Hyperglycemia in critical patients: Determinants of insulin dose choice

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Summary

Objective: To identify factors that can determine the choice of intermittent subcutaneous regular insulin dose in critically ill patients with hyperglycemia.
Method: Cross-sectional study in a general adult ICU with 26 beds, data collected between September and October 2014. The variables analyzed were: sex, age, previous diagnosis of diabetes mellitus, use of corticosteroids, use of lactulose, sepsis, fasting, enteral nutrition, use of dextrose 5% in water, NPH insulin prescription and blood glucose level. Patients with one or more episodes of hyperglycemia (blood glucose greater than 180 mg/dL) were included as a convenience sample, not consecutively. Those with continuous insulin prescription were excluded from analysis.
Results: We included 64 records of hyperglycemia observed in 22 patients who had at least one episode of hyperglycemia. The median administered subcutaneous regular human insulin was 6 IU and among the factors evaluated only blood glucose levels were associated with the choice of insulin dose administered.
Conclusion: Clinical characteristics such as diet, medications and diagnosis of diabetes mellitus are clearly ignored in the decision-making regarding insulin dose to be administered for glucose control in critically ill patients with hyperglycemia.

Keywords: blood glucose, insulin, intensive care units, hyperglycemia, diabetes mellitus, hypoglycemia.

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Introduction

Stress-induced hyperglycemia is elevated blood glucose in the presence of acute illnesses and is frequently observed in patients admitted to an intensive care unit (ICU), with or without a diagnosis of diabetes mellitus (DM).[1] A recent study demonstrates that stress hyperglycemia during ICU stay is associated with increased risk for the development of diabetes.[2] This phenomenon primarily involves the neuro-immune-endocrine response to stress, with increased secretion of cortisol, glucagon and adrenaline, and decreased secretion and action of insulin. Other factors may also be related to high blood glucose, such as exogenous glucose administration, enteral or parenteral nutrition, prolonged bed rest and use of drugs.[3]

Glycemic control in the ICU setting began to be important as of 2001, after the publication of a study by Van den Berghe et al.,[4] which demonstrated a 42% reduction in mortality and a 46% reduction in episodes of bloodstream infection in ICU surgical patients when normoglycemia (80-110 mg/dL) was achieved.[4] After these initial data, several prospective randomized studies have demonstrated that intensive glycemic control has suggested declines in mortality, multiple organ failure, systemic infections, hospital and ICU stay, and consequent reduction in total hospital costs.[4-7] Currently, preventing high blood glucose is a recommended and desirable intervention. However, the optimal range of glycemic control is controversial.[4] References to hypoglycemia in the literature include values between 40 and 80 mg/dL,[8-12] while the range of hyperglycemia is that of 180 to 200 mg/dL.[8-12]

The Brazilian Society of Diabetes (SBD) and the guidelines of the American Diabetes Association/American Association of Clinical Endocrinologists (ADA/AACE) recommend, for patients hospitalized in ICU, target blood glucose

ranges between 140-180 mg/dL and initiation of insulin therapy when blood glucose values are persistently greater than 180 mg/dL.[8,13] A US study analyzed blood glucose tests performed at the bedside in ICU and non-ICU wards of 126 hospitals in different regions of the country and showed a prevalence of hyperglycemia (> 180 mg/dL) of 46% in ICU and 31.7% outside the ICU. The prevalence of hypoglycemia (< 70 mg/dL), in turn, was 10.1% in ICU and 3.5% in non-ICU[14] settings. Other authors, in a similar study conducted in 635 hospitals, found a prevalence of hyperglycemia of 32.3% and 28.2% in non-ICU and ICU patients, respectively, whereas the prevalence of hypoglycemia was 6.1 and 5.6% in non-ICU and ICU patients, respectively.[15]

Insulin used to control hyperglycemia is categorized by the Institute for Safe Practice in the Use of Medications as a potentially dangerous drug,[16,17] that is, with increased risk of causing significant damage to patients as a result of failure to use.[18] Therefore, considering the negative clinical outcomes associated with the lack of glycemic control in critically ill patients, the implantation of glycemic control protocols in ICUs is a routine that could contribute to the increased safety of these patients.[19]

Our objective was to identify the determinants of the choice of intermittent subcutaneous insulin dose used to control hyperglycemia in critical hyperglycemic patients.

Method

Study design and population

A cross-sectional study was performed in the adult clinical and surgical ICU of a large hospital in the southern region of Brazil. This unit has 26 beds and serves patients of the public Unified Health System (SUS, in the Portuguese acronym), as well as those covered by health insurance and private patients.

The study sample consisted of patients admitted to the ICU from September to October 2014, who were not receiving continuous intravenous insulin. Patients hospitalized for less than 24 hours or without glycemic monitoring were excluded from the study.

Variables

The following variables were analyzed: age, sex, diagnosis of previous DM, presence or absence of sepsis, results of the capillary blood glucose test, insulin administration, number of episodes of hyperglycemia (blood glucose above 180 mg/dL) and amounts of International Units (IU) of regular insulin administered.

In addition, data were collected on the type of diet the patient was receiving during this period (enteral, parenteral nutrition or fasting), administration of fast insulin (regular) or intermediate-acting insulin (NPH), corticosteroids, 5% dextrose in water (D5W) or lactulose, and also the number of days of hospitalization.

The data were collected from the electronic medical chart and the vital signs sheet of each patient and refer to the 24-hour glucose monitoring of patients on a normal routine day. Patients were included for convenience and their data collected only once during the study.

Outcome

The dose of regular subcutaneous insulin to be used in episodes of hyperglycemia was indicated by the medical team on the patient's updated patient chart and administered by the nurses as prescribed.

Statistics

Quantitative variables were described as mean and standard deviation. Qualitative variables were described in the form of absolute numbers and percentages. As multiple episodes of hyperglycemia per patient were evaluated, the independence between the episodes can not be assumed. To address this limitation, we chose negative binomial regression as a valid tool for determining the association between the clinical factors of the patient and the choice of intermittent subcutaneous regular insulin dose in a sample of clustered data.[20]

Ethical aspects

We did not need to request informed consent from the patients in our study, since the data collected were tertiary and available in their medical charts. The project was approved by the Institution's Ethics Committee under the number: 737.699 on August 4, 2014.

Results

After excluding patients who were receiving continuous insulin, according to institutional protocol, 64 episodes of hyperglycemia were found in 22 patients. Among patients with episodes of hyperglycemia, we observed a mean age of 65.7 years, a higher frequency of male patients (68.2%), previous diagnosis of DM (70.3%), absence of sepsis (71.9%), treatment with D5W (54.6%), corticosteroids (43.7%), lactulose (4.6%) and enteral diet (84.4%), hospitalization time in days of 15.7 + 8.9, mean blood glucose levels at 256 + 69 mg/dL, and regular insulin dose per episode of hyperglycemia of 4.8 + 3.0 IU.

The median dose of regular subcutaneous insulin given in cases of hyperglycemia was 6 IU, and this value did not change on account of the presence of clinical factors such as age over 65 years, sex, previous diagnosis of

DM, use of corticosteroids, use of lactulose, presence of sepsis and use of NPH insulin, as shown in Figure 1.

Figure 2 showed a linear relationship between capillary blood glucose and regular insulin dose, indicating that at each 80 mg/dL increase in capillary blood glucose, there was an increase of 2 IU in the median dose of regular insulin administered.

In the univariate and multivariate analyzes, capillary blood glucose was the only factor significantly associated with the dose of regular insulin used, as shown in Table 1.

Discussion

Our study demonstrated that the only parameter valued in the choice of insulin dose to treat hyperglycemia in critical patients is the level of blood glucose. Thus, clinical characteristics of patients such as diet, drugs being used, presence or absence of sepsis or DM seem not to affect decision-making.

In the national and international literature, blood glucose level is seen as a determinant factor to choose the dose of regular subcutaneous insulin as recommended in protocols.[21] Although glycemic levels are important in normalizing blood glucose, critical patients have other important clinical features that influence glycemic control. Administration of vasopressors, corticosteroids, enteral or parenteral nutrition – as well as the discontinuation of these therapies due to a variety of procedures performed in critical patients – leads to significant daily variability in glycemic levels.[22]

Despite the benefits of adequate glycemic control in critically ill patients,[7,23-25] retrospective studies have shown an association between increased glycemic variability and increased mortality.[22,26] There is a thin threshold between protective care and a potentially harmful approach to the patient, significantly elevating the risk of severe hypoglycemia.[27] Five episodes of hypoglycemia were observed in the study population. Glycemic control should be done, avoiding the negative outcomes of hyperglycemia (> 180 mg/dL). However, it is imperative to define the safest strategy to offer this care to patients, so as to protect their health, without adding a potential risk. A study by Robba and Bilotta[28] confirms that continuous monitoring of blood glucose can contribute to minimize the risks associated with hyperglycemia, and immediate and effective management of blood glucose is necessary from the first hours of admission to the ICU. In addition, the need for a different, more individualized, glycemic control strategy targeting specific subgroups should be investigated.[27] Thorough glycemic control according to institutional protocols of continuous insulin is a practice adopted

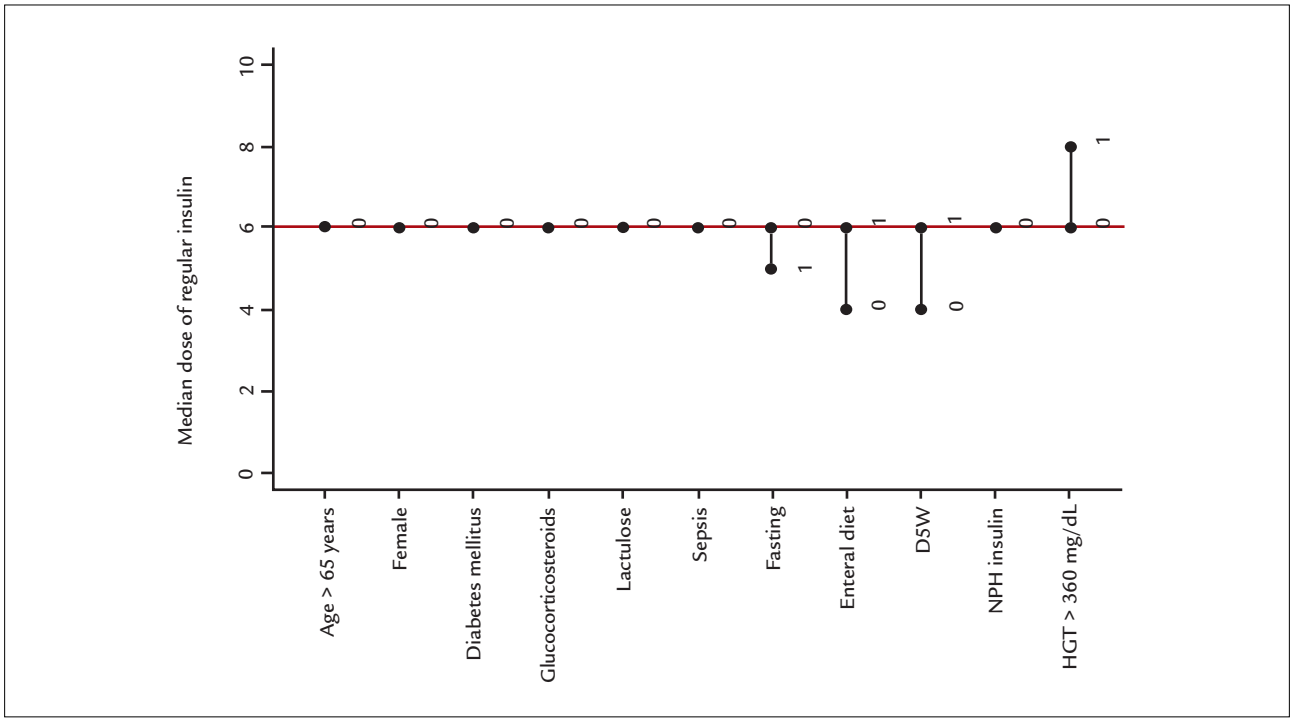

FIGURE 1 Median dose of regular insulin applied according to clinical situation.

Note: The horizontal centerline represents the median of the regular insulin dose of all episodes evaluated in the study. For each variable, 1 and 0 represent, respectively, the median of the dose of regular insulin applied in patients with and without the clinical characteristic indicated in the corresponding line.

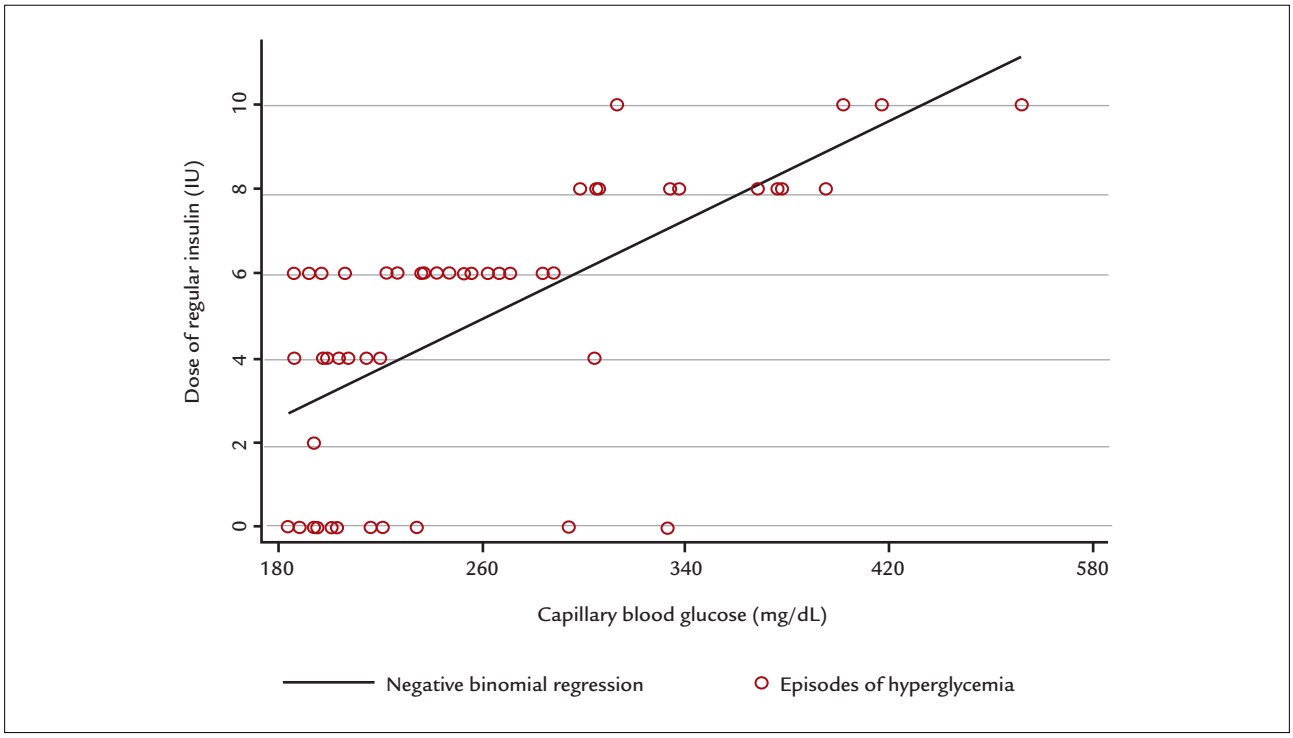

FIGURE 2 Multiple binomial regression of the dose of regular insulin given according to the capillary glycemia of the patient.

TABLE 1 Multiple binomial regression of factors associated with subcutaneously administered regular insulin dose in hyperglycemic patients who were not on continuous insulin (n=64 episodes).

Variables	Univariate Analysis		Multivariate Analysis	
	PR (95CI)	p-value	PR (95CI)	p-value
Female	1.03 (0.68-1.56)	0.9	...	...
Age per year	1.0009 (0.98-1.01)	0.87	...	...
Diabetes mellitus	1.0004 (0.65-1.53)	0.99	...	...
Corticosteroids	0.95 (0.64-1.41)	0.81	...	...
Lactulose	1.10 (0.44-2.73)	0.82	...	...
Sepsis	1.21 (0.79-1.85)	0.36	...	...
Fasting	0.84 (0.49-1.45)	0.54	...	...
Enteral diet	1.32 (0.8-2.24)	0.29	...	...
Dextrose 5% in water	1.34 (0.92-1.97)	0.12	...	...
NPH insulin	1.18 (0.76-1.84)	0.44	...	...
Capillary blood glucose	1.005 (1.003-1.007)	<0.001	1.005 (1.003-1.007)	<0.001

Note: Entry criterion for multivariate analysis: p<0.30 in the univariate analysis.
PR: prevalence ratio.

worldwide and recommended in important Guidelines.[4,29-31] However, data from more heterogeneous populations (clinical and clinical-surgical ICUs) did not show the same optimism regarding the application of this therapy for all patients.[32,33] Also, it is agreed that the need for rigorous glycemic control based on continuous insulin protocols is a marker of severity and worse prognosis in patients admitted to the ICU.[34]

The implementation of protocols for the monitoring of blood glucose in critically ill patients as well as for the establishment of intermittent administration of regular insulin to normalize blood glucose seems to be an important safety measure. The literature is filled with evidence-based guidelines and protocols designed to standardize care processes, reducing healthcare costs and improving outcomes,[35] with the expectation that patients receive better quality in care with a minimum of medical errors.[36] Theoretically, in every specialty, protocols can integrate up-to-date scientific evidence for patient management more efficiently in order to improve health outcomes and reduce inadequate care. Despite the benefits of using protocols, there is still a lack of adherence to them, which is explained by excessive hours of work among health care providers, differences in the interpretation of clinical trials and evidences, or simply hesitation in changing the practices.[35,37] Creating protocols, policies and educational programs for effective management of hyperglycemia in critically ill patients seems to be indispensable. On the other hand, considering the diverse and adverse characteristics of critical patients, these protocols need to be customized for groups with similar clinical characteristics. Since the presence of hyperglycemia in critically ill patients has a different impact on the different etiological groups, a distinct evaluation is necessary depending on the pathology and profile of the patients.[38]

Due to its cross-sectional design, our study has limitations to investigate a cause-effect relationship, and it is possible to present only associations in this outline. In addition, our study was conducted in a single center. Nevertheless, it was performed in a general ICU, covering different types of patients with multiple comorbidities, not restricted to a single specialty. In this ICU, there is no established protocol for administration of subcutaneous insulin, which was valid for the observation of different medical conducts.

Conclusion

We found that clinical characteristics of patients such as type of diet, pharmacotherapy, presence of sepsis, and previous diagnosis of DM are not taken into account to decide the dosage of insulin for glycemic control in critically ill patients.

Resumo

Pacientes críticos com hiperglicemia: determinantes da escolha da dose de insulina

Objetivo: Identificar os fatores associados à escolha da dose de insulina regular subcutânea intermitente em pacientes críticos com hiperglicemia.
Método: Estudo transversal em uma UTI geral adulta com 26 leitos. Pacientes com um ou mais episódios de hiperglicemia (glicemia capilar superior a 180 mg/dL) foram incluídos por conveniência, de forma não consecutiva. Aqueles com prescrição de insulina contínua foram excluídos da análise. As variáveis analisadas foram: sexo, idade, diagnóstico prévio de diabetes melito, uso de corticosteroide, uso de lactulose, presença de sepse, jejum, dieta enteral, uso de soro glicosado contínuo, prescrição de insulina NPH e valor da glicemia capilar.
Resultados: Foram incluídos 64 registros de hiperglicemia verificados em 22 pacientes que apresentaram pelo menos um episódio de hiperglicemia. O valor mediano administrado de insulina regular humana subcutânea foi de 6,0 UI e, entre os fatores analisados, o único associado à dose de insulina administrada visando à normalização dos níveis glicêmicos foi o valor da glicemia capilar.
Conclusão: Evidencia-se a inobservância de características clínicas dos pacientes, como dieta, uso de medicamentos e diagnóstico prévio de diabetes melito, para a tomada de decisão quanto à dose de insulina a ser administrada visando ao controle glicêmico em pacientes críticos com hiperglicemia.

Palavras-chave: glicemia, insulina, unidades de terapia intensiva, hiperglicemia, diabetes melito, hipoglicemia.

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