Insulin therapy of hyperglycemia in intensive care*

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Key words: hyperglycemia, diabetes, insulin treatment, hypoglycemia, intensive care unit

Abstract

Background: Hyperglycemia is common among patients admitted to intensive care units, and carries the risk for complications and prolonged ICU stay. With intensive insulin control of blood glucose, morbidity and mortality can be reduced.

Objectives: To determine whether intensive or conventional insulin control of blood glucose in hyperglycemic ICU patients correlated with the prognosis.

Methods: Following admission to the ICU, hyperglycemic patients were randomly assigned to a group treated intensively with insulin targeting glucose at 110–140 mg/dl, or to a conventional insulin therapy group, where glucose, upon exceeding 200 mg/dl, was controlled at 140–200 mg/dl. Rates of morbidity and mortality, hypoglycemic episodes, and insulin dosage were compared.

Results: In the 41 patients treated intensively with insulin the glucose level was 142 ± 14 mg/dl, as compared to 174 ± 20 mg/dl in the 48 patients on conventional insulin treatment. Both groups were similar in age, acute physiology and chronic health evaluation score. Morbidity was also similar, except for increased vascular damage in the conventional treatment group and slightly shorter ICU stay in the intensive therapy group. Both groups had similar in-ICU, in-hospital, and 28 day mortalities, and similar rates of hypoglycemic episodes. The daily dosage of insulin was significantly higher with the conventional treatment ($P = 0.004$).

Conclusions: Intensive insulin treatment did not affect the mortality or morbidity rates in ICU patients. The increased insulin dosage of conventional insulin treatment was attributable to the group's higher prevalence of diabetes. Future studies should address this bias and determine the optimal glucose target.

IMAJ 2007;9:140–142

Hyperglycemia and insulin resistance, often unrelated to a background of diabetes, are common among patients admitted to intensive care and increase upon initiation of parenteral nutrition or intravenous fluids containing dextrose. Indeed, with the growing prevalence of type 2 diabetes mellitus worldwide [1-3] and the high rates of associated secondary pathologies, such as diabetic nephropathy or peripheral vascular disease, that could result in ICU admission, there is an increasing number of hyperglycemic patients in the ICU.

It is safe to assume that control of blood glucose with insulin could improve the prognosis and decrease the morbidity and mortality among patients admitted to the ICU. Recent studies have demonstrated that control of hyperglycemia decreased mortality by 43% in the ICU and 34% in the wards, reduced morbidity such as sepsis, and shortened ICU stay [4]. The rate of infection in type 2 diabetes and hyperglycemia is also above normal, and with stress increasing glucose levels, hospitalized patients, especially those in ICUs, are even more susceptible. Thus, control of blood glucose also affects the rate of infection in the ICU.

Several recent studies have demonstrated a significant decrease in morbidity and mortality among patients in the ICU whose blood glucose was controlled at near normal values with extensive and prolonged infusion of insulin [4]. Krinsley and co-workers [5] examined 800 patients in intensive care whose glucose was controlled at 131 mg/dl under continuous insulin infusion, and found a 29% decrease in hospital mortality, reduced need for blood transfusions, decrease of 75% in renal insufficiency, and shortening of ICU stay by 10%. The conclusion of a meta-analysis of 35 randomized trials on in-hospital insulin therapy in patients with critical illness was that insulin therapy decreased short-term mortality by 15% [6]. Thus, it was concluded, "…the days of ignoring blood sugar levels or tolerating marked hyperglycemia in the ICU (which was commonplace even five years ago) are over" [7].

Conventional insulin treatment under continuous infusion aims to control glucose below 200 mg/dl, while the more recently introduced intensive therapy calls for continuous infusion of insulin to control glucose at 110–140 mg/dl, or even lower. Indeed, intensive insulin treatment could reduce the rate of mortality from sepsis and from multi-system failure also in hyperglycemic patients previously not defined as diabetic. However, attempts to control glucose at normal levels could result in hypoglycemic episodes that could jeopardize the patient.

The objectives of the present study were to compare conventional and intensive insulin therapy in hyperglycemic patients in the ICU in terms of morbidity and mortality, the rate of hypoglycemic episodes between these two groups, and the daily dosage of insulin required to achieve the targeting glucose level in patients in both groups.

Patients and Methods

The study group included patients admitted to the ICU from November 2004 through May 2005 and was conducted in the general and respiratory intensive care units of the Western Galilee Medical Center, which have a total of 10 beds and a patient load of 900 per year, 16% of whom present with abnormal glucose metabolism. The

* Presented at the 18th Israeli Medical Association World Fellowship International Conference

ICU = intensive care unit

Institutional Committee approved the study in accordance with the Helsinki Declaration.

After 24 hours in the ICU, patients were randomly assigned to one of two groups. The first group was treated intensively with continuous intravenous insulin targeting to control glucose at 110–140 mg/dl. The second group received conventional insulin therapy, whereby patients with blood glucose > 200 mg/dl received intravenous insulin to control glucose at 140–200 mg/dl. Blood glucose was determined in all ICU patients every 4 hours. All patients were treated with insulin HR (Lilly, France) or Insulin Actrapid HM® (Novo Nordisk, Denmark). The mean ICU stay was 7 days (range 3–21), and patients were followed until discharge from the hospital or for 28 days. Excluded were patients incompatible with this specific formulation of insulin, or patients who stayed in the ICU for less than 3 days.

Frequencies of qualitative variables were compared using the chi-square test or Fisher's exact test, as applicable. Quantitative variables were compared using the Student's *t*-test for independent samples or the Wilcoxon Rank Sum Test. Two-tailed probabilities were calculated and significance was set at $P < 0.05$.

Results

Table 1 depicts the demographic and clinical characteristics of the patients included in the two intervention groups. They were similar in gender, age, and APACHE score (Acute Physiology and Chronic Health Evaluation). They differed, however, in their initial blood glucose levels recorded before the hypoglycemic treatment: 204 ± 78 mg/dl in the intensive treatment group and 242 ± 99 mg/dl in the conventional treatment group. The groups also differed in the proportion of type 2 diabetes mellitus patients, 48.8% and 68.8%, respectively ($P = 0.055$); the hyperglycemia in the other patients was due to their condition at admission to the ICU.

The extent of morbidity in the two intervention groups was also similar, as detailed in Table 2. No significant differences were found in the rate of infection, including pneumonia, sepsis and peritonitis, and acute renal insufficiency or hepatic damage. Vascular damage, defined as acute cardiovascular event, cerebrovascular accident or thrombosis, was significantly higher in the conventional compared to the intensive insulin treatment group (12.2% versus 39.6%, $P = 0.004$).

The two groups also did not differ in the duration of ICU stay, but the proportion of patients staying more than 6 days was 56.3% in the conventional compared to 29.3% in the intensive insulin treatment group ($P = 0.011$). Mortality in the ICU and later in other wards was also similar in the two study groups [Table 2].

ICU patients require careful monitoring of their glucose values because it fluctuates with the state of infection, type of feeding, and caloric intake. Indeed, the amount of insulin required to control glucose at the target value was highly variable, and is presented as the mean daily dose. In the intensive insulin therapy group, this value was 38 ± 29 IU per patient (range 6.5–142.0) while in the conventional insulin group the mean daily dose of insulin was significantly higher, 52 ± 30 IU per patient (range 13.3–143.0), $P = 0.004$. The respective mean glucose levels that were reached with the interventions were 142 ± 14 mg/dl and 174 ± 20 mg/dl ($P < 0.001$). A significant difference in the insulin daily dosage was found between patients with type 2 diabetes and those without ($P = 0.029$).

Table 1. Demographic and clinical details of the study group

	Intensive insulin group (n=41)	Conventional insulin group (n=48)	*P*
Gender female	19 (46.3%)	24 (50%)	NS
Age (yrs) (mean ± SD)	71.86 ± 14.07	74.21 ± 12.74	NS
Median (range)	73 (35–90)	77 (36–95)	
APACHE score	22.3 ± 4.2	21.9 ± 4.4	NS
Type 2 diabetes	20 (48.8%)	33 (68.8%)	NS
Initial glucose (mg/dl) (mean ± SD)*	204.66 ± 78.28	242.68 ± 99.61	0.05
Median (range)	180 (81–460)	230 (73–434)	

* Values at 8 a.m. on day 1.
NS = not significant

Table 2. Morbidity and mortality in the study group

	Intensive insulin group (n=41)	Conventional insulin group (n=48)	*P*
Infection	30 (73.2%)	38 (79.2%)	NS
Pneumonia	24 (58.55%)	28 (58.3%)	NS
Sepsis	11 (26.8%)	17 (35.4%)	NS
Peritonitis	2 (4.9%)	2 (4.2%)	NS
Renal damage	22 (53.6%)	31 (64.6%)	NS
Vascular damage	5 (12.2%)	19 (39.6%)	0.004
Hepatic dysfunction	16 (39.0%)	21 (43.8)	NS
Mortality in ICU	16 (39.0%)	16 (31.3%)	NS
Mortality in wards	6 (14.6%)	6 (12.5%)	NS
28 day survival	19 (46.4%)	26 (54.2%)	NS
ICU stay (days) (mean ± SD)	7 ± 4.9	8 ± 4.85	

Table 3. Insulin treatment in the ICU, daily values

	Intensive insulin group (n=41)	Conventional insulin group (n=48)	*P*
Glucose (mg/dl) (mean ± SD)	141.96 ± 14.3	174.43 ± 19.56	<0.001
Median (range)	140.1 (109.1–170.8)	172.9 (139.8–220.2)	
Insulin (IU) (mean ± SD)	38.34 ± 29.07	52.57 ± 30.84	0.004
Median (range)	32.3 (6.5–142.0)	43.29 (13.33–143.0)	

Hypoglycemia is well recognized in diabetic patients controlled with hypoglycemic medications or insulin, especially those who are hemodynamically unstable, have infection or renal dysfunction. However, the number of such episodes in the intensive insulin therapy group was 23 (0.56 per patient), identical to the number of episodes in the conventional treatment group (0.48 episodes per patient).

Discussion

Most of the patients in the ICU are in severe or critical condition following trauma, infection or major surgery, in particular those remaining in the ICU for more than 5 days. They usually require respiratory support, parenteral nutrition and infusion of various drugs including vasopressors. Hyperglycemia and insulin resistance are very common among such patients, the result of acute endocrine response in the first days of admission even without a history of diabetes

[8]. Inflammatory cytokines and other mediators, such as cortisol, catecholamines or glucagon, mediate the hyperglycemia. Furthermore, overproduction of hepatic glycogen induces insulin resistance in peripheral tissues, which is characterized by alterations in the insulin signaling pathways.

Hyperglycemia is also accompanied by various infections, primarily pulmonary and systemic, resulting in high mortality, and this is especially critical in patients receiving intensive care. Therefore, the control of hyperglycemia in the ICU is extremely important. Indeed, previous research established the optimal target value of blood glucose in ICU patients at approximately 200 mg/dl, but recently the recommended values have been set between 80 and 110 mg/dl [4].

Intensive insulin treatment increases the uptake of glucose in muscles, including the myocardium, and this increased uptake reduces blood glucose more effectively than the inhibition of hepatic gluconeogenesis or glycolysis [8]. On the other hand, in other cells and tissues, primarily hepatocytes, neurons, renal tubules, or immunocytes, glucose is taken up passively and insulin is not required. These cells are therefore very susceptible to the toxic effects of hyperglycemia, and the detrimental effects are manifested in disturbances of the respiratory chain and exacerbated oxidative stress. This could explain why the positive effects exerted by intensive insulin treatment on morbidity and mortality are more related to the mean blood glucose level during the treatment and not directly to the dosage of insulin, as blood glucose reflects the metabolic state [9]. Insulin also improves the functionality of macrophages, which might explain its anti-inflammatory capacity [8,10].

In this study we examined the two methods of controlling blood glucose in intensive care patients and compared the response of hyperglycemic ICU patients. Our two study groups were very similar in morbidity and mortality, with the exception of vascular damage. Similar observations were reported in other studies, and it was suggested that the effect of blood glucose on endothelial cell function is even larger than that of the daily dosage of insulin [8,11]. Both mean blood glucose and insulin dosage were increased in the conventional treatment group, which had a higher rate of vascular morbidity, but also more patients with type 2 diabetes were associated with extensive vascular pathology. Indeed, the significantly higher daily dosage of insulin in the conventional treatment group could be attributed to this group's higher initial blood glucose level, probably due to the higher proportion of diabetic patients and the associated insulin resistance and toxicity of hyperglycemia. Because of this, it is important that in future studies such patients are distributed equally among the study groups.

Hypoglycemia is a known complication of sepsis, or cardiac, hepatic or renal insufficiency or hypoglycemic therapy. It is the result of decreased hepatic gluconeogenesis; reduced insulin renal clearance; increased glucose uptake in muscles, spleen and small intestine; and deficient nutrition [1]. Often, the early clinical signs of hypoglycemia are not recognized in ICU patients treated with insulin because of the severe condition of the patient and the masking by therapeutic measures such as anesthesia, sedation, or vasopression. Therefore, the monitoring of blood glucose every 4 hours, and every hour in unstable patients, is extremely important, as is the infusion of fluids and dextrose [12]. Recent reports have demonstrated that hypoglycemic episodes are frequent among patients receiving intensive insulin therapy targeting blood glucose level to the range of 80–110 mg/dl [4]. When the target was set at 130 mg/dl, no significant increase in hypoglycemic episodes occurred [5]. In our study, the frequency of hypoglycemic episodes was similar in the two treatment groups regardless of their different mean blood glucose, probably because the target was well above the normoglycemia level (80–110 mg/dl).

In conclusion, similar to published observations, intensive insulin treatment controlling blood glucose at 141 mg/dl does not affect mortality or morbidity of patients in intensive care, except for a slight reduction in ICU stay. Other studies that targeted intensive insulin therapy at normoglycemia noted reduced morbidity with this therapy, but not lower mortality, compared to the conventional insulin control [13]. We agree with Malhotra [7] that exogenous insulin should be provided to achieve target glucose values below 150 mg/dl, at least during the first 3 days, and only after that, reaching normoglycemia might be considered in ICU patients.

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