

ROLE OF INTRAVENOUS INSULIN THERAPY IN CRITICALLY ILL PATIENTS

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ABSTRACT

Objective: To summarize the novel evidence for maintaining normoglycemia with intensive insulin therapy during intensive care in critically ill patients, with or without diabetes, in the surgical intensive-care unit.

Results: Although the association between hyperglycemia and adverse outcomes of trauma or surgical procedures necessitating intensive care was known, only one intervention study has investigated the causality of this association. This study showed that tight blood glucose control with insulin, aiming for strict normoglycemia (80 to 110 mg/dL or 4.5 to 6.1 mmol/L) during intensive care, dramatically decreased morbidity and mortality. The clinical benefits were present whether or not patients had previously diagnosed diabetes, and they seemed independent of severity and type of critical illness. Multivariate logistic regression analysis indicated that metabolic control, rather than insulin dose per se, statistically explains the beneficial effects of intensive insulin therapy on outcomes of critical illness. Other metabolic effects besides blood glucose control, however, such as normalization of dyslipidemia, and immunologic effects, such as suppression of excessive inflammation and improvement of macrophage function, accompany glycemic control in critically ill patients. These effects seem to surpass the level of glycemic control in explaining the clinical benefits of intensive insulin therapy on sepsis, organ failure, and death. Ongoing studies are attempting to clarify the mechanisms that underlie the beneficial effects of this simple and cost-saving intervention.

Conclusion: The available evidence favors targeting normoglycemia (blood glucose levels of less than 110 mg/dL or 6.1 mmol/L) by insulin infusion in all adult surgical intensive-care patients. Whether these findings are applicable to nonsurgical intensive-care or to pediatric patients in the intensive care unit remains unclear. (Endocr Pract. 2004;10[Suppl 2]:17-20)

Abbreviations:

HDL = high-density lipoprotein; **ICU** = intensive-care unit; **IGFBP-1** = insulin-like growth factor-binding protein-1; **LDL** = low-density lipoprotein

INTRODUCTION

Unlike the diagnostic criteria for diabetes mellitus, no clear guidelines have been established for defining hyperglycemia in a critically ill patient. Consequently, wide variations exist in the reported prevalence of stress-induced hyperglycemia during critical illness, ranging from 3 to 71%. Stress-induced hyperglycemia is caused mainly by insulin resistance in the liver, skeletal muscle, and heart. Clinicians commonly accepted that a moderate level of hyperglycemia (blood glucose levels up to 220 mg/dL or 12 mmol/L) in critically ill patients was beneficial for organs such as the brain and the blood cells that rely solely on glucose for their energy supply and that do not require insulin for glucose uptake. Thus, until recently, blood glucose levels up to 220 mg/dL (12 mmol/L) in fed, critically ill patients were considered acceptable. Above this threshold, osmotic diuresis and fluid shifts occur, a situation that necessitates glycemic control with insulin. More pronounced hyperglycemia at hospital admission has been associated with a higher risk of adverse outcomes in patients after acute myocardial infarction, stroke, or burn injury. Besides hyperglycemia, a high serum concentration of insulin-like growth factor-binding protein-1 (IGFBP-1), in the setting of relatively low circulating insulin levels, also seemed to predict mortality in prolonged critically ill patients (1). This observation led to the hypothesis that hyperglycemia in critically ill patients may reflect lack of insulin effect in the liver, which may, in turn, contribute to adverse outcomes. Together with the risk associated with hyperglycemia, the rationale was thus generated for an intervention study that targeted normoglycemia with use of exogenous insulin infusion in critically ill patients.

RESULTS OF THE INTERVENTION STUDY

Recently, the opinion that stress-induced hyperglycemia is beneficial in critically ill patients in the

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intensive-care unit (ICU) was challenged by a large, prospective, randomized, controlled clinical trial, which studied the effects of strict glycemic control on mortality and morbidity in these patients (2). A total of 1,548 mechanically ventilated patients, who were admitted to the ICU predominantly after extensive or complicated surgical procedures or trauma, were enrolled in the study and randomly classified into two groups. In the intensive insulin therapy group, blood glucose levels were strictly maintained between 80 and 110 mg/dL (4.5 and 6.1 mmol/L) by exogenous insulin infusion; in contrast, in the conventional treatment group, insulin was administered only if blood glucose levels exceeded 220 mg/dL (12 mmol/L). Strict maintenance of normoglycemia by intensive insulin therapy notably reduced intensive care and hospital mortality in critically ill patients (Fig. 1), particularly in the population of patients with prolonged critical illness in whom mortality was reduced from 20.2% to 10.6% ($P = 0.005$). Post hoc analysis indicated a higher mortality even in patients with only moderate hyperglycemia (blood glucose levels of 110 to 150 mg/dL [6.1 to 8.3 mmol/L]) in the conventional treatment group, in comparison with the patients receiving the intensive insulin therapy and having blood glucose levels of less than 110 mg/dL (6.1 mmol/L) (3-7). The outcome benefit was present whether or not the patient had previously diagnosed diabetes mellitus. Furthermore, the reduced

relative risk of death was detectable in the various stratified subgroups of surgical indications for intensive care. Intensive insulin therapy also improved several morbidity-related factors, such as the need for prolonged ventilatory support, the duration of intensive-care stay, and the number of blood transfusions. In addition, lower incidences of bloodstream infections, excessive inflammation, and, even more strikingly, acute renal failure and critical illness polyneuropathy were observed.

In a subgroup of patients who received intensive care after brain operations for trauma, intracranial lesions, or hemorrhage, intensive insulin therapy also reduced the intracranial pressure, the risk of diabetes insipidus, and the occurrence of seizures. In addition, intensive insulin therapy improved the level of long-term rehabilitation, with a significantly larger number of patients being able to care for themselves 12 months after dismissal from the hospital (G Van den Berghe, unpublished observations, 2003).

Intensive insulin therapy was associated with an increased risk of hypoglycemia (from 0.8% to 5.2%). With the algorithm used, however, these episodes of hypoglycemia were always rapidly diagnosed and treated and, thus, caused no detectable serious adverse events nor permanent damage. Limiting the risk of hypoglycemia is of utmost importance; this necessitates certain precautions, including the following: (1) point-of-care measurement of blood glucose in order to shorten the delay between mea-

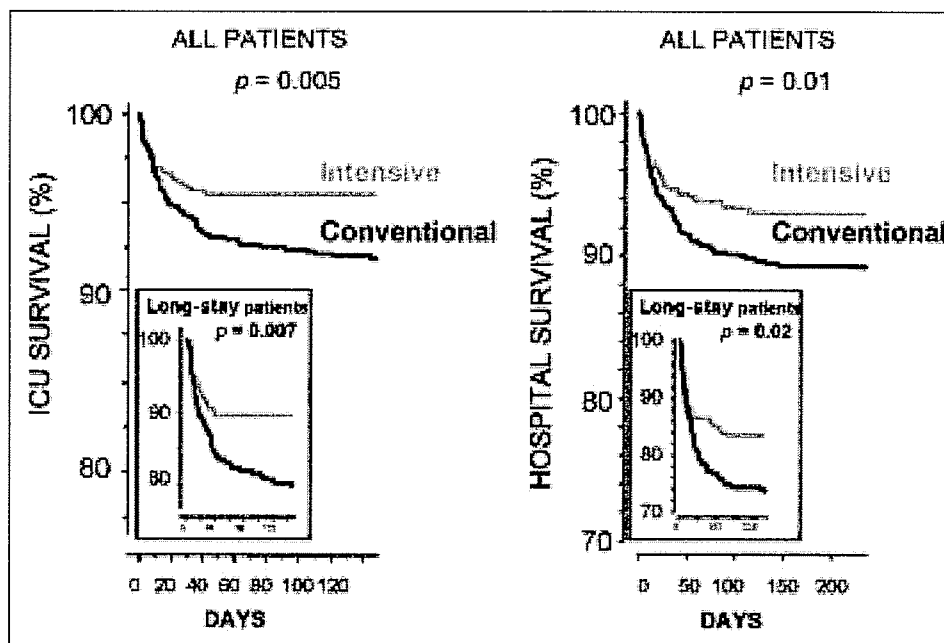


Fig. 1. Kaplan-Meier cumulative survival plots for intensive care and in-hospital survival, showing the effect of intensive insulin treatment in a study of 1,548 critically ill patients and in the 451 patients with a stay in the intensive-care unit (ICU) of more than 5 days (long-stay patients). Patients dismissed alive from the ICU (left panel) and the hospital (right panel), respectively, were considered survivors. P values were obtained by log-rank (Cox-Mantel) significance testing. The difference between the intensive insulin group and the conventional group was significant for intensive-care survival (unadjusted $P = 0.005$; adjusted $P < 0.04$) and for hospital survival (unadjusted $P = 0.01$).

surement and adjustment of insulin infusion; (2) use of a method for blood glucose measurement that is accurate, particularly in the low range; and (3) adequate training of the nursing and medical staff. Furthermore, the risk of hypoglycemia raises the important question of whether extremely tight blood glucose control is crucial. In other words, are the clinical benefits of intensive insulin therapy due to the glycemic control or to the extra insulin that was given, irrespective of glycemic control? Multivariate logistic regression analysis of the effect on mortality in intensive-care patients, correcting for all preexisting risk factors and entering both the insulin dose and the blood glucose level into the model, revealed that both were positive risk factors: a 12% (confidence interval, 4% to 18%) higher risk of death for every 20 U of insulin administered per day ($P = 0.005$) and a 75% (confidence interval, 45% to 205%) higher risk of death for every 50 mg/dL higher level of blood glucose ($P < 0.0001$). Indeed, there appeared to be no cutoff level for blood glucose below which there was no further risk reduction of ICU and hospital mortality as well as of most of the morbidity outcome measures. This finding indicated that it is important to titrate the insulin infusion to achieve the tightest possible blood glucose control (7).

Hyperglycemia in critically ill patients is known to be caused by (1) gluconeogenesis that is not suppressible by glucose availability and (2) a reduced glucose uptake in skeletal muscle. Therefore, the following question may be posed: Which of these pathways is most affected by intensive insulin therapy in order to achieve strict blood glucose control during critical illness? In contrast to otherwise healthy patients with diabetes, the liver in critically ill patients appeared totally resistant to the effects of insulin for all the classic insulin-regulated pathways of glucose control, including phosphoenolpyruvate carboxykinase, glucokinase, and *IGFBP1* gene expression, the last factor confirmed by the absence of a suppressive effect on the elevated circulating levels of the IGFBP-1 protein (8). In contrast, in skeletal muscle, gene expression of *GLUT4* and hexokinase-II was increased significantly by intensive insulin therapy; this result suggests that uptake of glucose in the muscle is likely to explain (to a large extent) the insulin-induced lowering of the circulating glucose levels in critically ill patients.

The metabolic disturbances of critically ill patients also include dyslipidemia, with high circulating levels of triglycerides and low circulating levels of high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol. The relationship between risk of death and triglycerides is linear, whereas the link between mortality and low HDL and LDL cholesterol is dichotomous, with a cutoff level of less than 20 mg/dL for LDL and less than 15 mg/dL for HDL, below which the risk of mortality increases steeply. Together with the control of blood glucose in critically ill patients, this dyslipidemia was favorably affected by intensive insulin therapy. Indeed, intensive insulin therapy almost completely prevented the increase in triglyceride level and significantly reduced the

risk of having LDL and HDL cholesterol concentrations below the dangerous cutoff levels by about 40% (9).

Excessive inflammation, as reflected by high levels of C-reactive protein and mannose-binding lectin, is also present in critical illness. Excessive inflammation from trauma or sepsis is presumed to contribute substantially to the pathogenesis of multiple organ failure. Tight blood glucose control with intensive insulin therapy was accompanied by an important suppression of both these markers of inflammation (10).

In an effort to understand which of the described effects of intensive insulin therapy is responsible for the outcome benefit of this intervention, multivariate logistic regression analysis was performed, with correction of the effect of intensive insulin therapy for the preexisting risk factors and for insulin dose and blood glucose control. Adding C-reactive protein levels to the model made the effects of glycemic control and insulin dose disappear. Moreover, addition of the effects on lipid metabolism isolated a lowered LDL and HDL cholesterol below the dangerous cutoff levels as the only independent factors statistically explaining the benefit of the intervention on mortality and rendered the insulin dose and the blood glucose levels insignificant. This statistical analysis suggests that the other metabolic effects of intensive insulin therapy titrated to normoglycemia that accompany this level of control may be involved as mediators. Furthermore, this analysis also indicates that the risk apparently associated with a high dose of insulin is simply explained by a higher degree of insulin resistance in the patients who are most ill. When metabolic control is achieved with this treatment and brought into the equation, this association between insulin dose and mortality disappears. This finding negates the interpretation by certain authors (11) that insulin would have deleterious effects in critically ill patients.

In an animal model of prolonged critical illness, we also observed that maintaining normoglycemia with intensive insulin therapy ameliorates immune function by increasing the phagocytosis capacity of monocytes and their ability to generate an oxidative burst (12). This improved capacity to clear bacteria is likely to have contributed to host defense in the clinical study and to explain the observed reduced risk of severe infections and lethal sepsis (2). Currently, ongoing studies are investigating the effects of intensive insulin therapy on the disturbed coagulation and fibrinolysis and the impaired endothelial function present in critically ill patients, particularly in those with sepsis.

An approximation of the financial implications of the demonstrated reduction in ICU stay with intensive insulin therapy shows the yearly cost savings to be at least \$40,000 (US dollars) per ICU bed. This figure is likely to be an underestimation of the potential cost savings with this treatment, however, because it does not take into account the reduced need for expensive treatments such as dialysis, transfusion, and antibiotics. An ongoing study is assessing the overall influence of this highly effective intervention on the health economics.

CONCLUSION

Maintaining normoglycemia with intensive insulin therapy in critically ill patients in a surgical ICU reduces morbidity and mortality in a cost-effective manner. Achieving glycemic control seems crucial, and the concomitant effects on lipid metabolism, inflammation, and immunity apparently contribute to the benefits achieved with this intervention. It remains to be shown whether the findings obtained in a predominantly surgical population of adult critically ill patients can be extrapolated to medical intensive care and to the pediatric population.

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