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Profile and long-term prognosis of glucose tight control in intensive care unit - patients: a cohort study

Perfil e prognóstico a longo prazo dos pacientes que recebem terapia insulínica em unidades de terapia intensiva clínico-cirúrgica: estudo de coorte

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ABSTRACT

Objectives: Stress-induced hyperglycemia is frequent in critically ill patients and has been associated with increased mortality and morbidity (both in diabetic and non-diabetic patients). This study objective was to evaluate the profile and long-term prognosis of critically ill patients undergoing tight glucose-control.

Methods: Prospective cohort. All patients admitted to the intensive care unit over 1-year were enrolled. We analyzed demographic data, therapeutic intervention, and short- (during the stay) and long-term (2 years after discharge) mortality. The patients were categorized in 2 groups: tight glucose control and non-tight glucose-control, based on the unit staff decision.

Results: From the 603 enrolled patients, 102 (16.9%) underwent tight control (glucose <150 mg/dL) while 501 patients (83.1%) non-tight control. Patients in the TGC-group were more severely ill than those in the non-tight control group [APACHE II score (14 ± 3 versus 11 ± 4, *P*=0.04), SOFA (4.9 ± 3.2 versus 3.5 ± 3.4, *P*<0.001) and TISS-24h (25.7 ± 6.9 versus 21.1 ± 7.2, *P*< 0.001)]. The tight control group patients also had worse prognosis: [acute renal failure (51% versus 18.5%, *P*<0.001), critical illness neuropathy (16.7% versus 5.6%, *P*<0.001)] and increased mortality (during the ICU-stay [60.7% versus 17.7%, *P*<0.001] and within 2-years of the discharge [77.5% versus 23.4%; *P*<0.001]).

Conclusion: Critically ill patients needing tight glucose control during the unit stay have more severe disease and have worse short and long-term prognosis.

Keywords: Blood glucose/analysis; Hyperglycemia/prevention & control**;** Insulin/therapeutic use; Hypoglycemic agents/therapeutic use; Prognosis; Intensive care

INTRODUCTION

Stress-induced hyperglycemia is frequent in intensive care unit (ICU) patients, and is associated with increased mortality and morbidity both in diabetic and non-diabetic patients.[1] The mechanisms involved in these patients' worsened outcome may be related to suppressive effects of immune function and increased risk of associated infection, endothelial dysfunction, hepatocyte mitochondrial injury, and possible tissue ischemia for acidosis or inflammation.[2]

Hyperglycemia predisposes to sodium, potassium and phosphorus imbalances.[3] Osmotic diuresis, secondary to serum hyperosmolarity, may cause symptomatic hyponatremia. Hypokalemia increases arrhythmias likelihood, and hypophosphatemia may affect platelet and leucocytes functions. Some microorganisms may have increased virulence in hyperglycemic environments.[3]

A randomized clinical trial in 2001[4] showed that tight glucose control in critically ill surgical patients reduced the in-hospital mortality. Extrapolation from these septic patients has added this therapeutic approach to treatment of these patients.[5,6] However, later randomized clinical trials[7-9] failed to show this benefit in critically ill surgical and clinical ICU patients.

Controversies keep surging, thus, on this established and worldwide applied approach in the ICU setting. Taking this into consideration, this study objective is to draw the profile of patients in need of tight glucose control in the ICU setting, and to evaluate their short- (during the ICU stay) and long-term (within 2 years after the ICU discharge) mortality.

METHODS

This is a retrospective cohort study, where all patients admitted to an 18-beds university hospital clinical and surgical ICU between January 2007 and January 2008 were included. The study was approved by the Institution's Ethics Committee.

Were studied the following variables: age, gender, associated comorbidities, reason for ICU admission (with or without sepsis), severity scores as the Acute Physiology and Chronic Health Evaluation (APACHE II), Glasgow Coma Scale, Sequential Organ Failure Assessment (SOFA), Therapeutic Intervention Scoring System (TISS) plus within the first 24 hours (TISS-24h), ICU stay length, mechanic ventilation (MV) need, acute renal failure (ARF) with or without dialysis support. Additionally, clinically relevant outcomes were also analyzed as acute myocardial infarction (AMI), brain stroke, critical illness polyneuropathy (CIPN), pressure sores and ICU mortality. After ICU discharge, the investigators followed the patients' hospital development up as well as made phone contacts with the patient or close family members (2 years after the ICU discharge) in order do define the patients' vital status. The Informed Consent Form (ICF) was sent by mail to the patients' home along with a postage-paid envelope.

For the data evaluation, the patients were categorized in two groups: with tight insulin glucose control started by the ICU staff (TGC group), and non-tight insulin glucose control patients (NTGC group).

Statistical analysis

The data were expressed as mean ± standard deviation (SD) or percent. The categorical variables were analyzed with the Chi-square test and Fisher test; the numerical variables with the t Student test for independent samples. A $P<0.05$ was considered significant. The variables which under univariate analysis appeared to increase the risk of death, were analyzed by logistic regression multivariate analysis. Relative risks (RR) with 95% confidence intervals (95% CI) were calculated. The data were analyzed using the SPSS version 16.0 software (Statistical Package for Social Science, Inc., Chicago IL, USA).

RESULTS

Of the 603 patients admitted to the ICU during 12 months, 102 (16.9%) underwent continued insulin administration for tight glucose control (capillary insulin < 150 mg/dL), while the remainder patients (n=501; 81.3%) did not need this control.

Table 1 presents the patients' characteristics. The mean age was similar between the groups (61.3 ± 16.8 years versus 61 ± 17.6 years), as well as were the male gender (49% versus 53.4%) and patients' comorbidities. Only the diabetics group was larger in the TGC group (34.3% versus 13.5%; $P<0.001$). Patients who needed TGC were more severely ill than those in NTGC group – APACHE II score (14±3 versus 11±4; $P=0.04$), SOFA score (4.9 ± 3.2 versus 3.5 ± 3.4; $P<0.001$), Glasgow score (11.7±4.5 versus 12.7±4.2; $P=0.03$), TISS within the first 24 hours (25.7±6.9 versus 21.1±7.2; $P<0.001$).

Regarding the ICU admission cause, presence or absence of sepsis was underlined. From all cases, 330 patients were admitted for sepsis, and 234 (70.9%) were diagnosed septic shock. From these, in 70 the insulin protocol was used, and in 164 was not. The septic shock mounted 68.6% of the TGC group patients, and only 32.7% of the NTGC patients.

Tables 2 and 3 show that the patients in the TGC group had worse prognosis during ICU stay than those in the NTGC. Increased dialysis need (34.3% versus 11.8%; $P<0.001$), increased CIPN (16.7% versus 5.6%; $P<0.001$), pressure sores (35.3% versus 8.8%;

P<0.001) and increased MV need (88.2% versus 51.5%; *P*<0.001) were seen in TGC patients. Table 4 shows the multivariate variables analysis for the variables which, in the univariate analysis, suggested increased patients' mortality. Insulin therapy need had 1.56 (95%CI 1.02-1.87) RR for death, however widely below the relative risk for ICU admission for septic shock [4.77 (95%CI 3.37-7.43)], ventilatory support need [1.68 (95%CI 1.42-2.11)] and dialysis need [8.76 (95%CI 6.39-10.32)].

Table 1 - Patients characteristics

Variables	Tight glucose control		
	Yes (N = 102)	No (N = 501)	P value
Age, years	61.3 ± 16.8	61 ±17.6	0.86
Gender, male (N = 318)	50 (49)	268 (53.4)	0.48
Severity scores			
APACHE II	14 ± 3	11 ± 4	0.04
Glasgow	11.7 ± 4.5	12.7 ± 4.2	0.03
SOFA	4.9 ± 3.2	3.5 ± 3.4	<0.001
TISS – 24 h	25.7 ± 6.9	21.1 ± 7.2	<0.001
Associated comorbidities			
Ischemic heart disease (N = 211)	45 (44.1)	176 (35.1)	0.06
Systemic hypertension (234)	46 (45)	189 (37.7)	0.07
Stroke (N = 68)	10 (9.8)	58 (11.6)	0.73
Neoplasm (N = 130)	22 (21.6)	108 (21.5)	1.00
AIDS (N = 26)	2 (2)	24 (4.8)	0.31
Diabetes mellitus (N = 103)	35 (34.3)	68 (13.5)	<0.001

APACHE - Acute Physiology and Chronic Health Evaluation; SOFA - Sequential Organ Failure Assessment; TISS - Therapeutic Intervention Scoring System; AIDS - Acquired Immunodeficiency Syndrome. Results expressed as N(%), mean ± standard deviation.

Table 2 - Clinical outcomes and mortality

Variables	Tight glucose control		
	Yes (N = 102)	No (N = 501)	P value
Clinical relevant outcomes			
AMI (N = 16)	1 (1)	15 (3)	0.49
Stroke (N = 21)	6 (5.9)	15 (3)	0.14
Acute renal failure (N = 145)	52 (51)	93 (18.5)	<0.001
Polyneuropathy (N = 45)	17 (16.7)	28 (5.6)	<0.001
Pressure sore (N = 80)	36 (35.3)	44 (8.8)	<0.001
Mortality (N = 151)	62 (60.7)	89 (17.7)	<0.001

AMI - acute myocardial infaction. Results expressed as N(%).

Table 3 – Intensive care unit-related admission intermediate outcomes

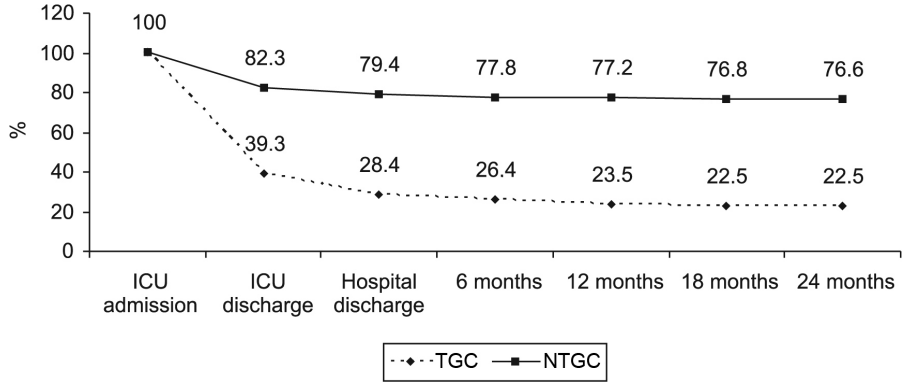
Variables	Tight glucose control		
	Yes (N = 102)	No (N = 501)	P value
Admission for sepsis (N = 330)	78 (76.5)	252 (50.2)	<0.001
Septic shock (N = 234)	70 (68.6)	164 (32.7)	<0.001
ICU stay (days)	19 ± 21	9 ± 20	<0.001
Mechanical ventilation need (N = 347)	90 (88.2)	258 (51.5)	<0.001
Mechanic ventilation days	13.8 ± 14.5	8.7 ± 11	0.001
Dialysis need (N = 94)	35 (34.3)	59 (11.8)	<0.001
Intensive support need TISS – 72h	26.1 ± 7	20.9 ± 7.3	<0.001

ICU - Intensive Care Unit; TISS - Therapeutic Intervention Scoring System. Results expressed as N(%), mean ± standard deviation.

Table 4 – Multivariate analysis of mortality increase-related factors

Variables	Univariate analysis	Multivariate analysis	RR (95%CI)
APACHE II	0.02	0.09	1.23 (0.86 – 1.54)
Glasgow	0.04	0.1	1.04 (0.54 – 2.34)
SOFA	< 0.001	0.01	3.22 (1.23 – 5.64)
TISS – 24h	< 0.001	0.01	2.99 (1.98 – 4.06)
Septic shock admission	< 0.001	< 0.01	4.77 (3.37 – 7.43)
Mechanic ventilation need	0.01	0.02	1.68 (1.42 – 2.11)
Dialysis support need	< 0.001	< 0.001	8.76 (6.39 – 10.32)
Continued insulin therapy	< 0.001	0.03	1.56 (1.02 – 1.87)

RR – relative risk; APACHE - Acute Physiology and Chronic Health Evaluation; SOFA - Sequential Organ Failure Assessment; TISS - Therapeutic Intervention Scoring System.



Survivors number	ICU admission	ICU discharge	Hospital discharge	6m	12m	18m	24m
TGC	102	40	29	27	24	23	23
NTGC	501	412	398	390	387	385	384

ICU – Intensive Care Unit; TGC – Tight Glucose Control; NTGC – Non-Tight Glucose Control; m - months Results expressed as percent of patients in the figure and number of patients in the table.

Figure 1 – Two-year follow-up survival curve: TGC (Tight Glucose Control) and NTGC (Non-Tight Glucose Control).

Figure 1 displays the patients' survival during the 2 years follow-up. The total ICU mortality was 25% (151/603 patients) and was higher in the TGC group (60.7% versus 17.7%; *P*<0.001). This significant difference increased during the hospital stay (71.6% versus 20.6%; *P*<0.001) and within the first 6 months after the hospital discharge (73.6% versus 22.2%; *P*<0.001), keeping constant within the next 18 months follow-up.

DISCUSSION

This retrospective cohort study showed that tight glucose control need, using continued insulin protocols, is a severity marker for poorer prognosis in ICU patients, also reflecting increased long-term mortality.

Tight glucose control, using the institution's continued insulin protocols, in critically ill patients is adopted worldwide and mentioned as *recommendation* in important Guidelines as the 2004 Surviving Sepsis Campaign,[5] and the recommendation was maintained in the 2008 update.[6] This is also referenced by important medical associations such as the American Association of Clinical Endocrinologists[10] and the American Diabetes Association.[11] Van den Berghe et al.[4] showed reduced mortality in patients randomized for the tight glucose control group between 80 and 110 mg/dL (4.6% versus 8%; *P*<0.04). However, later studies, conducted in more heterogeneous populations (clinical and clinical-surgical ICUs) did not share their optimism. Treggiari et al.[12] included 10,456 critically ill polytrauma patients, most of them surgical, and showed a trend to increased ICU mortality (OR: 1.15; 95%CI: 0.98-1.35) for the tight glucose control patients. Van der Berghe et al.[7], with predominantly clinical patients, did not evidence reduced hospital mortality in the TGC group (37.3%

versus 40%), except for the subgroup who stayed in the ICU for 3 or more days (43% versus 52.5%; *P*=0.009). In our study we identified increased ICU mortality for the TGC group as compared with the NTGC group (60.7% versus 17.7%; *P*<0.001), with a death RR 1.56 (95%CI: 1.02-1.87). However we stress that this finding is related to the TGC group patients' severity, according to worse APACHE II, SOFA, TISS-24h, TISS-72h scores and more frequent ICU admission for septic shock, showing a risk of death above the insulin therapy need. Additionally, these patients developed more acute renal failure, critical ill patient polyneuropathy and pressure sores, and stayed longer in the ICU and had longer time under MV, thus underlying their severity. In a 2008 metanalysis[13] including 29 clinical trials and n=8,432, tight glucose control was associated with significant reduction of sepsis, RR 0.76 (95%CI 0.59-0.97) in surgical patients. A recent study[14] showed that 90 days after randomization, tight glucose control increased the absolute risk of death in 2.6 percent point, difference which was sustained after adjustment for possible confounding factors. Considering these findings, the authors left a message on they do non-recommendation of such a rigorous control, as those established by the Guidelines for critically ill patients.

Diener et al.[15] and Azevedo et al.[16] showed no difference in hospital mortality between the groups (TGC versus NTGC), neither showed differences regarding neurological post-discharge recovery. Our study did not evaluate neurological sequelae; only mortality rates.

Previously, two DIGAMI sequential studies[17,18] evaluating long-term prognosis showed different results. The first one showed that tight glucose control reduced the mortality by 29% after one year in patients admitted to the hospital following acute myocardial infarction. However, the second didn't confirm this finding in a similar population. In our study, analyzing the data 2 years after the hospital discharge, we found increased TGC group mortality (77.5% versus 23.4%; *P*<0.001). Thus, the tight glucose control, using continued insulin protocol during ICU stay, was a marker for increased mortality in patients, even in long-term (2 years after ICU discharge).

We reiterate that this cohort did not aim to evaluate if tight glucose control has a direct influence on the outcomes, but to preview the severity in patients undergoing this intervention, and mainly, their long-term prognosis.

CONTRIBUTIONS

Márcia Inês Boff, Cassiano Teixeira and Cláudia da Rocha Cabral reviewed the literature and wrote the manuscript. Roselaine Pinheiro de Oliveira, Márcio Pereira Hetzel and Daniele Munaretto Dallegrave collected data and significantly contributed to the article. Cassiano Teixeira performed the statistical analysis. Márcia Inês Boff assures these data accuracy.

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RESUMO

Objetivos: Hiperglicemia induzida por estresse ocorre com freqüência em pacientes criticamente doentes e tem sido associada a aumento de mortalidade e morbidade tanto em pacientes diabéticos, quanto em não diabéticos. O objetivo deste estudo foi avaliar o perfil e prognóstico a longo prazo dos pacientes críticos que recebem terapia insulínica contínua na unidade de terapia intensiva.

Métodos: Coorte prospectiva, em que foram estudados os pacientes internados na unidade de terapia intensiva no período de 1 ano. Foram analisadas variáveis demográficas, escores de gravidade e o prognóstico a curto na unidade de terapia intensiva, e a longo prazo (2 anos da alta da unidade de terapia intensiva). Os pacientes foram classificados em 2 grupos: pacientes que receberam terapia insulínica contínua para controle glicêmico indicada pela equipe da unidade de terapia intensiva e pacientes que não receberam terapia insulínica.

Resultados: Dos 603 pacientes incluídos no estudo, 102 (16,9%) receberam terapia insulínica contínua, objetivando níveis glicêmicos <150 mg/dL e 501 pacientes (83,1%) não receberam insulina contínua. Os pacientes que necessitaram terapia insulínica contínua eram mais graves que os do grupo não necessitou de terapia insulínica: escore APACHE II (14 ±3 *versus* 11 ±4; p =0,04), escore SOFA (4,9 ±3,2 *versus* 3,5 ±3,4; p <0,001) e TISS das 24h (25,7 ±6,9 *versus* 21,1 ±7,2; p <0,001). Os pacientes do grupo que recebeu terapia insulínica contínua tiveram também pior prognóstico: insuficiência renal aguda (51% *versus* 18,5%; p <0,001), polineuropatia da doença crítica (16,7% *versus* 5,6%; p <0,001)] e maior mortalidade [na unidade de terapia intensiva (60,7% *versus* 17,7%; p <0,001) e 2 anos após a alta da unidade de terapia intensiva (77,5% *versus* 23,4%; p <0,001).

Conclusão: A necessidade de controle glicêmico rigoroso através do uso de protocolos de insulina contínua é um marcador de gravidade e de pior prognóstico dos pacientes internados na unidade de terapia intensiva, refletindo também maior mortalidade a longo prazo.

Descritores: Glicemia/análise; Hiperglicemia/prevenção & controle; Insulina/uso terapêutico; Hipoglicêmicos/uso terapêutico; Prognóstico; Cuidados intensivos

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