

Intensive Insulin Therapy In The Critically-Ill Patients: Does Benefit Extend Beyond Normoglycemia?

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Abstract

Objective: To review studies on intensive insulin therapy in critically ill patients and understand possible mechanisms of benefit beyond glycemic control. The Ovid, Pub Med and Medline databases were searched for articles using the keywords insulin, glycemic control and critically ill.

Data Synthesis: Beyond normoglycemia, insulin therapy seems to offer additional benefit by its direct effects on the lipid metabolism, the skeletal muscles and cardiac function. The effect of insulin infusion on nitric oxide pathway is investigational. Continuous infusion of insulin improves white cell functions. The lowering of acute phase reactant C-reactive protein levels by insulin infusion in critically ill patients also suggests that it may have anti-inflammatory properties.

Conclusion: Emerging evidence shows that insulin therapy may have additional beneficial metabolic effects on lipids, vascular tone, skeletal muscles, cardiac, hematological or the immune system in critically ill patients beyond glycemic control.

INTRODUCTION

Modern critical care practice and understanding is fundamentally based on the 19th century French physiologist Claude Bernard's reasoning that body systems respond to insult or injury by maintaining the delicate homeostatic equilibrium. Further, restoration of the abnormal physiologic function determines the degree of benefit achieved. (1)

Among a variety of physiologic targets in the modern management of critically ill patients, blood glucose control has become an important goal. Recent scientific experiments have clearly shown that strict blood sugar control in the range of 80-110 mg/dl significantly improves morbidity and mortality among critically ill patients. (2) However, the mechanism of the favorable outcome has not been adequately understood.

Prevention of delay in progression to end organ damage in diabetic patients is achieved over several years of diabetic therapy. (3) Therefore, it is difficult to postulate that the immediate benefit achieved by intensive insulin therapy in critically ill patients may be solely due to glycemic control alone. To understand the mechanisms of benefit from glucose control on critical illness, we refer the reader to the

detailed review of insulin effects on glucose control and metabolism published recently (4).

The pivotal role of insulin in favorably modifying the metabolic, endocrine and immunological milieu has been the subject of research and analysis. The purpose of this paper is to shed some light on the current clinical studies and understand the level of evidence regarding the metabolic effects of insulin infusion among critically ill patients beyond glycemic control.

METHODS

We conducted a literature search in the OVID, Medline and Pub med databases during the period 1990 to 2005. Studies were identified using keywords insulin, glucose, intensive care and critically ill. The studies have been selected for their relevance to the topic, design, and validity.

REVIEW OF LITERATURE

In the landmark prospective randomized, controlled clinical trial conducted by Van den Berg et al involving adults admitted to surgical intensive care unit (ICU) who were on mechanized ventilation, intensive insulin therapy reduced overall in-hospital mortality by 34%, blood stream infections

by 46%, acute renal failure requiring dialysis by 41%, the median number of red blood cell transfusions by 50% and critical care neuropathy by 44%, and reduced length of mechanical ventilation and ICU care. (2) The strengths of this study were large sample size, randomization and controls, blinded insulin adjustments performed by a physician who was not involved in direct care of the patient according to a strict algorithm. However, it was not feasible to conduct the study in a strictly blinded fashion because adjustments of insulin required close blood glucose monitoring. Moreover, lack of blinding could result in better control of blood sugars preferably in the intensive insulin treatment group. Further, the study involved predominantly cardiovascular surgery patients admitted to a surgical ICU which limits extrapolation of results to patients admitted to the medical ICU. The patients in this study were post cardiac surgery and it is known that insulin-glucose infusion improves cardiac functions and hence the improved outcome may be secondary to improved cardiac function. Patients undergoing surgery develop a stress response and manifest hyperglycemia as part of a hyper-metabolic phase in contrast to the chronically ill, severely septic patients who are in a state of endocrine exhaustion. It can therefore be argued that administration of insulin rather than control of blood sugar might have led to improved outcome.

To address this issue, the investigators performed an interesting post-hoc analysis of the study data to analyze the effect of insulin dose independent of glycemic control on mortality and morbidity. In this analysis, a multi-variate regression model proved that both mean insulin dose and mean blood glucose had an independent negative effect on the mortality. This led the authors to conclude that the benefit seen in their original study was likely to be related to glycemic control. (3) However, some argue that the poor outcomes in those who receive higher doses of insulin may be related to insulin resistance underlying the severity of illness in these individuals rather than a direct effect of insulin per se. (4)

In another study by Finley et al. demonstrated using a prospective cohort design that hyperglycemia determines outcome rather than lack of insulin, since increased insulin administration was associated with an increased risk of death, irrespective of prevailing glucose level in their study patients. (5) Despite these results based on a complex mathematical model analysis, this finding could be attributed to insulin resistance in individuals who require higher doses of insulin to achieve metabolic control rather than the direct

effect of insulin dosing on mortality. The limitations of this study include inclusion of pre-dominantly cardio-thoracic ICU patients, treatment bias due to the lack of blinding and a surprising lack of an independent effect of time spent in strict glucose control group on mortality.

In contrast to the homogenous study sampling of the above studies, Krinsley et al conducted a study of a large heterogeneous consecutive sample of critically ill patients to assess the effect of an intensive glucose management protocol on mortality. The study consisted of 800 consecutive patients admitted to a community hospital ICU and 800 patients admitted immediately preceding institution of the protocol. The protocol involved intensive monitoring using both subcutaneous and or intravenous insulin treatment to maintain plasma glucose values lower than 140mg/dl. After institution of the protocol mean glucose values reduced from 152.3 to 130.7mg/dl and the percentage of patients with glucose more than 200mg/dl decreased by 56.3%. The development of new renal insufficiency decreased to 75%(p=0.03), the number of patients undergoing blood transfusion reduced to 18.7%(p=0.04) and hospital mortality decreased by 29.3%(p=0.002) and length of ICU stay decreased by 10.8%(p=0.01) (6). The merits of this study include a heterogeneous population of critically ill patients and hence generalization is possible. The large number of patients enrolled, strict management protocols that included both subcutaneous and intra-venous insulin protocols and consistency of findings among the sub-groups of critically ill patients are noteworthy. The major limitation of the study is its use of historical control in a non-randomized design. Treatment of hyperglycemia, caloric intake or frequency of blood glucose determination were not standardized in the historical control group, thereby significantly impacting the internal validity of the study findings. (8)

Studies that analyze disease specific outcomes such as infections in ICU and myocardial infarction also provide insights into the mechanisms of benefit due to intensive insulin therapy in critically ill patients. Grey et al investigated whether hyperglycemia in glucose intolerant patients without diabetes could lead to increased nosocomial infections in the surgical ICU. In a prospective, randomized controlled clinical trial in the surgical ICU, adult patients requiring treatment of hyperglycemia (glucose values ≥ 140 mg/dl) were randomly assigned to receive standard insulin therapy (target blood glucose 180-220 mg/dl) or strict insulin therapy (target 80-120mg/dl) throughout their

stay in the ICU. The strict insulin therapy group demonstrated a significant reduction ($p < 0.05$) in the incidence of total nosocomial infections including intravascular device, blood stream and surgical site infections. ⁽⁹⁾ The limitations of this study include a small number ($N=61$) of a selected group of surgical ICU patients and the lack of mortality data.

The DIGAMI study was a randomized controlled double-blinded study, which tested the hypothesis that modifying the gluco-metabolic state with insulin-glucose infusion among patients with diabetes and acute myocardial infarction improves mortality. The study involved 620 patients of whom 306 received intensive insulin treatment. The mean follow up was 3.4 years, the absolute reduction in mortality being 11%, which corresponded to a relative risk reduction of 30%. The reduction in mortality was most evident in patients with low cardiovascular risk and also in the subgroup of patients who were never previously treated with insulin. ⁽¹⁰⁾ The proposed mechanisms include restoration of impaired platelet function, lipoprotein pattern and decreased activity of plasminogen activator inhibitor, which is high in diabetic patients.

In the DIGAMI 2 study, a randomized controlled study examining the effects of intensive insulin therapy glucose control in type 2 diabetic patients with suspected acute myocardial infarction, there was no mortality benefit demonstrated at 2 years of follow-up in the intensive insulin treated group compared to patients who received usual care. However, the major limitation of this trial is because of the lack of sufficient power (power achieved was 50%) as the investigators were unable to enroll sufficient subjects to detect a 25% difference in mortality at the end of the study period among all three arms of the study. ⁽¹¹⁾

Further, reviewing studies on mechanisms of insulin activity associated with clinical benefit independent of glycemic control, we found interesting data published in literature. Using a cohort of critically ill patients with length of ICU stay more than 7 days from the Van den Berge study, Mesotten et al. addressed the contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. They studied 363 patients requiring intensive care for more than 7 days who were assigned to conventional or intensive insulin therapy. Intensive insulin therapy normalized blood sugar in 24 hours and increased serum low-density lipoprotein (LDL) ($P=0.007$) and high-density lipoprotein (HDL) ($P=0.005$)

decreasing triglycerides (TGL) ($p=0.0001$). Multivariate logistic regression analysis indicated that lipid rather than glucose control independently determined the beneficial effects of intensive insulin therapy on morbidity and mortality. Post mortem analysis showed that intensive insulin therapy increases the mRNA of skeletal muscle. ⁽¹²⁾ This study exposes the possibility of the role of LDL and HDL as scavengers for endotoxin or as transporters for cholesterol as an essential substrate for the integrity of cell membrane.

In an interesting study of nitric oxide modulation and its effect on outcome in critically ill patients, Siroen et al showed using a small subset of the Van De Berghe cohort patients that insulin infusion significantly suppressed the levels of asymmetric dimethylarginine (ADMA), a nitric oxide inhibitor ($p < 0.048$). Levels of ADMA showed a weak but significant correlation with length of stay or mechanical ventilation, blood transfusions, antibiotic and vasopressor treatment and death among these patients. Insulin by decreasing ADMA levels improves nitric oxide activity that is essential for preservation of organ blood flow and interaction of endothelium with white cells & platelets. ⁽¹³⁾ The limitations of the data include a small sample size and weak correlation coefficient values (highest value = + 0.47) for all endpoints and ADMA levels.

Hansen T.K. et al have studied the anti-inflammatory effects of insulin therapy in another sub set of critically ill patients from the Van den Berge study cohort. The study involved 451 patients requiring more than 5 days of ICU care who were randomly assigned to either conventional or intensive insulin therapy. C-reactive protein (CRP) and mannose binding protein (MBP) levels were noted at baseline and day 5, day 15 and last day in ICU. Serum MBP increased with time, CRP decreased with time particularly in intensive insulin group $p < 1 = 0.02$. Multivariate logistics regression analysis revealed anti-inflammatory action of CRP explained the benefits of insulin therapy. ⁽¹⁴⁾

In an independent study, Athos J Rassias et al. analyzed the effect of insulin infusion on neutrophil function among diabetic cardiac surgery patients. Patients were randomly allocated to receive either aggressive insulin therapy or standard insulin therapy during surgery. Blood was drawn for neutrophil function before and after cardiopulmonary bypass and on the first post-operative day. Neutrophil phagocytosis activity decreased to 75% of baseline activity in the aggressive insulin group and 47% in the standard

group ($p < 0.05$). No important differences in neutrophil antibody dependent cell cytotoxicity were found. Thus, a continuous infusion of insulin and glucose control during surgery improves white cell functions in diabetic patients and may increase resistance to infections after surgery. (15)

DISCUSSION

As discussed, several studies have elucidated different mechanisms of insulin activity independent of glycemic control such as its effect on lipids, vascular tone, muscle, heart and immune and inflammatory mediators that may be associated with clinical benefits seen in the large clinical studies. The potential physiologic mechanisms of benefit during intensive insulin therapy are of great interest and clinical relevance, which are summarized in the following sections.

EFFECT ON LIPID METABOLISM

Clinical data indicates that insulin therapy in addition to its beneficial normoglycemic effect also increased LDL and HDL, and lowered TGL. Restoration of lipoproteins may facilitate scavenging of endotoxins as shown in animal models. (16) Reduction of TGL and plasma free fatty acids (FFA) by insulin also may normalize endothelium dependent vasodilatation, replete intracellular calcium and prevent arrhythmias.

EFFECT ON NITRIC OXIDE INHIBITOR MODULATION

Early data suggests that Insulin infusion may have an effect on vascular tone through modulation of nitric oxide by suppressing ADMA levels. High levels of ADMA are known to be associated with mortality and organ dysfunction in critically ill patients.

EFFECT ON NEUROMUSCULAR TISSUE

The potent anabolic effects of insulin on the skeletal muscle promote protein synthesis and tissue repair and may underlie the benefit of decreased requirement of dialysis and less incidence of critical care neuropathy. The improved skeletal muscle strength also partly explains the decreased need for ventilatory support.

EFFECT ON IMMUNE FUNCTION

Continuous infusion of insulin has been shown to improve white cell functions. The anti-inflammatory role of insulin was revealed by the reduction in the acute phase reactant CRP in the intensively treated patients.

EFFECT ON CARDIAC FUNCTION

The improvement in cardiac contractility results from increased glucose utilization by oxidative phosphorylation as against inadequate energy production from use of FFA as substrate. The improved cardiac function and tissue oxygenation also may be partly the reason for the benefit in the critically ill non-cardiac patients.

INSULIN STATUS IN CRITICALLY ILL PATIENTS

The difficulty in understanding how insulin therapy actually works is that the endogenous insulin secretion becomes unpredictable in the setting of sepsis induced insulin resistance. The beneficial effect of insulin therapy does not seem to correlate with absolute dosage of insulin administered. This evidence needs to be viewed in the light of the fact that the patients who required more insulin may have fully established insulin resistance in the setting of severe sepsis. Moreover, it is certainly prudent to use this derivation cautiously as it would prematurely discredit the beneficial effect of insulin in the critically ill.

In the early hyper-metabolic phase there exists a state of insulin resistance triggered and sustained by inflammatory mediators. The mechanisms postulated include besides the counter-regulatory hormones the phenomena of tissue resistance due impaired glucose transporter 4 translocation, tyrosine kinase inhibition by tumor necrosis factor- α , interleukins 6 and 1, inhibition of phosphoinositide 3-kinase and impaired mitogen activated protein kinase phosphorylation. In the latter phase of critical illness characterized by a state of endocrine exhaustion there is a relative deficiency of insulin production. This dynamic phenomena of insulin resistance followed by relative deficiency may partly explain the lack of correlation of insulin requirement and outcomes.

Finally, to try and quantify the interaction of the effects of exogenous and the endogenous insulin and view existing data in the setting of a dynamic state of variable insulin resistance and therefore unpredictable insulin requirements is a challenge that remains to be addressed in any clinical setting or clinical trial.

CONCLUSION

In summary, there is credible evidence to support the use of intensive insulin therapy to achieve strict glucose control in the critically ill regardless of their diabetic state. The overwhelming evidence from experimental, biological and clinical studies support and reiterate the need to incorporate

the concept of aggressive insulin therapy in achieving normoglycemia in ICU protocols. However, it is unclear at this time, regarding the exact role of insulin therapy and if benefit of this therapy extends beyond normoglycemia. The role of insulin on lipids, vascular tone, skeletal muscle, heart and the immune system underlie additional mechanisms of benefit of insulin therapy in the critically ill patient.

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