Beneficial effects of intensive insulin therapy in critically ill patients

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Critically ill patients in intensive care units (ICU) for more than a few days have a mortality of approximately 20% worldwide. These critically ill patients, in the absence of a previous diagnosis of diabetes, commonly exhibit stress hyperglycemia and insulin resistance [1]. Many of these critically ill patients die of multiorgan dysfunction (MOD) and sepsis. Since stress hyperglycemia has been shown to associate with impaired polymorphonuclear neutrophil function and bactericidal activity [2], the question arose whether lowering of blood glucose in critically ill patients would decrease morbidity and mortality.

To address this question the Leuven group of Van den Berghe and associates performed a prospective, randomized control study in 1548 patients admitted to their surgical ICU who were receiving mechanical ventilation [3]. The patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose between 80 and 110 mg/dl) or conventional treatment (insulin treatment only if blood glucose exceeded 215 mg/dl and then to maintain blood glucose between 180 and 200 mg/dl). At baseline, the two groups were comparable relative to age, gender, body mass index, APACHE II score and therapeutic intervention scoring system (TISS) and blood glucose. Two-thirds of the admissions to the surgical ICU were due to cardiac surgery in both groups.

The primary endpoint of the Leuven study was ICU mortality. The intensive insulin treatment group had a significantly lower ICU mortality (4.6 vs 8%, \( P = 0.04 \)). This difference in mortality was primarily observed in those 451 patients who were in the ICU longer than 5 days (10.6 vs 20.2%, \( P = 0.005 \)). Multiple organ dysfunction (MOD) with a proven septic focus was also decreased (8 vs 33 cases, \( P = 0.02 \)) in the intensive insulin group as was the percentage of patients requiring greater than 14 days of ventilatory support (7.5 vs 11.9%, \( P = 0.003 \)). Other beneficial effects of intensive insulin therapy as compared to conventional treatment are shown in Table 1.

In the total Leuven study population, the mean morning blood glucose value was 103 ± 19 mg/dl in the intensive treatment group and 153 ± 33 mg/dl in the conventional treatment group. Hypoglycemia (blood glucose less than 40 mg/dl) occurred in approximately 5% of the intensive treatment group without serious complications. Blood glucose measurements were performed every 1–4 h and the insulin dose was adjusted according to a strict algorithm by intensive care nurses supervised by a physician not involved in the study. Although the Leuven study was performed in a surgical ICU, similar results have been recently reported from a medical-surgical ICU [4].

In a posthoc analysis of the Leuven results, a linear correlation between hyperglycemia and risk for death was observed, thus suggesting a direct toxic effect of glucose [5]. Moreover, in the conventional treatment group those patients with moderate hyperglycemia (110–150 mg/dl) had a lower risk of death than those patients with a blood glucose between 150 and 200 mg/dl. The moderate hyperglycemia group in the conventional treatment arm of the study, however, had a higher risk of death than the intensive insulin treatment group who had a blood glucose less than 110 mg/dl.

In the presence of insulin resistance, glucose toxicity could be mediated by glucose overload in tissue sites in which glucose uptake is independent of insulin, including endothelial, epithelial and immune cells as well as central and peripheral nervous system and hepatocytes [6]. In that regard, of note are the observations in the Leuven study that the incidence of acute renal failure, the need for red blood cell transfusions and critical illness polyneuropathy were significantly less in the intensive insulin treatment group [3]. The beneficial effect of the decreased incidence of polyneuropathy may have been a factor in the diminished duration of mechanical ventilation in the intensive insulin treatment group. In contrast to the mitochondrial abnormalities observed in hepatocytes of the conventional treatment group, there was no morphological or functional evidence of
mitochondrial perturbations in hepatocytes of nonsurvivors in the intensive insulin treated group [7]. In the total group of 1548 patients the bilirubin concentration was also significantly lower in the intensive insulin treated group [3].

In addition to direct cellular glucose toxicity, increased generation of reactive oxygen species (ROS) and/or decreased ROS scavengers, such as superoxide dismutases (SOD) in mitochondria, mnSOD; cytoplasm, cuZnSOD and outside the cell, ecSOD during activated glycolysis and oxidative phosphorylation could contribute to the toxic effects of glucose. Specifically, with increased entry of glucose into cells more superoxide anion ($O_2^-$) is produced. This $O_2^-$ can interact with the increased nitric oxide associated with cytokine-induced nitric oxide synthase (iNOS) in critically ill, septic patients and produce peroxynitrite, a very injurious ROS. ROS can in turn lead to mitochondrial damage and further worsen the cellular oxidant injury [8].

There is also recent evidence from the Leuven study that insulin may also afford protection in critically ill patients by exerting an effect on the abnormal lipid profile observed in these patients [9]. In critically ill patients circulating triglyceride levels are increased whereas high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentrations are decreased. An analysis of 363 patients who were in the surgical ICU for longer than 7 days demonstrated that the intensive insulin treatment led to a significant decrease in serum triglycerides and increase in LDL and HDL. Multivariate logistic regression analysis indicated that this effect on the lipid profile in the intensive insulin treated group may be even more important than the decrease in blood glucose with respect to diminished morbidity and mortality in these critically ill patients [9]. The mechanism of such an effect of insulin on the lipid profile is not understood, however, lipoproteins have been shown to scavenge endotoxins [10].

Critical illness is also associated with activation of the inflammatory cascade and C-reactive protein (CRP) is increased several fold. In an analysis of 451 patients from the Leuven clinical trial who were in the ICU longer than 5 days, the CRP was significantly more decreased at all time points in those patients who were randomized to the intensive insulin treatment group [11]. Multivariate logistic regression analysis implicated the anti-inflammatory effect, as assessed by CRP, in the intensive insulin group as a factor in the beneficial effects on morbidity and mortality. The anti-inflammatory action of insulin may relate to suppression of proinflammatory substances including TNFα, macrophage migration inhibitory factor, superoxide anion, and nuclear factor-KB (NFKB) [12].

This Science Watch article for NDT was stimulated by another subanalysis study from the larger Leuven clinical trial. In this study the authors hypothesized that excessive activation of the endothelium in critically ill patients contributes to a compromised microcirculation and resultant cellular hypoxia and that intensive insulin treatment might protect the endothelium [13]. In support of this hypothesis elevated circulating levels of intercellular adhesion molecule-1 (ICAM-1) were significantly decreased in the critically ill patients randomized to intensive insulin therapy as compared to the conventional treatment group. This decrease in ICAM-1 was associated with a decrease in plasma nitric oxide (NO). In post-mortem tissue, iNOS gene expression in liver and skeletal muscle was significantly reduced in the intensive insulin therapy patients. The authors concluded that intensive insulin therapy during chronic illness decreases morbidity and mortality, at least in part, by protecting the endothelium. This protective effect may be related to the action of insulin to decrease NFKB, thereby inhibiting iNOS induced release of NO, adhesion molecules and cytokines.

Taken together, the major Leuven clinical trial and additional subanalysis studies have been seminal in demonstrating the effect of intensive insulin therapy to decrease morbidity and mortality in critically ill patients. Moreover, the potential mechanisms whereby aggressive control of blood glucose and lipid abnormalities, as well as insulin per se, mediate the protective effects against MOD acute renal failure, critical illness polyneuropathy, nosocomial bacterial infections, anaemia and death in insulin-resistant, critically ill patients afford numerous opportunities for future clinical and basic research in this important area of critical illness.

Conflict of interest statement. None declared.

References


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