another study, the rate of hypoglycemia could be reduced when improvements were made to the insulin infusion protocol.<sup>5</sup> These changes included decreasing the insulin infusion rate when nutrition or renal replacement therapy was discontinued, changing bolus dosing and increasing the frequency of blood sampling. The frequency of sampling has been infrequently reported in the prior literature. The low incidence

of severe hypoglycemia in our patients may, in part, be due to the relatively frequent sampling of blood glucose. The frequency of blood glucose monitoring is suggested to correlate inversely with the frequency and magnitude of severe hypoglycemia.<sup>9</sup> In surgical patients, a change from a physician-driven management of blood glucose treatment to a nurse-driven insulin infusion protocol with a target glucose range of 6.6–8.3 or 4.4–6.1 mmol/l led to more rapid and more effective glucose control. The incidence of severe hypoglycemia (<2.2 mmol/l) ranged from 1.1% to 3.4%.<sup>10</sup> Of importance is that five of six of hypoglycemias occurred when a nurse failed to comply with the protocol.<sup>10</sup> Our findings also support the view that nurses can safely manage insulin infusions with a low risk of severe hypoglycemia.

The success of a given protocol is not only dependent on the incidence of hypoglycemias but also how often the target range of glucose level is achieved. It is clear that if glucose values are often above the upper limit of the targeted range, the incidence of hypoglycemia is probably relatively low, but then the beneficial effects of glycemic control may be lost. However, the proportion of glucose values within the target range is often not reported in previous clinical studies. In the literature, obtaining the target range of strict glucose control varies from 22% to 53%.<sup>4,11</sup> In another study, when a complex intensive insulin protocol was evaluated, in 53% of the patient-days the protocol was followed and in 24% of the patient-days there were major deviations from the protocol.<sup>10</sup> Computerized assistance was proposed to overcome the complexity of the protocol.<sup>10</sup> In our ICUs, the goal of strict glucose control was generated for every patient by the data management system and, accordingly, the use of intensive insulin therapy was expected to be high. The adherence to the tight glucose control was estimated by measuring the proportion of glucose values in the target range. The somewhat low success rate to achieve tight glucose control in clinical practice is similar to that in prior clinical trials. Recently, failure to achieve glycemic control with intensive insulin therapy in medical ICU patients was identified as an independent risk factor for ICU mortality.<sup>12</sup>

With decreasing blood glucose values, not only the degree of hypoglycemia is harmful but also the duration of hypoglycemia should probably be noted.<sup>9</sup> Accordingly, we calculated the AUC of hypoglycemia in our patients. AUC is commonly used in pharmacokinetic studies when estimating the exposure of an individual to a drug. It has also

been used to test the importance of hypotensive episodes to outcome in critically ill patients.<sup>13</sup> In our study, the AUC of hypoglycemia was not an independent risk factor for mortality. A possible explanation for this could be the low number of hypoglycemic patients. In addition, many of the patients experiencing hypoglycemia had only one short episode of hypoglycemia.

Mortality was not increased significantly in patients with severe hypoglycemia, nor did the presence of severe hypoglycemia or its AUC predict mortality in our patients. In several studies, hypoglycemia as well as variability in blood glucose concentration have been associated with increased mortality in ICU patients.<sup>2,6,14–16</sup> In the study by Krinsley and Groever,<sup>6</sup> the presence of severe hypoglycemia increased the risk of death to more than twofold. A smaller case-control study in the ICU failed to demonstrate the relationship between incidental hypoglycemia and mortality.<sup>17</sup> In type 1 diabetics, no decline in cognitive function has been shown despite relatively high rates of recurrent severe hypoglycemia.<sup>18</sup>

Although the data for this study were collected online, the retrospective nature of this study is a limitation. The intensive insulin treatment, however, had been introduced before the study period and, accordingly, the personnel were familiar with the concept. Even though the intensive insulin therapy was intended to be used in all patients, the adherence to the treatment could not be verified afterwards. Because of the large number of patients, the bias is likely to be small. Secondly, for precise evaluation of the association between a rare event (as hypoglycemia) and the mortality, our sample size exceeding 1000 patients is still inadequate. Therefore, it should be noted that this evaluation was not the primary aim of this study.

We conclude that severe hypoglycemia during intensive insulin therapy is quite rare in clinical practice compared with previous trials. Therefore, the possibility of hypoglycemia should not limit the standardized use of intensive insulin therapy, if the benefits of the tight glycemic control can be confirmed in future trials.

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