Impact of Tight Glycemic Control on Outcome in Critically Ill Patients

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in Critical Care Medicine

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Abstract

Introduction: Hyperglycemia and insulin resistance are a common occurance in critically ill patients and are associated with adverse outcome. Thus, intensive insulin therapy is advocated increasingly for hyperglycemic intensive care unit (ICU) patients to redcue morbidity and mortality. Nevertheless convincing evidence of benefit comes mainly from trials carried out on surgical ICU patients while studies of the effects of intensive insulin therapy in mixed medical & surgical ICU patients have yielded conflicting results.

Methods: This study aimed at determining the efficacy of tight glycemic control and impact on morbidity and mortality measures in mixed medical/surgical ICU patients. On admission, sixty patients were randomly assigned to recive intensive insulin therapy (IIT) (30 patients) using insulin infusion (target blood glucose= 90-149 mg/dl) or conventional glycemic control (30 patients) (target blood glucose $\leq$199 mg/dL).

Results: There was no statistically significant difference between both groups in the mean age (41.6$\pm$19 vs 50$\pm$23.9 years, P= 0.13), sex (P = 0.6), or the presence of history of diabetes mellitus (P = 0.25) but there was statistically significant higher mean APACHE II in (IIT) group (15.5 vs 13.2, P= 0.043). the tight glycemic control group showed a statistically higher mean daily insulin dose (53.1 vs 12.7 units, P< 0.001), higher mean duration of stabilization within target blood glucose range (21.8 vs 12.2 hour (P< 0.001) & lower mean blood glucose level (136 vs 166.6, P= 0.004) compared to conventional group. There was no statistically significant difference between the two groups as regards need for vasopressor use (P = 0.79) or the need for renal replacement therapy (P = 0.71), however, the incidence of acute kidney injury was lower in the tight control group (33.3% vs 53.3%) but lacks statistical significance (P = 0.09). Beneficial effect significantly was found in the tight glycemic control group regarding incidence of bacteremia (P = 0.037), mean duration of ICU stay (6.6 vs 14.1 days, P= 0.03) & accelerated weaning from mechanical ventilation (MV) (2.5 vs 8.2 days, P= 0.028). The tight glycemic control medical subgroup showed statistically significant less duration of ICU stay (7.9$\pm$3 vs 16$\pm$4.9, P= 0.05). As regards the study surgical subgroup, tight glycemic control was associated with statistically significant lower bacteremia rate (6.7% vs 46.7, P= 0.013), accelerated weaning from MV (0.5 vs 6.6 days, P= 0.009) & lower mean duration of ICU stay (5.3 vs 12 days, P= 0.023). There was no statistical significant difference between the two group regarding frequency of hypoglycemia [tight (16.7%) vs conventional (30%), P= 0.063)]. We found lower mortality rate in the tight glycemic control group (26.7%) compared to conventional group (40%), yet with no statistical significance (P= 0.412). Meanwhile on subgroup analysis, there was statistically significant lower mortality in surgical ICU patients who assigned to receive IIT compared to those who receive conventional glycemic regimen (6.7% vs 26.7%, P = 0.045). Also, there was significant reduction in mortality with IIT among long stayers (> 5 days) compared to conventional group (16.7 vs 33.3%, P = 0.05).

Conclusion: Tight glycemic control significantly reduce morbidity in mixed medical and surgical ICU patients by the prevention of newly acquired bacteremia during ICU course, acceleration of weaning from mechanical ventilation and early discharge from intensive care unit with insignificant reduction in mortality rate among the whole mixed medical / surgical ICU patients yet with significant survival beneficial in surgical ICU patients & in mixed group of patients who stayed more than 5 days in the intensive care unit.

Keywords: Tight glycemic – mixed medical/surgical –intensive insulin.

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Mahmoud Khaled

Contents

List of Abbreviations

ACTH	**:**	Adrenocorticotrophic Hormone
AKI	**:**	Acute Kidney Injury
AMI	**:**	Acute Myocardial Infarction
AMP	**:**	Adenosine Monophosphate
ANS	**:**	Autonomic Nervous System
APACHE II	**:**	Acute Physiology And Chronic Health Evaluation II
ARR	**:**	Absolute Risk Reduction
ATP	**:**	Adenosine Triphosphate
BG	**:**	Blood Glucose
CABG	**:**	Coronary Artery Bypass Grafting
c-GMP	**:**	Cyclic Guanosine Monophosphate
CIPNP	**:**	Critical Illness Polyneuropathy
CoA	**:**	Coenzyme A
CRP	**:**	C-Reactive Protein
DM	**:**	Diabetes Mellitus
DNA	**:**	Deoxyribo Nucleic acid
DNR	**:**	Do Not Resuscitate
EMG	**:**	Electromyogram
eNOS	**:**	Endothelial Nitric Oxide Synthase
GCS	**:**	Glascow Coma Score
GFR	**:**	Glomerular Filtration Rate

GH	**:**	Growth Hormone
GI	**:**	Gastro – Intestintal
GIK	**:**	Glucose-Insulin-Potassium
GLUT	**:**	Glucose Transporter
GSIS	**:**	Glucose – Stimulated Insulin Secretion
HDL	**:**	High Density Lipoprotein
HPA	**:**	Hypothalamic Pituitary Adrenal
HPG	**:**	Hypothalamic Pituitary Gonadal
HPT	**:**	Hypothalamic Pituitary Thyroid
I[Kappa]B	**:**	Inhibitor Kappa B
ICAMS	**:**	Intra Cellular Adhesion Molecules
ICUs	**:**	Intensive Care Units
IGF-I	**:**	Insulin Like Growth Factor-1
IIT	**:**	Intensive Insulin Therapy
IL	**:**	Interleukin
IMGU	**:**	Insulin Mediated Glucose Uptake
iNOS	**:**	Inducible Nitric Oxide Synthase
IRS	**:**	Insulin Receptor Substrates
IV	**:**	Intravenous
Kcal	**:**	Kilo Calories
LDL	**:**	Low Density Lipoprotein
MCP-1	**:**	Monocyte Chemoattractant Protein-1.
MMP	**:**	Matrix Metalloproteinase
MMP-9	**:**	Matrix Metalloproteinase - 9

MV	**:**	Mechanical Ventilation
NAD(P)	**:**	Nicotinamide Adenosine Diphosphate
NF	**:**	Nuclear Factor
NF_KB	**:**	Nuclear Factor Kappa B
NMDA	**:**	N-Methyl-D-Aspartate
nNOS	**:**	Neuronal Nitric Oxide Synthase
NO	**:**	Nitric Oxide
NOS	**:**	Nitric Oxide Synthase
PCI	**:**	Percutaneous Coronary Intervention
POC	**:**	Point Of Care
RCTs	**:**	Randomized Controlled Trials
RNA	**:**	Ribonucleotide Adenosine
ROS	**:**	Reactive Oxygen Species
RRT	**:**	Renal Replacement Therpay
SC	**:**	Subcutaneous
SGLT	**:**	Sodium/Glucose Co Transporter
TGC	**:**	Tight Glycemic Control.
TGCIIT	**:**	Tight Glycemic Control By Intensive Insulin Therapy
TGF	**:**	Transforming Growth Factor
TNF-α	**:**	Tumor Necrosis Factor-alpha
VCAMS	**:**	Vascular Cell Adhesion Molecules
VEGF	**:**	Vascular Endothelial Growth Factor
WBCs	:	White Blood Cells

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Introduction

Hyprglycemia in response to critical illness has long been associated with adverse outcomes. Large observational studies have recently confirmed and fine-tuned this association reporting the lowest risk of death with blood glucose levels between 5 and 7 mmol/L or between 6 and 8 mmol/L for patients with diabetes mellitus [1,2]. This association is thought to be causal based on potential glucose toxicity & studies in patients and animals support the hypothesis of toxicity induced by excess glucose, specifically toxicity to the mitochondria that takes up glucose independent of insulin and in proportion to the circulating levels of glucose [3,4,5].

The first trial that had tested the hypothesis that tight glycemic control improves outcome in critically ill patients, targeted a strictly normal blood glucose level (80-110 mg/dl) compared with usual care in adult patients in surgical intensive care units (ICUs). The intervention was labeled "intensive insulin therapy" and was found to reduce morbidity and mortality [6].

A subsequent study in a medical ICU setting documented similar organ protective effects, although not as strikingly as in the

surgical ICU study and mortality was not different in the intention to treat analysis [7].

Systematic reviews and meta-analyses have also led to differing conclusions [8,9]. Trials that examine the impact of tight glycemic control on the outcome of critically ill patients revealed also conflicting results [10-14].

In a recent meta-analysis of 26 studies, Grisdale and colleagues [15] concluded that intensive insulin therapy doesn't provide an overall mortality benefit, but it may decrease mortality among surgical ICU patients. The differences among the individual studies are likely important. First, the type of patients and logistics of the intensive care units differed substantially. Second, the accuracy of insulin titration and glucose monitoring differed among studies and most importantly the blood glucose targets also differed markedly [15].

When used in such different ways, the term "intensive insulin therapy" (IIT) may not always describe the same intervention. In some settings, such therapy may have induced large flactuations in blood glucose possibly with undetected hypoglycemia alternating with hyperglycemia. This might have resulted in a reduced average blood glucose level; however the fluctuations in blood glucose may

be worse than constant moderate hyperglycemia [15].

The issue of hypoglycemia is critical, as it represents the major fear when starting intensive insulin therapy, not surprisingly the increased incidence of hypoglycemia in the intensive insulin therapy groups justified the interruption of 2 large multicenter, prospective trials of IIT, the German VISEP & the European GLUCONTROL studies due to higher incidence of hypoglycemia (< 2.2 mmol/L) in the intensive insulin therapy groups as compared to conventional groups [16,17].

Although the incidence of hypoglycemia was substantial in both Leuven studies, the condition of patients who experienced hypoglycemia was not worsened as compared to those who did not present any hypoglycemic episode [6,7].

Application and performance of Tight Glycemic Control with Intensive Insulin Therapy (TGCIIT) definitely require the use of protocols that need to be implemented, validated and explained in details to health care professionals involved in the care of critically ill patients [18]. The various algorithms already published have been reviewed [19], and discussed the steps required to implement protocols for TGCIIT [20].