

The efficacy of intensive glucose management on hospitalized critically ill patients associated mortality rate in intensive care unit

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ABSTRACT

Background and Purpose of the study: Hyperglycemia and insulin resistance are common findings among critically ill patients. Intensive insulin therapy reduces morbidity and mortality in patients of surgical and medical intensive care units (ICUs), but its role in patients of general intensive care units still remains unknown. The present study was designed to determine the effect of intensive insulin therapy on ICU mortality.

Methods: Adult patients admitted to general intensive care units in Valiy-e- Asr Hospital, who required intensive care for at least five days were considered for a prospective, randomized and control study. On admission, patients were randomly chosen either to normalize their blood glucose levels or to prepare them for conventional therapy.

Results: Intensive insulin therapy reduced blood glucose levels of 129 patients but did not have any significant effect on reduction of mortality rate of hospitalized patients (30.6% in the conventional-treatment group vs. 38.8% in the intensive-treatment group, $p > 0.05$). However, the morbidity rate was significantly plummeted as a consequence of acceleration in the process of weaning of the patient from mechanical ventilation, and subsequently discharging from the ICU. The benefit of intensive insulin therapy was attributed to its effect on mortality among patients who remained in the intensive care unit for more than five days (78.9% conventional-treatment group vs. 46.2% intensive-treatment group, $p = 0.04$).

Conclusion: Intensive insulin therapy significantly reduced morbidity but not mortality among the patients in general intensive care units. The very possible risk of subsequent disease-associated and fatal complications was reduced in patients who were treated for five days or longer time. Further studies are required to confirm these preliminary results.

Keywords: Intensive glucose therapy, Mortality, Intensive care unit, Critically ill.

INTRODUCTION

Among ill patients with critical conditions, elevations in serum glucose, a marker previously ignored or described as adaptive, has become a major therapeutic target following a study which was performed in 2001, wherein the benefit of intensive insulin therapy among patients in a surgical intensive care unit was indicated. (1). Critically ill patients who require intensive care for more than five days have shown to be at an estimated 20 percent risk of death and substantial morbidity. (2). Hyperglycemia and insulin resistance are common in severe illness and are associated with adverse outcomes. (3-6). polyneuropathy and skeletal-muscle wasting, as two complications associated with critical stage of illness may prolong the need for mechanical ventilation. (7-10). Moreover,

increased susceptibility to severe infections with subsequent vital organs failure may enhance the risk of any adverse outcome. The present study was carried out to determine the effect of intensive management on mortality rate and morbidity of critically ill hospitalized patients who are under observation in ICU.

MATERIALS AND METHODS

Two hundred and six patients who admitted to the general ICU in Vali Asr Hospital with medical, surgical or emergency problems and had blood glucose more than 200 mg/dl were evaluated in a randomized clinical trial study. Patients with scores less than 10 of APACHE II scale system were excluded from the study. Twenty nine more

Table 1. Baseline clinical characteristics of the patients.

	<i>Conventional Treatment</i>	<i>Intensive Treatment</i>	<i>P value</i>
Age	56.62 ± 14.08	54.45 ± 16.98	p > 0.05
Gender			p > 0.05
Male	32 (51.6%)	35 (52.2%)	
Female	30 (48.6%)	32 (47.8%)	
Reason for intensive care			p > 0.05
Medical	51 (82.3%)	46 (68.7%)	
Surgical	11 (17.7%)	21 (31.3%)	
History of diabetes	40 (64.5%)	28 (41.8%)	p > 0.05
Mortality	19 (30.6%)	26 (38.8%)	p > 0.05
Time of death (day)	9.11 ± 3.34	5.62 ± 3.32	p > 0.05

patients were excluded at the time of admission because of risk-group concerning intensive glucose management or with contraindication for this study according to diagnostic of responsible. As the patients couldn't sign the written form of consent by themselves, their closest family member signed the forms. The concerned protocol and consent letters were further approved by the ethics committee Tehran University of Medical Sciences.

At the time of admission to the intensive care unit, patients were randomly assigned to receive either intensive or conventional insulin therapy. For the intensive-treatment group, insulin infusion (50 IU of Actrapid HM, Novo Nordisk in 50 ml of 0.9 percent sodium chloride) was administered continuously by the use of pump (Perfuser-JSM pump, England) where, the blood glucose level exceeded 110 mg/dl and was then adjusted to maintain normoglycemia (80-110 mg/dl). The maximal continuous intravenous insulin infusion was arbitrarily set at 50 IU per hour. For the conventional-treatment group, continuous insulin infusion was started when the blood glucose level exceeded 125 mg/dl and was adjusted in the way that maintains a blood glucose level between 125 and 225 mg/dl. When the blood glucose level fell below 125 mg/dl, the insulin infusion was tapered and eventually stopped. The dose of insulin was adjusted according to whole-blood glucose levels, measured at 2hrs intervals to maintain normoglycemia then every 4hrs intervals in arterial blood or, in cases when an arterial catheter was not available, in capillary blood, by the use of a point-of-care glucometer (Bionime B-glucose analyzer, Switzerland). Adjustments were made by the nurses in the ICU. The dose was adjusted according to a strict algorithm by a team of intensive care nurses, assisted by a physician who was not involved in the clinical care of the patients. Enteric feeding of the patients was commenced right after patient reached to a hemodynamical stability.

Protocol of study

Data collection

At baseline, data on demographic and clinical

characteristics of the patients were obtained, including necessary information regarding the severity of illness, methods used to determine this severity, and the use of intensive care resources (Table 1).

These data were scored according to the Acute Physiology and Chronic Health Evaluation (APACHE II), (11) where higher values indicate more severe illness and more therapeutic interventions, respectively. Blood was systematically sampled and blood glucose levels were measured on admission and subsequently every 4 hrs in all patients. More frequent blood glucose measurements were performed whenever the attending nurse considered it necessary and whenever there were a steep rise or fall in the blood glucose level in comparison with the previous reading. Blood glucose levels were measured on admission and also on a diurnal basis in morning- time during the study, and hypoglycemic events (defined as blood glucose levels of ≤ 40 mg/dl) were analyzed.

The clinical cause of a death in the ICU was determined by a senior physician blinded to the treatment assignments. The causes of deaths occurring after discharge from the ICU could not be identified.

Outcome measures

The primary outcome measure was death from any cause during intensive care. Secondary outcome measures were in-hospital death, the number of days in the intensive care unit, blood transfusion, acute renal failure in the intensive care unit, the number of days required for mechanical ventilation.

Statistical analyses

Statistical analyses were undertaken by SPSS version 12 (SPSS Inc., Chicago, IL, USA). A P value less than 0.05 was considered statistically significant. The baseline and outcome variables were compared by the use of Student's t-test, the chi-square test, and the Mann-Whitney U test, as appropriate. The effect of the intervention on time

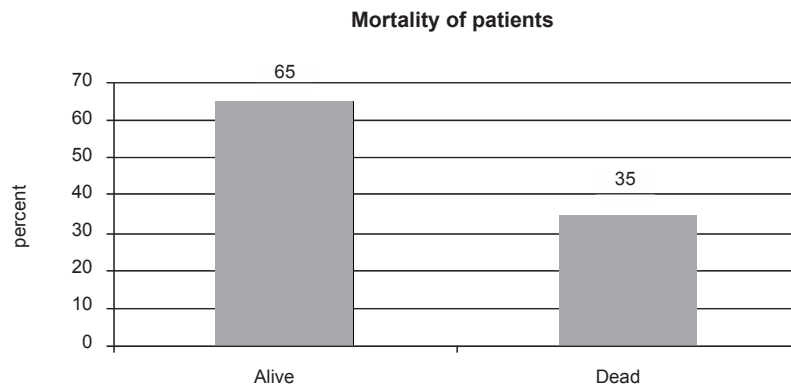


Figure 1. Compares of Mortality in the Patients.

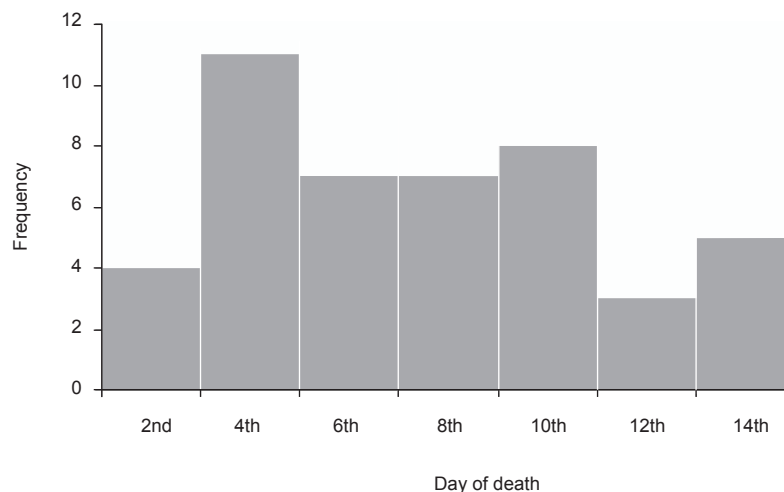


Figure 2. Day's number of death in the patients. Mean=7.1, Std.Dev=7.3 and N=45

of death in hospital was assessed with the use of Kaplan-Meier estimations and proportional-hazards regression analysis. The data are presented as mean \pm SD or medians (with interquartile ranges), unless otherwise indicated. Separate analyses were performed for the group staying in ICU for one day or longer time.

RESULTS

Table 1 gives the baseline characteristics of all 129 patients enrolled in the study at the time of admission. Mean of staying days in ICU was 8.98 ± 4.15 . Mortality rate among patients in the ICU was estimated as 30.6% in the conventional-treatment group, as compared to 38.8% in the intensive-treatment group which did not show any significant difference. Death cases within 6 to 14 days of staying in intensive care unit was 24.2% concerning the conventional-treatment group, as compared with 17.9% in intensive-treatment group, which indicated a significant difference ($p = 0.002$). Rate of mortality of patients and number of death

cases during the forth night of staying in intensive care unit are shown in figures 1 and 2.

Comparison of mortality rates between two groups didn't show any significant difference (Figure 3).

The average survival for the conventional-treatment group was 9.11 ± 3.34 and for the intensive-treatment group was 5.62 ± 3.32 days ($p > 0.05$). An estimated of 38.7% of the patients related to the conventional-treatment group could receive packed cells during their staying in ICU; whereas, the percentage of the patients in intensive-treatment group who received these pack-cells proved to be lower with the estimation of 37.3% ($p > 0.05$). Patients requiring dialysis comprised 12.9% of all the total number of the individuals related to the conventional-treatment group, as compared with the 10.4% in the intensive-treatment group. This finding implies clearly that intensive insulin treatment results in reduction of necessity for dialysis. A comparison carried between two groups concerning the need for intubation, revealed that the need for intubation among the individuals of the intensive-treatment group were lower than those of the other group (54 vs 42, $p <$

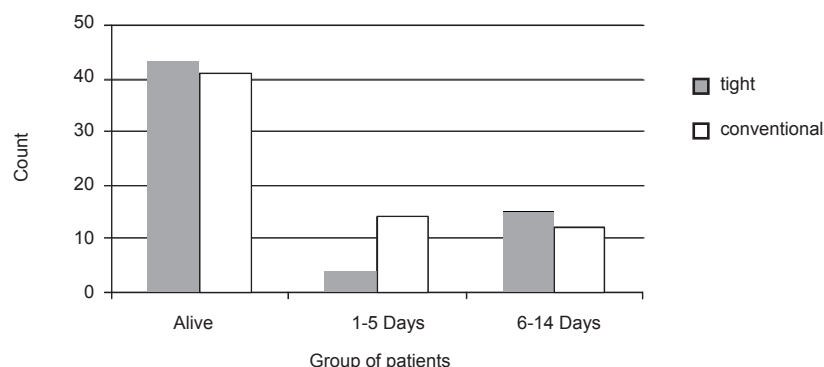


Figure 3. Comparison of mortality between intensive-treatment group and conventional-treatment group.

0.05). The average duration of stay in ICU in the intensive- treatment group was lower, compared to the other groups (7.87 ± 4.01 vs 10.19 ± 3.99 , $p = 0.001$). Furthermore; the average number of days required for mechanical ventilation in the intensive-treatment group was lower in comparison with other group (5.62 ± 4.01 vs 8.8 ± 4.38 , $p = 0.001$).

During the first five days of staying in ICU there was no significant difference in mortality rate of two groups. (14 versus 4 for conventional treatment intensive care group, $p > 0.05$)

During days 6-14 of ICU staying, mortality rate in intensive treatment group was significantly lower (16 for intensive treatment group versus 15 for conventional treatment group, P value = 0.04)

Intensive glucose management had significant effect on duration of staying in ICU ($p = 0.001$) and number of days required for intubations ($p = 0.001$).

DISCUSSION

Hyperglycemia and resistance to insulin are common events among ill patients in critical condition. Intensive insulin therapy while in ICU reduces mortality and morbidity in those who received appropriate therapeutical care in-patients in the aforesaid unit for five days or more.

On the basis of the result of another study, intensive insulin treatment decreased the death-toll incurred on account of multiple-organ failure together with sepsis, regardless of the presence or absence of any documented or undocumented history of diabetes or hyperglycemia. (12). In this study, glycemic control was a preventive approach that is more broadly applicable to critically ill patients and as a consequence caused reduction in mortality while in ICU; reduction in exploiting the intensive care resources and decreasing the risk of complications which is frequently observed among patients undergoing intensive care therapy. Acute Renal Failure was also prevented by intensive insulin treatment. On the basis of the result of the previous study, aside from optimization

of hemodynamic status, no other strategy to prevent renal failure has proved effective. (13, 16). The reduced number of transfusions in the intensive-treatment group may reflect improved erythropoiesis or reduced hemolysis, since this benefit was associated with a lower incidence of hyperbilirubinemia. Alternatively, intensive insulin therapy may diminish the risk of cholestasis, since adequate provision of glucose and insulin to hepatocytes is crucial for normal cholestasis. (17, 18). Although ,the exact cause of critical-illness associated with polyneuropathy is still remained unknown,such factors like sepsis; the usage of neuromuscular blocking agents; corticosteroids, and aminoglycosides are considered to play a major role in the above-mentioned complication. (7, 10). The decrease in risk of polyneuropathy that happened by the application of intensive insulin therapy, regardless of the concomitant usage of the above-mentioned medications, suggests that hyperglycemia, insulin insufficiency, or both may contribute to axonal dysfunction and degeneration. (9). Findings of this study suggests that maintenance of blood glucose level as lowest as possible is a true necessity. The decreased need of mechanical ventilation in patients who could enjoy the intensive insulin therapy can be explained partly by the decreased in the rate of critical-illness- associated polyneuropathy; though, a direct anabolic effect of insulin on respiratory muscles (20) may be involved in this regard. However, the exact mechanisms through which morbidity and mortality rates were reduced remain quite speculative, since the effects of glycemic control cannot be distinguished from those of increased insulin levels. Prospective studies regarding control of the blood glucose in patients suffering from diabetes has not yet shown any decrease in the mortality rate. (21, 22).

Analysis of the subgroup treated in the ICU for five or more days showed not only a beneficial effect on morbidity but also a reduction in mortality that was absent in the total study population.

However, since the length of staying in ICU cannot be predicted for an individual patient and analysis based on the length of staying inevitably requires post-randomization stratification, which might result in a risk of bias. It is unclear whether intensive insulin therapy received for less than five days caused harm, as might be inferred from the greater number of deaths among patients staying less than five days in the ICU. Result of the previous study suggests that brief exposure to insulin therapy conveyed no significant effect on the risk of death. (1). An insulin therapy only for 48 hrs or less may prove to be detrimental, whereas sustained treatment would be beneficial, the reason of which still unclarified. Indeed, the intervention is aimed not to cure the disease but to prevent emerging complications, perhaps partly as a result of intensive care. Intervention should not be applied for a patient who is considered at high risk for death from the disease which led him to admission to the ICU for a short time. However,

in patients with complications resulting from intensive care, such a preventive strategy could be effective if it continues long enough. In the present study, normoglycemia was achieved with insulin titrated by the attending nurses in the ICU. Thus, targeting blood glucose levels to below 110 mg/dl with insulin therapy reduced morbidity and mortality among critically ill patients in the surgical and medical intensive care unit, regardless of the presence or absence of any history of diabetes. For critically ill patients who are in group of intensive treatment, in general intensive care unit, morbidity was significantly reduced, but mortality had not substantially decreased before fifth day.

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