RISK FACTORS ASSOCIATED WITH HYPOGLYCEMIA AND ANALYSIS OF ADVERSE EVENTS IN INTENSIVE THERAPY

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ABSTRACT

Objectives: to assess the predictive factors associated with the occurrence of severe hypoglycemia, and to analyze the adverse events related to the use of insulin and oral hypoglycemic agents in patients admitted to an intensive care unit (ICU).

Method: it is a cohort study developed in a large hospital in the city of Rio de Janeiro. The process of identification of hypoglycemia occurred through the daily and prospective review of the medical records based on the trigger tool "glucose 50 ≤ mg/dL".

Results: 355 patients were assessed and monitored throughout the intensive care unit hospitalization, and 16 insulin-related hypoglycemia events were confirmed in 10 patients, which corresponded to an incidence of 2.8% and an incidence rate of 0.6 hypoglycemia events per 100 patients-day.The risk factors associated to hypoglycemia in the studywere: liver disease (OR=3.06, CI 95%=1.22-7.66), sepsis (OR=3.53, CI 95%=1.53-8.18) and occurrence of adverse event (OR=3.89, CI 95%=2.05-7.41). The one point increase in the APACHE severity score (OR=1.15; CI 95%=1.09-1.20) and the occurrence of hypoglycemia (OR=7.46; CI 95%=3.88-14.33) increased the chance of death in the ICU.

Conclusion: this study emphasizes the impact of hypoglycemia on mortality in intensive care and the predictive factors for its occurrence, as well as examines the insulin-related adverse events.

DESCRIPTORS: Hypoglycemia. Quality of health care. Patient safety. Intensive therapy. Adverse event.

FATORES DE RISCO ASSOCIADOS À HIPOGLICEMIA E ANÁLISE DE EVENTOS ADVERSOS EM UMA TERAPIA INTENSIVA

RESUMO

Objetivos: avaliar os fatores preditivos associados à ocorrência de hipoglicemia grave e analisar os eventos adversos relacionados ao uso de insulina e hipoglicemiantes orais em pacientes internados em uma unidade de terapia intensiva.

Método: trata-se de um estudo de coorte desenvolvido em um hospital de grande porte no município do Rio de Janeiro. O processo de identificação de hipoglicemia ocorreu por meio da revisão diária e prospectiva de prontuários baseada no critério de rastreamento "glicose 50 ≤ mg/dL".

Resultados: foram avaliados 355 pacientes, seguidos durante toda a internação na unidade de terapia intensiva e 16 eventos de hipoglicemia relacionados ao uso de insulina foram confirmados, ocorridos em 10 pacientes, o que correspondeu a uma incidência de 2,8% e uma taxa de incidência de 0,6 eventos de hipoglicemia por 100 pacientes-dia. Os fatores de risco associados à hipoglicemia encontrados no estudo foram: presença de doença hepática (OR=3,06; IC 95%=1,22-7,66), sepse (OR=3,53; IC 95%=1,53-8,18) e ocorrência de evento adverso (OR=3,89; IC 95%=2,05-7,41). O aumento em um ponto no escore de gravidade APACHE (OR=1,15; IC 95%=1,09-1,20) e a ocorrência de hipoglicemia (OR=7,46; IC 95%=3,88-14,33) implicaram em aumento da chance de óbito na UTI.

Conclusão: este estudo enfatiza o impacto da hipoglicemia na mortalidade em terapia intensiva e os fatores preditivos para sua ocorrência, bem como analisa os eventos adversos relacionados à insulina.

DESCRITORES: Hipoglicemia. Qualidade da assistência à saúde. Segurança do paciente. Terapia intensiva. Evento adverso.

FACTORES DE RIESGO ASOCIADOS A LA HIPOGLICEMIA Y ANÁLISIS DE EVENTOS ADVERSOS EN UNA TERAPIA INTENSIVA

RESUMEN

Objetivos: evaluar los factores predictivos asociados con la ocurrencia de hipoglicemia grave y analizar los eventos adversos relacionados con el uso de insulina e hipoglucemiantes orales en pacientes internados en una unidad de terapia intensiva.

Método: se trata de un estudio de cohorte desarrollado en un hospital de gran porte en el municipio de Rio de Janeiro. El proceso de identificación de hipoglicemia ocurrió por medio de la revisión diaria y prospectiva de prontuarios y basado en el criterio de rastreo "glucosa 50 ≤ mg/dL".

Resultados: se evaluaron 355 pacientes que fueron seguidos durante toda la internación en la unidad de terapia intensiva y en 16 eventos de hipoglicemia relacionados con el uso de insulina fueron confirmados. Esto ocurrió con 10 pacientes y correspondió a una incidencia del 2,8% y una tasa de incidencia de 0,6 eventos de hipoglicemia por cada 100 pacientes por día. Los factores de riesgo asociados a la hipoglicemia encontrados en el estudio fueron la presencia de una enfermedad hepática (OR=3,06; IC 95%=1,22-7,66), sepsia (OR=3,53; IC 95%=1,53-8,18) y la ocurrencia de un evento adverso (OR=3,89; IC 95%=2,05-7,41). El aumento en un punto en el resultado de gravedad APACHE (OR=1,15; IC 95%=1,09-1,20) y la ocurrencia de hipoglicemia (OR=7,46; IC 95%=3,88-14,33) implicaron en el aumento de la posibilidad de óbito en la UTI.

Conclusión: este estudio enfatiza el impacto de la hipoglicemia en la mortalidad en terapia intensiva y los factores predictivos para su ocurrencia, y también, analiza los eventos adversos relacionados con la insulina.

DESCRIPTORES: Hipoglicemia. Cualidad de la asistencia para la salud. Seguridad del paciente. Terapia intensiva. Evento adverso.

INTRODUCTION

Hypoglycemia in diabetic patients is the most common adverse event(AE)due to the use of insulin and oral hypoglycemic agents, which can lead to irreversible brain damage, organ/tissue failure, and even death. Severe hypoglycemia, with blood glucose values below 50 mg/dL, may occur to diabetic or non-diabetic patients, who are hemodynamically unstable and hospitalized in intensive care units (ICUs). It is also associated with hospital mortality, with a significant clinical impact on patients' morbidity and quality of life.[1-3]

Patients hospitalized in ICUs are particularly vulnerable to the occurrence of hypoglycemia, especially those who are intubated, sedated or unable to recognize and report characteristic signs and symptoms. Factors such as kidney insufficiency, hypothyroidism, cognitive impairment, and decreased regulatory mechanisms, with reduced glucagon and adrenaline release, insufficient glucose supply, and use of strict glycemic control therapy are associated with a greater risk of severe hypoglycemia.[4-6]

The multicenter study *Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation* (*NICE-SUGAR*) followed 6026 patients hospitalized in ICUs. Of the patients in strict glycemic control (glycemia 80-110 mg/dL), 45% presented moderate hypoglycemia (glycemia 41 to 70 mg/dL) and severe hypoglycemia (glycemia less than or equal to 40 mg/dL); there was an association between the occurrence of hypoglycemia and death. In the group with no venous infusion of insulin (conventional treatment), there was an increase in the moderate hypoglycemia (15.8%) and severe hypoglycemia (0.5%).[4] These findings are reiterated in other studies.[7-9]

In a cohort study with patients hospitalized in a university hospital wards, 10.5% of the group had at least one episode of hypoglycemia, 51.2% of which were spontaneously classified as non-drug related hypoglycemic.[2] The occurrence of hypoglycemia among diabetic patients does not imply an increased risk of death (RR=1.67, CI 95%=1.33-2.09). It should be highlighted that only the spontaneous hypoglycemia was associated with hospital mortality (RR=2.84; 95% CI=2.14-3.76).[2]

The glycemic variability, followed by episodes of hypoglycemia, reflects the progression of diabetes complications, as well as the worsening of the morbidity of patients hospitalized in intensive care.[10-11] The interruption in the monitoring of the glycemic levels may contribute to the high incidence of hypoglycemia, increasing the variability of glycemia in severe patients.[10,12]

An episode of hypoglycemia may produce damage or injury to the patient in care, compromising the quality of care. The constant assessment and careful monitoring of glycemia may contribute to the reduction of AEs related to the use of insulin and oral hypoglycemic agents occurring in the hospital environment.[13] The spontaneous reporting, the chart review, and the direct observation are the main methods for the event assessment.[13-14] According to the World Health Organization (WHO), the AE is an incident that resulted in unnecessary harm to the patient.[15]

In Brazil, four important studies have identified the occurrence of hypoglycemia related to the use of glibenclamide, metformin and insulin by the retrospective review of medical charts using the "glucose 50 ≤ mg/dL" trigger tool.[16-19] In these studies, the incidence of drug-related hypoglycemia ranges from 0.4 to 4.5 per 100 hospitalized patients. [16-19]

This study aimed to assess the predictive factors associated with the occurrence of severe hypoglycemia and to analyze the adverse events related to the use of insulin and oral hypoglycemic agents in patients admitted to an ICU of a hospital in the city of Rio de Janeiro.

METHOD

This is a concurrent cohort study of patients admitted to an ICU of a large public hospital located in the city of Rio de Janeiro.[20] It was based on a method adaptation proposed by the *Institute for Healthcare Improvement* (IHI) and involved a medical chart review process based on 17 trigger tools.[14]

Of the trigger tools proposed by the IHI, it was employed 1 related to health care ("pressure ulcer"), 4 to intensive care ("pneumonia onset", "readmission to intensive care", "in-unit procedure" and "intubation/reincubation") and 12 to the use of drugs ("*Clostridium difficile positive stool*", "PTT>100 seconds", "INR>6", "rising bun or serum creatinine>2 times baseline", "glucose≤50 mg/dL", "vitamin K administration", "anti-allergy use", "flumazenil use", "naloxone use", "anti-emetic use", "over-sedation/hypotension", "abrupt medication stop").[14]

The research was carried out in a tertiary hospital, a reference for high complexity cases, which develops teaching and research actions. The cohort consisted of patients over 18 years old, admitted from August 2011 to July 2012, monitored from the ICU admission until discharge from the unit, due to transfer to the ward or death.Obstetric patients and ICU admissions whose time was inferior than 6 hours were excluded from the study.

Patients were monitored to identify safety-related incidents based on the use of the IHI trigger tool.[14]Of the 378 patients hospitalized in the period, 355 were considered eligible. There were no losses during the monitoring. During the study period, 27 patients were readmitted.

The outcome of interest (severe hypoglycemia) was assessed at least twice daily throughout the hospital stay. The process of identifying events followed three stages.The first, performed by two nurses, involved a daily and prospective review of medical records. The presence of the trigger tool"glucose≤50 mg/dL"[14] has allowed the identification of hypoglycemic events associated with the use of insulin or oral hypoglycemic agents, considered as adverse drug event (ADE).

In the second stage, a review of the medical record was carried out to identify clinical evidence and to establish the causal chain of a possible incident.

In cases where the medical record was insufficient, additional information was extracted from different sources (analysis of additional documents, patient reports, consultation with the medical, nursing, physiotherapy and resident teams).

In the third stage, through a consensus strategy, a physician, a pharmacist and two nurses confirmed the occurrence of ADE, due to hypoglycemia associated with the use of insulin and oral hypoglycemic.

The Naranjo algorithm was used for the judgment and establishment of the causal relationship of ADEs.[21] Disagreements were solved during consensus meetings from the clinical trial. Only hypoglycemia events occurred during the intensive care were considered.

The severity profile of the patients was established using the Charlson Comorbidity Index (CCI) and the *Acute Physiology and Chronic Health disease Classification II* (APACHE).[22] The CCI was calculated according to the algorithm developed by Quan et al.,[22] adapted to the International Classification of Diseases, tenth revision (ICD-10).

The co-variables analyzed were related to sociodemographic characteristics (age, gender, race/ethnicity, schooling); severity of the patient (assessed by the ICC and APACHE); number of comorbidities; presence of diabetes, kidney disease, liver disease or sepsis; type of admission (clinical, surgical); length of the hospital stay; length of stay in the ICU; number of medicines used; use of insulin; occurrence of AE and mortality in the ICU.

Student's t-test for the independent samples, the chi-square test with the Yates' correction and Fisher's exact test were applied for the comparison of the means and categorical variables. The results were considered statistically significant for a value of $p < 0.05$.

The association between the occurrence of AE and the response variable (severe hypoglycemia in the ICU) was assessed using multiple logistic regression models that estimated the odds ratio. In order to assess the association of interest, models adjusted by gender, age (in years), kidney disease, liver disease, sepsis, insulin use and the occurrence of AE were analyzed.

Another outcome assessed was the association between the presence of hypoglycemia and the occurrence of death in intensive care, adjusted the risk by the variables gender, age and APACHE, using multiple logistic regression models. The significance level of 0.05 was used. The suitability of the final model was verified using the Deviance, Hosmer-

Lemeshow and Pearson's tests. Statistical analyzes were performed using the public domain program R 3.1 (*R Foundation for Statistical Computing*).

The current study was approved by the Ethics and Research Committee of the hospital studied under the opinion No. 171/10 and CAAE 20268713.2.0000.5257 and 52434716.0.00005240, in compliance with the Resolution 466/12 of the National Health Council. There was no conflict of interest in the study.

RESULTS

The cohort consisted of 355 patients and 120 events of severe hypoglycemia were identified. 4129 trackers were detected in 311 patients with potential AEs through daily and prospective review of the medical records and voluntary notification stimulation. The average age of the patients was 60.18 years old (SD 17.92); the majority presented high severity, considering the Charlson's index (88.7%), an important predictor of mortality (Table 1).

The presence of severe or moderate kidney disease, chronic liver disease and cirrhosis, severe or moderate liver disease and metastasis were related to the occurrence of hypoglycemia (value of p≤0.01). The APACHE index, an important predictor for re-admission, was related to episodes of hypoglycemia in the study population (Table 1).

Table 1 - Sociodemographic characteristics and severity pattern of patients admitted to the intensive care unit, according to the occurrence of hypoglycemia. Rio de Janeiro, RJ, Brazil, 2011-2012.(n=355)

Characteristics	No hypoglycemia n (%)	With hypoglycemia n (%)	Total n	Value of p*
Average age [years (SD)]	60.01 (18.13)	60.92 (17.10)	60.18 (17.92)	0.709
Gender				
Female	155 (53.63)	34 (51.51)	189	0.862
Male	134 (46.37)	32 (48.49)	166	
Race/ethnicity				
Black	39 (14.18)	7 (10.77)	46	0.541
Brown-skinned	87 (31.63)	18 (27.69)	105	
White	149 (54.19)	40 (61.54)	189	
CCI [score]				
0	63 (21.80)	8 (12.12)	71	0.108
≥1	226 (78.20)	58 (87.88)	284	
Average Apache [score (SD)]	13.22 (7.04)	17.39 (6.85)	14.00 (7.07)	0.000*
Average number of comorbidities (SD)	1.97 (1.72)	2.21 (1.54)	2.01 (1.69)	0.229
Diabetes	57 (19.72)	18 (27.27)	75	0.230
Kidney disease	19 (6.57)	9 (13.63)	28	0.095
Hepatic disease	19 (6.57)	10 (15.15)	29	0.040*
Sepsis	19 (6.57)	13 (19.69)	32	0.001*
Type of admission				
Clinical	58 (20.70)	31 (46.97)	89	0.000*
Surgical	231 (79.30)	35 (53.03)	266	
Average length of stay in the ward [days (SD)]	9.83 (18.63)	10.03 (12.16)	9.87 (17.59)	0.915
Average length of stay in the ICU [days (SD)]	8.06 (12.66)	17.55 (15.12)	9.83 (13.64)	0.000*
Number of medicines				
1-4	47 (16.26)	1 (1.51)	48	0.003*
5 or more	242 (83.74)	65 (98.49)	307	
Insulin use				
No	156 (53.98)	21 (31.82)	177	0.001*
Yes	133 (46.02)	45 (68.18)	112	
Occurrence of AE				
No	216 (74.75)	27 (40.90)	243	0.000*
Yes	73 (25.25)	39 (59.10)	112	
Mortality in the ICU				
No	246 (85.12)	26 (39.40)	272	0.000*
Yes	43 (14.88)	40 (60.60)	83	

SD: standard deviation; CCI: Charlson's Comorbidity Index; AE: adverse event; ICU:Intensive Care Unit; *Chi-square and Student's t-test

Of the patients, 18.6% presented hypoglycemia (66 events in 355 patients, CI 95%=14.5-22.6) and an incidence rate of 3.5 per 100 patients-day in the period (120 of 3448 patients-day). Most of the hypoglycemia cases were hospitalized for intensive surgical therapy (53.0%). The average length of stay in the ward was 10 days (standard deviation (SD) 12.2) and in the ICU, 17.5 days (SD 15.1), ranging from 1 to 248 days (Table 1).

The number of medications was directly related to the occurrence of severe hypoglycemia. Of the patients who presented hypoglycemia, 98.5% used 5 or more medications. It was observed a statistically significant difference between the occurrence of hypoglycemia and the presence of an AE categorized in different groups, as proposed by the WHO[15] (value of p ≤ 0.000) (Table 1).

Considering hypoglycemia as an event of interest, six models were adjusted in multiple logistic regression analysis (Table 2). In the first model, the variables considered for the adjustment of severity (gender and age) were included. Of the associated factors, gender, age and presence of kidney disease, even without statistical significance, were maintained in all models due to their clinical and epidemiological significance.

In the final model, severity adjustment variables, presence of liver disease and sepsis, insulin use and the occurrence of AE were included (model 6). The presence of liver disease (OR=3.06; CI 95%=1.22-7.66), sepsis (OR=3.53; CI 95%=1.53-8.18) and the occurrence of AE (OR=3.89; CI 95%=2.05-7.41) increased the chance of hypoglycemia in intensive care (Table 2).

Table 2 - Association between characteristics related to the patient and the occurrence of severe hypoglycemia. Rio de Janeiro, RJ, Brazil, 2011-2012 (n=355)

	Model 1* OR (CI 95%)	Model 2* OR (CI 95%)	Model 3* OR (CI 95%)	Model 4* OR (CI 95%)	Model 5* OR (CI 95%)	Model 6* OR (CI 95%)
Male	1.08 (0.63-1.85)	1.10 (0.64-1.88)	1.03 (0.59-1.78)	1.03 (0.59-1.79)	1.04 (0.59-1.82)	1.16 (0.65-2.08)
Age	1.00 (0.98-1.01)	1.00 (0.98-1.01)	1.00 (0.98 -1.02)	1.00 (0.98-1.02)	1.00 (0.98-1.01)	1.00 (0.98-1.01)
Kidney disease	-	2.26 (0.97-5.26)	2.32 (0.98-5.44)	2.07 (0.86-4.98)	1.96 (0.81-4.76)	1.53 (0.60-3.90)
Hepatic disease	-	-	2.68 (1.15-6.20)	3.00 (1.28-7.02)	2.45 (1.03-5.83)	3.06 (1.22-7.66)
Sepsis	-	-	-	3.59 (1.64-7.85)	3.32 (1.50-7.38)	3.53 (1.53-8.18)
Insulin use	-	-	-	-	2.16 (1.20-3.89)	1.25 (0.64-2.42)
Presence of AE	-	-	-	-	-	3.89 (2.05-7.41)

OR: Odds Ratio; CI: confidence interval; AE: adverse event; * Multiple logistic regression model

Of the 83 deaths occurred during the hospitalization period, 40 cases (60.60%) presented hypoglycemia during the intensive care hospitalization; there was an average of 1.7 episodes of hypoglycemia per patient (70 of 40). A statistically significant difference was observed between the occurrence of hypoglycemia and death (value of p ≤ 0.000) (Table 1).

To estimate the effect of the association between the presence of hypoglycemia and the oc-currence of death, two models of multiple logistic regression were adjusted. In the second model, the risk adjustment variables of the patient and the occurrence of hypoglycemia were included. Each increase in one point in the APACHE severity score (OR=1.15; CI 95%=1.09-1.20) and the occurrence of severe hypoglycemia (OR=7.46; CI 95%=3.88-14.33) implied in an increase in the chance of death in the ICU (Table 3).

Table 3 - Association between the presence of severe hypoglycemia and the occurrence of death. Rio de Janeiro, RJ, Brazil, 2011-2012. (n=355)

	Model 1* OR (CI 95%)	Model 2* OR (CI 95%)
Male	1.29 (0.75-2.24)	1.26 (0.70-2.28)
Age	1.00 (0.99-1.02)	1.00 (0.99-1.02)
Apache	1.16 (1.111-21)	1.15 (1.09-1.20)
Hypoglycemia	-	7.46 (3.88-14.33)

OR: Odds Ratio; CI: confidence interval; * Multiple logistic regression model

Most cases of hypoglycemia were not related to the use of oral hypoglycemic agents and insulin of the regular and NPH type (n=103). Of the total number of events investigated, 16 episodes of hypoglycemia in 10 cases were associated with medications (regular insulin and NPH) (Table 4) and one case was related to the interruption of the enteral diet. The proportion of patients with hypoglycemia associated with the insulin use was 2.8% (10 out of 355, CI 95%= 1.28-4.90), and the incidence rate of insulin-associated events was 0.5 per 100 patients-day (16 out of 3448 patients-day).

Of the 10 cases of severe hypoglycemia associated with the insulin use, 4 cases were related to subcutaneously administered NPH insulin (SC) (Table 4, cases designated as N. 18, 189, 212 and 261), 3 cases associated to the combination of regular insulin and to NPH SC (Table 4, patients designated as cases No. 90, 194 and 328), 2 occurred due to the use of venous insulin (cases No. 137 and 151) and one case was related to the use of regular insulin via SC (Table 4 cases No.72). Of the patients, 70% were previously diagnosed as diabetes.

Table 4 - Cases of adverse events related to the use of insulin in patients admitted to the intensive care unit. Rio de Janeiro, RJ, Brazil, 2011-2012.(n=10)

Patient's characteristics (age, gender and diagnosis)	No. of hypoglycemic events	Hypoglycemia event day	Medication suspect
Case No. 18 - 52 years old, female, systemic arterial hypertension and diabetes mellitus	1	21st day	NPH Insulin (SC)
Case No. 189 - 79 years old, male, colon neoplasm	1	28th day	NPH Insulin (SC)
Case No. 212 - 45 years old, female, asthma	1	18th day	NPH Insulin (SC)
Case No. 261 - 67 years old, female, systemic arterial hypertension and diabetes mellitus	2	18th and 29th days	NPH Insulin (SC)
Case No. 90 - 63 years old, male, emphysematous cholecystitis, diabetes mellitus and chronic kidney failure	2	15th and 18th days	Regular insulin (IV and SC) and NPH (SC)
Case No. 194 - 20 years old, male, diabetic ketoacidosis and chronic kidney failure	4	9th, 11th, 15th and 16th days	Regular insulin (IV) and NPH (SC)
Case No. 328 - 75 years old, female, acute pulmonary edema, systemic arterial hypertension and diabetes mellitus	2	7th and 8th days	Regular Insulin (SC) and NPH (SC)
Case No. 137 - 33 years old, female, liver and pancreatic neoplasia	1	11th day	Regular Insulin (IV)
Case No. 151 - 45 years old, female, diabetes mellitus, hypothyroidism and hepatitis C	1	5th day	Regular Insulin (IV)
Case No. 72 - 77 years old, male, systemic arterial hypertension, diabetes mellitus and chronic kidney failure	1	21st day	Regular Insulin (SC)
Total	16	-	-

SC: subcutaneous; IV: intravenous

The glycemia of patients who presented severe hypoglycemia associated with the insulin use ranged from 16 to 449 mg/dL. Figure 1 shows the evolution of the lowest blood glucose levels observed daily in each patient during the ICU stay (up to the 30th day). Regarding the variation of the average response throughout the assessment, no regularity was observed in the pattern of capillary glycemia behavior. On the 18th and 29th days of hospitalization, case No. 261 (Table 4) presented two episodes of hypoglycemia related to the NPH use, SC route (49 mg/dL and 46 mg/dL). It is worth noting one of the cases that presented four consecutive events of severe hypoglycemia (45 mg/dL, 49 mg/dL, 45 mg/dL and 40 mg/dL) on the 9th, 11th, 15th and 16th days of ICU stay, respectively (case No. 194); all the events were related to the use of regular venous insulin and NPH.

Figure 1 - Evolution of the lowest glycemia of each patient hospitalized in the intensive care unit, according to the occurrence of hypoglycemia related to the use of insulin and oral hypoglycemic agents. Rio de Janeiro, RJ, Brazil, 2011-2012. (n=10)
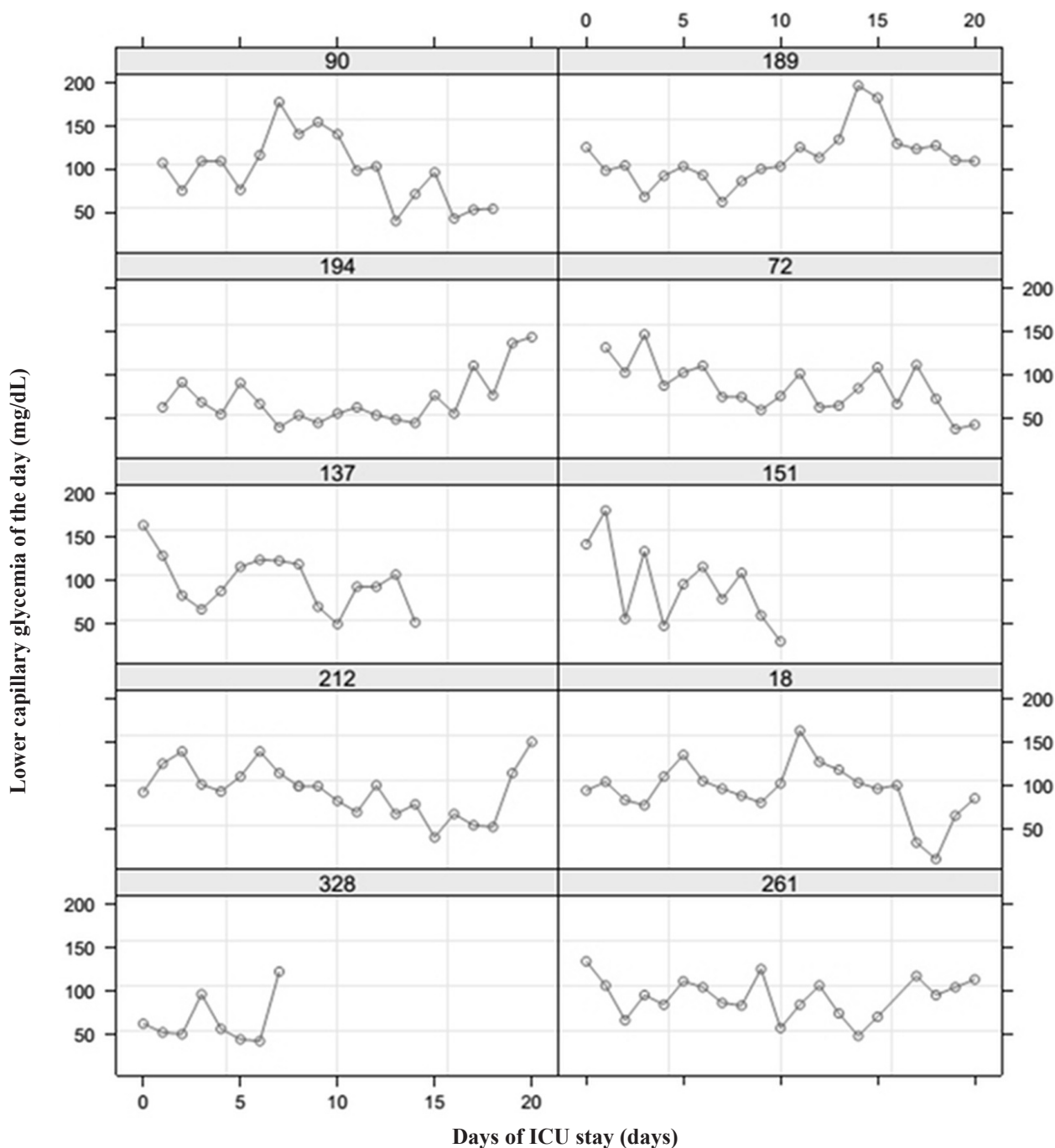
DISCUSSION

In intensive care, hypoglycemia is a serious event in patients diabetes and the incidence rate ranges from 3.7 to 10.0 per 100 patients admitted to the ICUs.[4,6-7] In this study, the proportion of hypoglycemia was high, being higher than the estimates of international studies.[4,6-7] It is worth observing that the definition of hypoglycemia adopted in this study (glucose≤50 mg/dL) and advocated byhe IHI[14] diverges from the cut-off point proposed in some studies.

The results of these studies may be influenced by the way the measures of interest are operationalized. The relevance of hypoglycemic events and their relationship with the use of oral hypoglycemic agents and insulin requires the criteria standardization in studies of monitoring incidents related to patient safety in order to allow their comparability over time and between groups.

It is believed that the glycemic assessment should be performed at least twice a day throughout the hospitalization, favoring the identification of a higher proportion of severe hypoglycemia. Additionally, the rationale used in the identification and confirmation of an episode of hypoglycemia may explain a large part of the variability of the estimates of this event.

The episodes of hypoglycemia were associated with the occurrence of death in intensive care, reaffirming the important clinical impact on the morbidity and quality of life of patients, already highlighted in other studies.[4,7,23] *NICE-SUGAR*,[4] Todi & Bhattacharya,[5] Kalfon et al.,[6] Hermanides et al.,[7] Garg et al.'s,[23] studies observed a statistically significant association between hypoglycemia and mortality. The Boucaiet al.[2] study emphasizes that the occurrence of spontaneous hypoglycemia increases the risk of hospital death; however, drug-related hypoglycemia was not a risk factor for mortality. The glycemic liability and difficulties in maintaining satisfactory glycemic control should be considered in severe patients in order to reduce the occurrence of damage resulting from the care provided.

The logistic regression analysis showed that liver disease, sepsis and occurrence of AE are factors related to an increased chance of hypoglycemia. Studies describe that female patients, the severity defined by the APACHE score, mechanical ventilation support, glucocorticoid use, need for hemodialysis, cardiac failure, strict glycemic control therapy, and length of stay in intensive care are risk factors for hypoglycemia.[4,24] Identifying the risk factors related to hypoglycemia allows nursing professionals to guide the improvement of issues related to safety in glycemic control and the quality of care provided, and also intervene in the care process in order to create strategies and preventive measures aimed at reducing the harm.

In the current study, all the glycemiatypes with values equal to or less than 50 mg/Dl were identified; however, only those episodes related to drug use (regular insulin and NPH) were considered as AE. Hypoglycemia events that met the established cut-off point and were not related to the use of medications (insufficient caloric support, prolonged fasting, among others) were not submitted to expert's consensus assessment.

It is also known that the hospitalization in intensive care involves changes in the daily dietary pattern (frequency, quantity and type of diet) and the concomitant use of several medications are factors that may influence the serum glucose level in critically ill patients.[25] It is believed that the reassessment of these cases will allow the detection of new events, based on other knowledge, that is, causes not related to medicines.

It is important to highlight that the reduction of the infusion of glucose in venous hydration or parenteral diet and the interruption of the enteral diet are factors that increase the risk for the occurrence of hypoglycemia.[25] There are situations in which the enteral diet is unexpectedly interrupted for examinations or administration of medications, and there should be a prescription of glucose serum and change or suspension of the insulin regimen during the food break.

Of the 10 patients with drug-associated hypoglycemia, half of the cases were due to the combination of regular intravenous (IV) and NPH or regular insulin (n=11 episodes). Insulin is among the five drugs that cause the most damage to adult and pediatric patients, considered a high-alert medications because of the high risk of injury to the patient when the use process fails.[26-27] The main complication of continuous insulin infusion is the occurrence of severe hypoglycemia (<40mg/dL), increasing the risk of developing the event by six times.[28]

The clinical management of the glycemic values, however, is not a trivial task in the intensive care of critically ill patients. The glycemic control, performed by the nursing team, involves the monitoring of the blood glucose every hour, the application of protocols to the results, the need for adjustments in the IV infusion rate and adequate nutritional support.[29] Failures in this care process

cause harm to the patient, which can manifest from sweating to coma and death.[26-27]

An effective glycemic control is essential to avoid/reduce the occurrence of ADE. In addition to the factors related to the severity of the patient, one must consider the conditions related to the service structure and the processes adopted in the unit, aspects that involve from the absence/deficiency of standardized procedures, training of the nursing team, blood collection technique for blood glucose measurement, availability of portable glucose meter apparatus, delayed blood glucose measurements, interruption of enteral or parenteral nutrition, inadequate clinical record and failure of communication between the health teams.[9,29-31] Failures in the structure and in the process can result in adverse or undesirable outcomes, such as death, injury, illness or patient's dissatisfaction.[32]

Errors involving the use of insulin are associated with failure to interpret abbreviations, inadequate dose administration and rate of infusion, missed dose, exchange by vial with other medicinal products, administration to the incorrect patient, and interactions with other medications or diet.[28]

The use of a care protocol for the glycemic control aims to maintain glycemia within the selected range, to avoid/reduce the occurrence of hypoglycemia and to provide specific instructions for the immediate treatment of hypoglycemia, in case it occurs. However, protocols that show low effectiveness increase the risk of complications, especially ADE.[9]

Among the patients who presented insulin-related hypoglycemia, there was a great variability in the glycemic levels (16 to 449mg/dL), which may represent a low effectiveness of the glycemic control protocol. The glycemic variability increases the risk of hypoglycemia and favors the chronic complications of diabetes.[11]

CONCLUSION

The occurrence of hypoglycemia is a common problem in hospitalized patients, particularly for those who are seriously ill, and it has an impact on mortality in intensive care. The detection of the magnitude of severe hypoglycemia and its predictive factors (presence of liver disease, sepsis and AE) favors the implementation of measures aimed at improving the nursing processes in the management of the glycemic control of hospitalized patients, quality of the care provided and security.

Hypoglycemia related to the use of regular insulin and NPH is an unnecessary harm to the patient due to health care. The implementation of a care protocol for the glycemic control in intensive care is essential to maintain glycemia in the adequate range and to avoid and treat the occurrence of hypoglycemia. This protocol should cover the management of the glycemic control in diabetic and non-diabetic patients, in prolonged fasting or in other clinical situations at risk of hypoglycemia.

Properly understanding the process underlying the occurrence of undesirable and detrimental events to the patient, family, hospital and society requires the incorporation of assessment strategies into the everyday care routine. It is possible to implement measures that, far from being punitive, guide the standards based on the best evidence and strengthen actions that minimize the occurrence of failures.

Analyzing the causes not related to medications, but associated to the occurrence of hypoglycemia in the ICU will allow the detection of new ADs, based on another rationality. New studies need to advance regarding the assessment of aspects related to the physical structure of the intensive unit, the availability of materials/equipment and human resources and to analyze this association with hypoglycemia.

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