Intensive Care Med (2004) 30:1685–1688
DOI 10.1007/s00134-004-2325-2

BRIEF REPORT

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Hyperglycaemia and mortality in critically ill patients

A prospective study

Received: 10 June 2003
Accepted: 22 April 2004
Published online: 18 May 2004

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Abstract *Objective:* To describe hyperglycaemia as a possible marker of morbidity and mortality in critically ill medical and surgical patients admitted to a multidisciplinary ICU. *Design:* Prospective cohort study. *Setting:* A 13-bed non-cardiac multidisciplinary ICU in a university hospital. *Patients and participants:* Adult patients consecutively admitted to the ICU in a 6-month period. Patients with fewer than 2 days' stay in the ICU and patients with known diabetes were excluded. *Measurements and results:* At admission a registration form was filled in including demographic data, first and second day APACHE II scores, infections and daily maximum blood glucose level. In surgical patients, high maximum blood glucose level during the stay in ICU was correlated with increased mortality, morbidity and frequency of infection. In medical patients, we found a non-significant trend towards a correlation between hyperglycaemia and morbidity and mortality, respectively. *Conclusions:* High blood glucose level during the stay in ICU was a marker of increased morbidity and mortality in critically ill surgical patients. In medical patients the same trend was found, but non-significant. The population of patients in the present study are heterogeneous and the results from surgical critically ill patients should not be generalised to medical patients.

Keywords Critical illness · Hyperglycaemia · Intensive care unit · Morbidity · Mortality

Introduction

Stress-induced hyperglycaemia in critically ill patients is common, even in patients without a history of diabetes [1, 2]. Hyperglycaemia increases the risk of nosocomial infections in diabetic patients undergoing cardiac surgery [3]. By decreasing the blood glucose level to 11.1 mmol/l using insulin infusion, Furnary et al. [3] observed a significant reduction in the incidence of deep sternum wound infection in diabetic patients submitted to cardiac surgery. Umpierrez et al. [4] found that non-diabetic patients admitted with stress-induced hyperglycaemia (blood glucose level above 11.1 mmol/l) had a higher in-hospital and in-ICU mortality, increased length of hospital stay and higher admission rate to the ICU than normoglycaemic patients.

In a randomised clinical trial Van den Berghe et al. found lowered mortality and morbidity in surgical patients treated with intensive insulin therapy [5]. Sixty-three percent of the patients were admitted to the ICU following cardiac surgery and in these patients a well-defined endocrine-metabolic stress response was described consisting of hyperglycaemia and insulin resistance.

In this prospective study, blood glucose levels in surgical and medical patients admitted to a multidisciplinary ICU were recorded. We studied the role of hyperglycaemia as an indicator for morbidity and mortality.

Materials and methods

This prospective cohort study was conducted in a 13-bed non-cardiac multidisciplinary ICU. The study was approved by the regional scientific ethics committee. Adult patients (age $\geq$18 years) admitted to the ICU in a 6-month period were enrolled. Patients with a stay of fewer than 2 days in the ICU were excluded as well as patients with known diabetes mellitus.

Registration on admission included age, sex, body-mass index, reason for admission and history of diabetes. Daily records included maximum blood glucose level during the preceding 24 h. Blood glucose measurements were routinely obtained when analysing arterial blood samples on the ABL 700 (Radiometer Medical A/S, Copenhagen, Denmark). The APACHE II score [6] was performed on the first and second day after admission. Together with a modified total maximum SOFA score [7, 8], the APACHE II score was used to describe morbidity. The registration form was completed on discharge or death, including the recording of infections and insulin treatment. Primary infection was defined as infections within the first 4 days in ICU, while infections later in the stay were secondary infections. A modified first day and total maximum SOFA score (without CNS evaluation) were obtained retrospectively for each patient. Patients were treated according to a conventional insulin protocol, i.e. blood glucose levels exceeding 12 mmol/l were treated with insulin.

Concerning statistical analysis, the data were described with medians and inter-quartile ranges. They were statistically analysed using STATA version 8.0 (Stata, Texas, USA). To describe possible correlations, Spearman's ρ was used as a test of independency between high blood glucose level and mortality, morbidity and infections, respectively. The time course of hyperglycaemia in relation to secondary infections was described with the difference between the first day maximum blood glucose level and the day of total maximum blood glucose level using the Mann-Whitney test. Probability values of 0.05 or less were considered statistically significant.

Results

Altogether 135 patients were included in the study period after 11 patients with a history of diabetes had been excluded. The populations were heterogeneous both between and within the groups of medical and surgical patients (Table 1). The majority of the surgical patients had undergone upper abdominal surgery. No patients with head injury or stroke were included.

In the surgical patients, increased blood glucose level was correlated with increased mortality (Fig. 1a), increased severity of illness on first day (APACHE II score) (Fig. 1b) and maximum organ failure (modified total maximum SOFA score) ($p<0.01$). A non-significant trend towards a correlation was found in medical patients. In surgical patients, high blood glucose level was correlated with increased numbers of primary and secondary infections ($p<0.05$).

Primary infections were common in medical patients, while secondary infections were common in surgical patients (Table 1). Pulmonary infection was the predominant focus in medical patients, while a more heterogeneous distribution was seen in surgical patients. In surgical patients, the median first day maximum blood glucose level was 9.2 mmol/l in patients who became sec-

Table 1 Characteristics of the patients

		Reasons for admission	
	All patients	Surgical[a]	Medical[b]
	(*n*=135)	(*n*=97)	(*n*=38)
Male sex, *n* (%)	74 (55)	56 (58)	18 (47)
Age (years)[c]	58 (46–69)	58 (41–67)	63 (51–75)
Body-mass index	24.2 (21.5–27.5)	24.3 (21.5–27.1)	24.2 (21.5–27.7)
APACHE II score			
First day[c]	16 (12–23)	15 (10–20)	21 (17–26)
Second day[c]	13 (9–19)	12 (8–17)	16.5 (11–21)
Maximum blood glucose, *n* (%)			
>6.1 mmol/l	135 (100)	97 (100)	38 (100)
>11.1 mmol/l	73 (54.1)	48 (49.5)	25 (65.8)
>11.1 mmol/l more than once	56 (41.5)	34 (35.1)	22 (57.9)
Maximum blood glucose level[c]	11.35 (9.45–14.3)	11.15 (9.3–14)	13.7 (9.9–16.8)
Duration of hyperglycaemia (%)[c,d]	7.7 (0–50)	1.9 (0–25)	25.1 (0–63.6)
Insulin dose (IU/day)[c,e]	8.3 (0.9–22.7)	5.3 (0.6–20.6)	10.8 (7.6–22.7)
Primary infection, *n* (%)	63 (47.7)	37 (39.4)	26 (68.4)
Secondary infection, *n* (%)	29 (21.8)	25 (26.0)	4 (10.8)
Duration of intensive care (days)[c]	5 (3–13)	5 (3–13)	5 (2–13)
Death during intensive care, *n* (%)	20 (14.8)	14 (14.4)	6 (15.8)

n number of patients

[a] After acute surgery (*n*=18), after elective surgery (*n*=27), trauma (*n*=27), surgical complications (*n*=21) and gastrointestinal bleeding without operation (*n*=4)

[b] Pneumonia (*n*=12), other pulmonary diseases (*n*=7), liver disease (*n*=7), poisoning (*n*=2), cardiac disease (*n*=1), neurology (*n*=4, none with stroke or neurotrauma) and others (*n*=5)

[c] Median (interquartile range)

[d] Percent of days in ICU with maximum blood glucose >11.1 mmol/l

[e] In patients treated with insulin

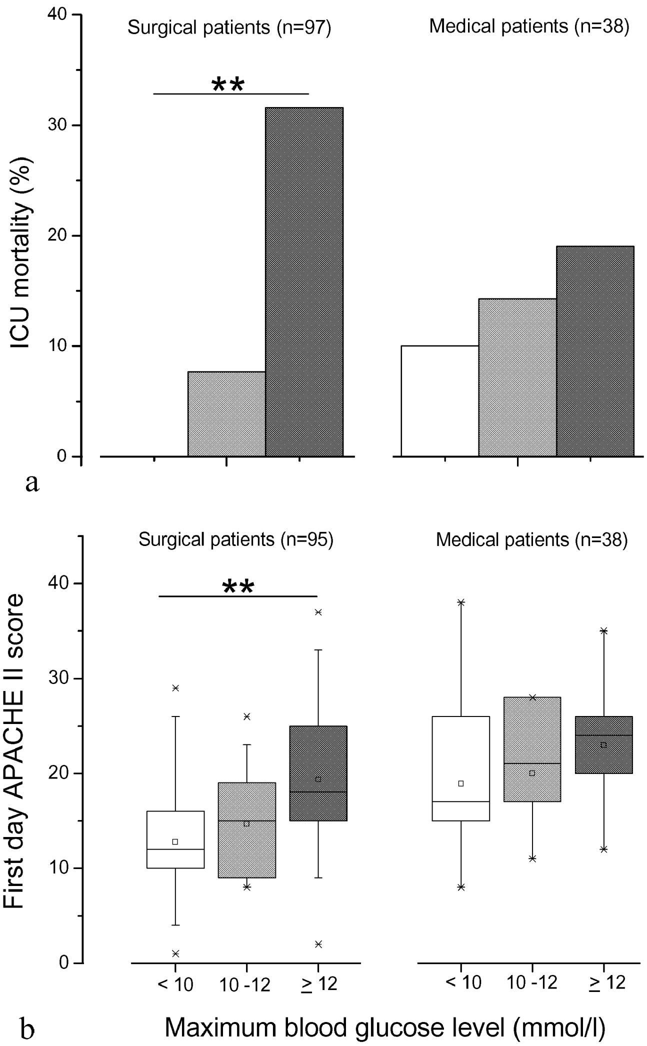

Fig. 1 The correlation between **a** maximum blood glucose level and mortality and **b** severity of illness by first day APACHE II score, respectively. Stratified on reason for admission. Boxes indicate 25th, 50th and 75th percentiles, whiskers indicate 5th and 95th percentiles while 1st and 99th percentile are indicated by crosses. $^{**}p<0.01$ (test of trend)

ondarily infected and 9.4 mmol/l in those who did not ($p=0.74$). In medical patients, secondarily infected patients had a median first day maximum blood glucose level of 11.2 mmol/l compared to 9.55 mmol/l in those who did not become infected ($p=0.21$).

Patients who became secondarily infected had their median day of maximum blood glucose level later than those who did not have secondary infections. In surgical patients with secondary infections, the median day of maximum blood glucose level was 8 days after admission compared to 1 day after admission in patients who have no secondary infections ($p<0.001$). Medical patients with secondary infections had maximum blood glucose level median 13.5 days after admission compared to 1 day after admission in patients without any secondary infections ($p<0.001$).

Discussion

We found that high blood glucose level was a marker of increased morbidity and mortality in non-cardiac critically ill surgical patients. These results are in accordance with the retrospective study by Umpierrez et al. [4], who observed a correlation between hyperglycaemia and mortality in the overall population of patients admitted to hospital. Other studies have shown that hyperglycaemia in non-diabetic patients with acute stroke [9, 10] and in patients with severe burn trauma was associated with a worse prognosis [11]. Our results are also in accordance with studies showing that stress-induced hyperglycaemia after myocardial infarction is associated with an increased risk of in-hospital mortality in patients both with and without diabetes mellitus [12, 13].

While other studies have included well-defined populations, such as patients with stroke or acute myocardial infarction, the population in the present study included other types of patients which were much more diverse. The mortality in the two groups was alike, but the APACHE II scores were different. The medical patients were older than the surgical patients and age may therefore have contributed to a higher mean APACHE II score. In general, the medical patients were at the height of the severity of their disease when admitted to the ICU. No interventions were performed to stabilise their condition. This may be reflected in the high mean APACHE II score at admission. The surgical patients, on the other hand, often came from the operation theatre where they had been stabilised during anaesthesia and surgery. This may have contributed to the lower mean APACHE II score during the first 24 h in the ICU.

We observed a significant correlation between hyperglycaemia and organ dysfunction. The impaired organ function may explain the association between hyperglycaemia and mortality. In surgical patients, a significant association between hyperglycaemia and infections was found. This is in accordance with findings in diabetic, as well as non-diabetic, patients [3, 5]. The increased mortality and increased risk of postoperative infections associated with stress hyperglycaemia might be explained by the detrimental effects of increased blood glucose levels on the immune system [14].

A post hoc analysis of the temporal relationship between hyperglycaemia and secondary infections was made. No difference in first day maximum blood glucose level was found in patients who later became secondarily infected compared to those who did not. High maximum blood glucose level did not precede secondary infections in our study and further studies are needed to reveal whether hyperglycaemia is a mediator of morbidity or only a marker, as shown in the present study. However, this type of post hoc analysis should be performed with caution and further studies are needed to clarify this issue.

So far, the study by van den Berghe et al. [5] is the only study of critically ill patients randomised to a strict glycaemic control or conventional therapy. Our patients, admitted to a multidisciplinary ICU, were more severely ill than those of Van den Berghe, as estimated by a much higher APACHE II score. It has been discussed whether the effect of glucose-insulin-potassium infusion to patients with acute myocardial infarction and the strict glycaemic control by insulin therapy in critically ill patients [5] could be explained by a beneficial effect of insulin per se. Insulin not only lowers the blood glucose concentration, it also exerts a number of strong anti-inflammatory effects.

In medical patients, only a trend towards a correlation between high blood glucose levels and morbidity and mortality was found. However, it must be emphasised that this was only a trend and no conclusions can be made because of the small number of medical patients.

Patients admitted to the multidisciplinary ICU were heterogeneous and the results from one group of patients should not be generalised to another group. A randomised clinical trial should be performed to investigate the effects of intensive insulin therapy in a well-defined group of critically ill medical patients.

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