A randomized controlled trial comparing a computer-assisted insulin infusion protocol with a strict and a conventional protocol for glucose control in critically ill patients

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Abstract
Purpose: The objective of this study is to evaluate blood glucose (BG) control efficacy and safety of 3 insulin protocols in medical intensive care unit (MICU) patients.
Methods: This was a multicenter randomized controlled trial involving 167 MICU patients with at least one BG measurement ≥150 mg/dL and one or more of the following: mechanical ventilation, systemic inflammatory response syndrome, trauma, or burns. The interventions were computer-assisted insulin protocol (CAIP), with insulin infusion maintaining BG between 100 and 130 mg/dL; Leuven protocol, with insulin maintaining BG between 80 and 110 mg/dL; or conventional treatment—subcutaneous insulin if glucose >150 mg/dL. The main efficacy outcome was the mean of patients' median BG, and the safety outcome was the incidence of hypoglycemia (≤40 mg/dL).
Results: The mean of patients' median BG was 125.0, 127.1, and 158.5 mg/dL for CAIP, Leuven, and conventional treatment, respectively (P = .34, CAIP vs Leuven; P < .001, CAIP vs conventional). In CAIP, 12 patients (21.4%) had at least one episode of hypoglycemia vs 24 (41.4%) in Leuven and 2 (3.8%) in conventional treatment (P = .02, CAIP vs Leuven; P = .006, CAIP vs conventional).

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Conclusions: The CAIP is safer than and as effective as the standard strict protocol for controlling glucose in MICU patients. Hypoglycemia was rare under conventional treatment. However, BG levels were higher than with IV insulin protocols.

1. Introduction

A randomized controlled trial involving 1548 surgical patients admitted to intensive care observed 42% relative reduction in death risk and significant morbidity reduction in the group under strict glycemic control compared with conventional treatment [1]. Further randomized trials did not show mortality reduction with intensive insulin therapy [2-4] or observed a beneficial effect on mortality restricted to the subgroup with length of intensive care unit (ICU) stay longer than 3 days [5]. Nevertheless, guidelines from professional organizations have recommended strict glycemic control with continuous intravenous insulin infusion for the management of critically ill patients [6,7], and it has become routine practice in many ICUs.

The major concern of strict glucose control is hypoglycemia [2,8]. In addition to a higher risk of hypoglycemia, implementation of a strict glucose control protocol in ICU routine may face difficulties because of increased workload and lack of experience of nursing staff. Therefore, to guarantee successful implementation of strict glucose control in critical care, it is essential that the protocol be efficacious, safe (low risk of hypoglycemia), and practical to use. Algorithms for glucose control in critical care patients have been evaluated in several studies [9]. However, most studies were case series or before-after comparisons, with the lack of an adequate standard strict glucose control group limiting the interpretation of results [9]. More recently, randomized trials were conducted to compare a nonlinear model predictive control algorithm delivered by a computerized system with conventional strict glucose control protocol [10,11]. Hypoglycemic episodes were virtually absent, and very strict glucose control was achieved with model predictive control. However, the software is not currently available for routine use.

We developed an intravenous insulin infusion algorithm, which aims to maintain blood glucose (BG) levels between 100 and 130 mg/dL. To make it user friendly, we developed a computer program for Windows desktops or handhelds to display the algorithm (computer-assisted insulin protocol [CAIP]). The desktop and printed version of the program is available as electronic supplemental material.

The study primary efficacy objective was to compare glucose control during ICU stay obtained with CAIP vs a standard strict glycemic control protocol (Leuven protocol) [1] or a conventional intermittent insulin administration protocol (conventional treatment) in critically ill patients. The primary safety objective was to compare the incidence of hypoglycemia during ICU stay with CAIP vs a standard strict glycemic control protocol (Leuven protocol) or a conven-

tional intermittent insulin administration protocol (conventional treatment) in critically ill patients.

2. Methods

2.1. Participants

The study was conducted in 5 ICUs from 5 different Brazilian institutions: Hospital Estadual Mário Covas, Santo André, Brazil, a 32-bed, teaching, closed ICU in a 321-bed hospital; Hospital Israelita Albert Einstein, São Paulo, Brazil, a 30-bed, teaching, open ICU in a 450-bed hospital; Hospital Municipal São José, Joinville, Brazil, an 8-bed, teaching, closed ICU in a 200-bed hospital; Hospital Dona Helena, a 7-bed, nonteaching, closed ICU in a 120-bed hospital; Centro Hospitalar UNIMED, Joinville, Brazil, a 8-bed, nonteaching, closed ICU in a 140-bed hospital.

Adult medical patients admitted to the ICU were eligible for the study if they had at least one BG measurement 150 mg/dL or higher plus one of the following: (1) mechanical ventilation for an acute process, with expected duration of 24 hours or longer; (2) trauma; (3) burn; (4) systemic inflammatory response syndrome (SIRS, modified criteria), with at least 3 of the following: (*a*) core temperature $\geq38°C$ or $\leq36°C$; (*b*) heart rate of 90 beats/min or higher, except in patients with a medical condition or receiving a medication known to prevent tachycardia; (*c*) respiratory rate of 20 breaths/min or higher, or a $PaCO_2$ of 32 mm Hg or lower; (*d*) white blood cell count $\geq12,000$ or $\leq4000/mm^3$ or >10% immature neutrophils. Patients were excluded if they were younger than 21 years, were surgical patients, were admitted because of diabetic ketoacidosis or nonketotic hyperosmolar state, or were in a state in which death was perceived as imminent.

The study protocol and consent form were approved by the ethics review board of each institution. The study was performed in accordance with ethical standards stated in the Declaration of Helsinki. Written consent was obtained from every patient or the next of kin when the patient was unable to give it. The study protocol was registered at ClinicalTrials. gov with the number 00410852.

2.2. Interventions

The following treatments were evaluated:

1. Computer-assisted insulin protocol: the target range for BG was 100 to 130 mg/dL using continuous

intravenous insulin infusion. Insulin dose adjustments were assisted by a computer program running on an ICU desktop or a handheld (electronic supplemental material: computer program and printed version).

2. Strict glycemic control protocol (Leuven protocol): continuous intravenous insulin infusion with adjustments according to a protocol developed and used by Van den Berghe et al [1,5], which aims to maintain BG between 80 and 110 mg/dL.

3. Conventional treatment: intermittent subcutaneous insulin administration according to a sliding scale. Insulin is given for BG levels higher than 150 mg/dL.

Computer-assisted insulin protocol was developed with the aim of being easier to use and safer and with a similar efficacy in controlling BG than the standard protocol for strict BG control in critically ill patients [1]. The characteristics of CAIP are as follows:

1. Blood glucose goal between 100 and 130 mg/dL. This was chosen because there is no evidence that an intermediate level (between 110 and 180 mg/dL) is inferior to a very strict range (80 to 110 mg/dL) and the risk of hypoglycemia may be lowered. Lately, other studies have suggested that targets up to 140 mg/dL are associated with the highest survival rates [12,13].

2. Adjustments in insulin infusion are delivered according to the current insulin infusion rate, glucose level, and variation per unit of time between the last and current glucose measurements. A table developed by one of the authors (ABC) based on actual management of patients in a 10-bed ICU in 2002 guides the adjustments. It was further refined during a 2-year period of use. The table is used as follows: (*a*) The current BG level is identified in the first column of the table, which contains 10 intervals for current BG. (*b*) The appropriate interval of variation in glucose (between current and last measurements) is identified. (*c*) The guidelines for insulin adjustments and time to repeat glucose measurement are available in the same row.

3. In fact, the guidelines on starting and adjusting insulin infusion and timing of glucose measurements are delivered by a simple computer program for Windows PCs or handheld devices. The program is based on the table described above. The program has a simple layout and is very user-friendly, needing minimal training. The aim is to eliminate the need of calculations, thus, making the use of CAIP easier and faster.

4. Increases in insulin infusion are always additive (eg, if current BG is 140 mg/dL and it increased 15 mg/dL per hour, then insulin should be increased by 0.6 U/h), whereas decreases are proportional (eg, if current BG is 140 mg/dL and it decreased 80 mg/dL per hour since the last measurement, then insulin infusion should be reduced by 50%). The objective was to prioritize safety as well to avoid fluctuations in glucose control when patients are closer to the target range. For instance, if a patient is receiving insulin at a high rate (eg, 10 U/h) and his/her BG dropped fast to a near normal level, then an absolute decrease in insulin rate may be insufficient to avoid further decrease in BG, whereas a proportional reduction (eg, 50%) may be more adequate. The inverse situation is also true; if a patient is receiving a low dose of insulin, then an absolute decrease might be too much, leading to hyperglycemia, whereas a proportional decrease may be more appropriate.

5. Intervals between measurements are not fixed. Instead, their sizes depend on both current glucose level and variation per unit of time between last and current measurement.

6. Adjustments in insulin infusion and time to make the next BG measurement are always specific values, not ranges, to standardize conduct, and decrease reliance on experience and time spent to make decisions.

In all groups, insulin adjustments were made by the nursing staff. Randomized treatment was administered until ICU discharge. Other insulin formulations or oral hypoglycemic agents were not used during the ICU stay. When the patient was discharged to the step-down unit or the ward, BG was controlled according to his/her physician discretion.

Feeding was prescribed according to each participating ICU routine practice. However, it was recommended that patients receive adequate caloric and glucose intake. The study protocol suggested infusion of 200 to 300 g of glucose per day for patients without enteral or parenteral nutrition. Enteral nutrition was initiated as soon as possible. Parenteral nutrition was recommended when enteral nutrition could not be administered from the second ICU day. An energy intake between 105 and 147 kJ/kg per day was suggested, with adjustments for special situations.

Blood glucose was measured with Advantage glucometer using Accu-Chek Advantage test strips (Roche Diagnostics, Mannheim, Germany). Measurements were made using capillary whole blood obtained from patient's fingertip. For patients with shock or receiving vasoconstrictors, it was recommended that arterial sampling be used to measure BG.

Clinical and demographic data were collected at baseline for all patients, including information necessary to calculate APACHE (Acute Physiology and Chronic Health Evaluation) II and Sequential Organ Failure Assessment scores [14,15].

2.3. Outcome measures

The mean of patients' median BG during the ICU stay was the primary efficacy outcome, and the incidence of hypoglycemia (≤40 mg/dL) was the primary safety outcome. A variable number of BG measurements, in some cases, hundreds, were obtained from each patient. To deal with the repetitive measurements, we defined the primary efficacy end point as the mean of each patient's median; that is, we calculated a summary measure for each patient [16].

The secondary outcomes were as follows: (1) hyperglycemic index, with a cutoff at 140 mg/dL (HGI 140); (2) proportion of hypoglycemic episodes (<40 mg/dL) in relation to total BG measurements per patient; (3) number of BG measurements obtained per patient; (4) proportion of time with BG controlled between 60 and 140 mg/dL; (5) nurse perception about the feasibility of the 3 protocols. The HGI is the area under the curve and above a predefined BG cutoff (we used 140 mg/dL) divided by time under observation [12]. The index is calculated after simple interpolation of each patient's BG measurements. It represents the burden of BG above "normal" and is the best glucose index to predict mortality [12].

A questionnaire was issued to all 60 nurses who applied the study's protocols to evaluate their perception regarding the protocols. For each protocol, CAIP, Leuven, or conventional, the following question was asked: "In relation to the use of the protocol (CAIP, Leuven, or conventional), considering issues related to time spent to execute protocol tasks and protocol complexity, do you believe it was (*a*) very easy, (*b*) easy, (*c*) difficult, or (*d*) very difficult?" It also asked which of the 3 tested protocols the nurse would like to be adopted as the standard protocol in his/her ICU.

2.4. Randomization

The randomization list with 3 groups (CAIP, Leuven protocol, and conventional treatment), with blocks of 6, stratified by the center, was generated by computer. The system analyst who generated the randomization list did not take part in any other aspects of the study. Investigators enrolling a patient into the study obtained the assigned treatment in the study Web site only after registering the patient.

There was no blinding of patients or investigators because it was not feasible to conceal the different glycemic control protocols.

2.5. Statistical methods

We defined the sample size as 165 patients (55 per group) to detect a difference of 20 mg/dL between the highest and lowest of group mean BG levels using 1-way analysis of variance, assuming a SD of 33 mg/dL for each group, 2-tailed type 1 error of 0.05, and power of 80% [1].

Categorical variables were displayed as absolute and relative frequencies. Numerical variables were presented as means and SDs or medians and interquartile (IQR) ranges, as appropriate. Comparisons of proportions were made using χ^2 test. Comparisons of quantitative variables were carried out using Mann-Whitney test. We evaluated whether different participant centers modified the effect of glucose control protocols on mean glucose and on the risk of hypoglycemia using 2-way analysis of variance and logistic regression, respectively. All *P* values presented are 2-tailed.

3. Results

Between May 4, 2005, and December 4, 2006, we randomized 168 patients in 5 ICUs: 56 allocated to CAIP, 58
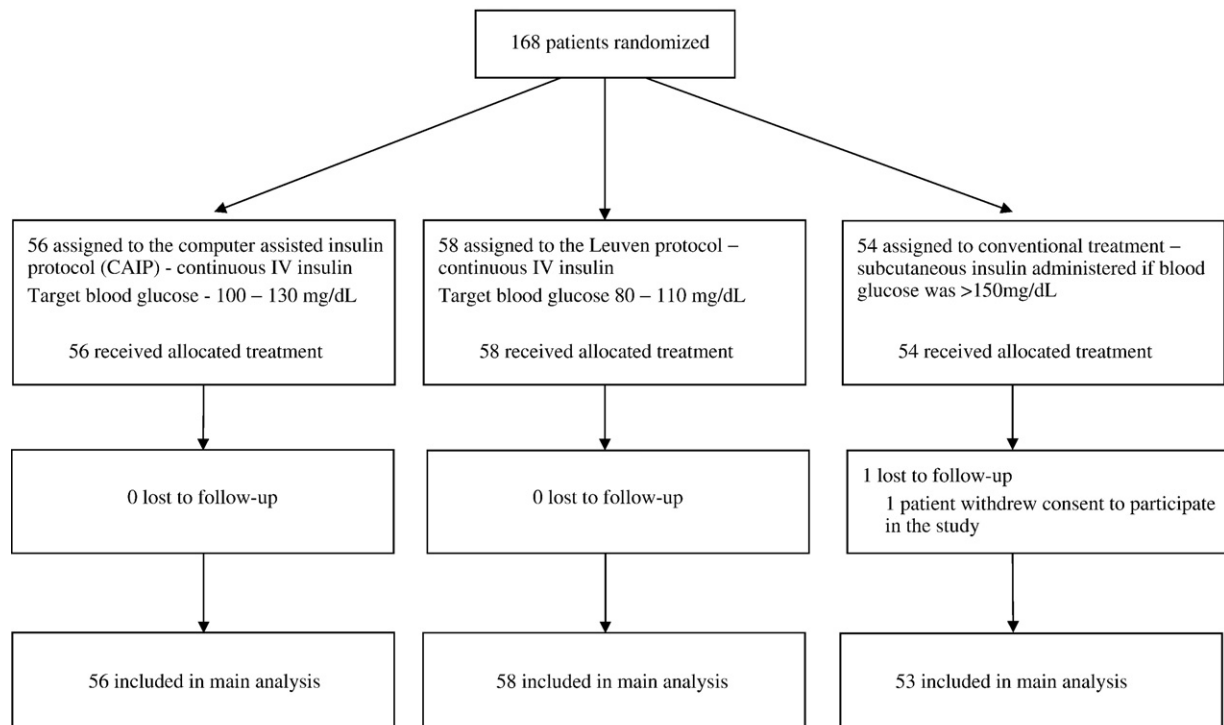

Fig. 1 Study flow diagram.

Table 1   Baseline demographic and clinical characteristics

Characteristic	CAIP (n = 56)	Leuven protocol (n = 58)	Conventional treatment (n = 53)
Female sex, no. (%)	24 (42.9)	32 (55.2)	27 (50.9)
Age (y)			
Mean (SD)	63.6 (17.6)	58.8 (18.4)	61.0 (19.7)
Inclusion criteria, no. (%)			
Mechanical ventilation	47 (83.9)	47 (81.0)	41 (77.4)
Trauma	2 (3.6)	3 (5.2)	6 (11.3)
SIRS	46 (82.1)	48 (82.8)	36 (67.9)
Diagnostic category, no. (%)			
Respiratory	13 (23.2)	18 (31.0)	18 (34.0)
Other sepsis	13 (23.2)	8 (13.8)	4 (7.6)
Cardiovascular	10 (17.9)	10 (17.2)	6 (11.3)
Neurologic	7 (12.5)	7 (12.1)	14 (26.4)
Hematologic or oncologic	6 (10.7)	6 (10.3)	0 (0.0)
Trauma	3 (5.4)	4 (6.9)	8 (15.1)
Gastrointestinal, liver or pancreas	3 (5.4)	4 (6.9)	1 (1.9)
Metabolic or renal	1 (1.8)	1 (1.7)	2 (3.8)
History of diabetes mellitus, no. (%)	17 (30.4)	20 (34.5)	14 (26.4)
Treated with diet only [a]	2 (11.8)	4 (20.0)	0 (0.0)
Oral antidiabetic agent (no insulin) [a]	10 (58.8)	7 (35.0)	8 (57.1)
Insulin (±oral antidiabetic agent) [a]	5 (29.4)	9 (45.0)	6 (42.9)
Body mass index (kg/m^2)			
Mean (SD)	25.5 (5.2)	26.4 (4.6)	25.0 (3.9)
SOFA			
Median (IQR)	8 (5-10)	7.5 (5-11)	6 (4-8)
APACHE II score			
Median (IQR)	24.5 (17-27)	21 (17-26)	20 (15-27)

to Leuven protocol, and 54 to conventional treatment (Fig. 1). We followed up all patients until ICU discharge (primary efficacy and safety outcome analysis) and hospital discharge, except for one (conventional treatment group) whose consent to participate in the study was withdrawn by her next of kin. Ninety-day follow-up was obtained from all patients except one who had been assigned to conventional treatment. All patients were analyzed according to the group they were randomly allocated (intention-to-treat principle), except for the patient who withdrew consent.

Groups were generally comparable at baseline (Table 1). Mean age was approximately 60 years, and approximately half of the patients were female. Patients were very sick as denoted by around 80% needing mechanical ventilation at

baseline, 68% to 83% having 3 or more SIRS criteria, and median APACHE II score varied from 20 to 25. Length of stay in ICU was similar in all groups (median, 7 days).

The mean of patients' median BG was 125.0 ± 17.7, 127.1 ± 32.2, and 158.5 ± 49.6 mg/dL for CAIP, Leuven, and conventional treatment, respectively (P < .001, CAIP vs conventional treatment; P = .34, CAIP vs Leuven) (Table 2). The incidence of hypoglycemia (≤40 mg/dL) was lower in CAIP group than in Leuven group, although it was higher in CAIP than conventional treatment (Table 2).

When episodes of hypoglycemia were considered in relation to the number of BG measurements done, we have found that each patient in CAIP protocol had a mean 0.43% of glucose measurements below 40 mg/dL compared with

Table 2   Primary outcomes: mean of patients' median BG and incidence of hypoglycemia

Outcome	CAIP (n = 56)	Leuven protocol (n = 58)	Conventional treatment (n = 53)	P	
				CAIP vs Leuven	CAIP vs conventional treatment
Median BG [a] (mg/dL)					
Mean	125.0	127.1	158.5	.34	<.001
Patients with hypoglycemia [b]					
No. (%)	12 (21.4)	24 (41.4)	2 (3.8)	.02	.006

  [a] Each patient's median BG was used as a summary measure to derive a group mean.
  [b] Patients with at least one BG of 40 mg/dL or less for all patients.

Table 3 Secondary outcomes: efficacy and safety of the protocols in attaining BG control

Outcome	CAIP (n = 56)	Leuven protocol (n = 58)	Conventional treatment (n = 53)	P	
				CAIP vs Leuven	CAIP vs conventional treatment
Episodes of hypoglycemia [a] (%)					
Mean	0.43	0.55	0.03	.04	.007
HGI 140 (mg/dL per hour)					
Median (IQR)	4.2 (2.0-9.6)	8.7 (2.5-20.2)	20.5 (5.1-42.8)	.10	<.001
No. of BG measurements					
Median (IQR)	100 (33-192)	105 (35-312)	49 (39-77)	.52	.01
Proportion of time BG controlled between 60 and 140 mg/dL (%)					
Mean (SD)	71.8 (18.0)	67.9 (20.8)	47.1 (30.2)	.50	<.001

[a] Percentage of hypoglycemic episodes per patient = ([BG ≤40 mg/dL for all BG measurements] * 100).

0.55% in Leuven group (P = .04) and 0.03% in conventional group (P = .007) (Table 3). Other secondary outcomes are also presented in Table 3.

We found no difference of BG control among centers (P = .71), as assessed by the means of glucose medians, nor was there modification of the BG control protocols effect by center (interaction P = .35). Likewise, there was no difference in the incidence of hypoglycemia between centers (P >.05), nor did the center influence the risk of hypoglycemia observed in the 3 groups (all interaction P > .05).

The nurses' perception regarding the protocols' feasibility is depicted in Fig. 2. All 60 nurses answered the questionnaires. In terms of complexity and time spent to execute the protocol tasks, 11.7% found the CAIP difficult or very difficult, as compared with 38.4% for Leuven protocol and 13.3% for conventional treatment (P = 0.78 for CAIP vs conventional treatment; P <.001 for CAIP vs Leuven). Fifty-six percent of the nurses would like the CAIP to be adopted as the standard protocol in their ICU, 22% preferred the Leuven protocol, 15% preferred the conventional protocol, and 7% believe all the protocols were alike.
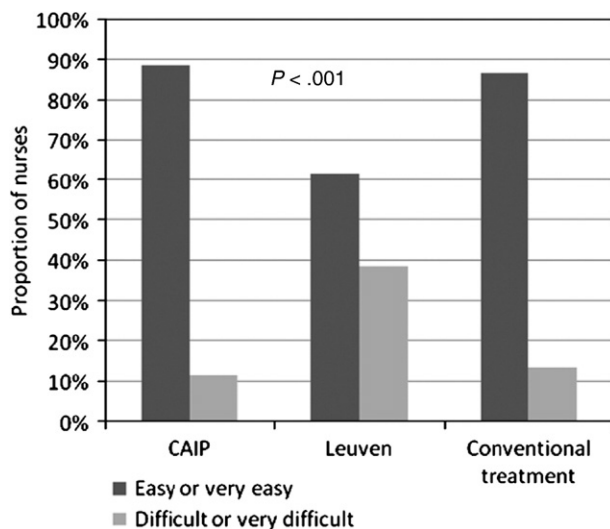
Fig. 2 Nurses' perceptions about feasibility of protocols.

4. Discussion

4.1. Summary of findings

The CAIP allows a BG control as effective as the standard protocol for tight glucose control proposed by Van den Berghe et al [1,5]. Both maintained BG at normal nonfasting levels. However, the risk of hypoglycemia was lower with the computer-assisted protocol, and it was considered easier to use than the Leuven protocol. The conventional protocol led to a minimal risk of hypoglycemia, although it was clearly inferior to the intravenous protocols in avoiding hyperglycemia.

4.2. Strengths and limitations

Great care was taken to guarantee the integrity of results of this clinical trial. Randomization was central using a Web site that assured concealment of the allocation list. Other items such as careful data collection and intention-to-treat analysis were used in this study.

This study has also some limitations. We did not collect data regarding the number of patients assessed for eligibility, because of a shortage of human resources. Nevertheless, whenever one of the researchers was in the participant centers, all potentially eligible patients were systematically approached to be enrolled in the study. Therefore, we believe there is no limitation on external generalization of this study's results.

Adherence to the protocols was suboptimal in one of the study ICUs because of understaffing. Many hypoglycemic episodes might have been avoided if adherence had been better. Glucometers used to measure BG at the bedside, such as those used in this study, have been recently shown to have insufficient accuracy [17-19]. Blood glucose control in this study may have been more effective and the risk of hypoglycemia may have been lower if it was carried out in hemogasometers. However, it is unlikely that this factor would neutralize the superiority of CAIP compared with Leuven protocol. In addition, most ICUs

use point-of-care glucometers and do not have hemogasometers. Therefore, the results of this study may be more applicable in most settings.

4.3. Comparison with previous literature

Patients from CAIP group had mean BG median level similar to those of Leuven group, approximately 125 mg/dL, even though the target BG range of the latter is 80 to 110 mg/dL. The failure of Leuven protocol to achieve the target range in this study, as opposed to the trials of Van den Berghe et al [1,5], might be due to the fact that it is difficult to implement this protocol into the routine of different ICUs, because it depends mainly on the experience and motivation of the nursing team. Instructions for insulin dose adjustments are not always precise in the Leuven protocol, demanding decisions to be made by nurses. Another explanation for the mean glucose level being higher than the Leuven protocol's target might be that the patients included in this study had higher baseline glucose levels than those evaluated in the 2 Leuven trials [1,5]. This is because, as opposed to the Belgium studies, hyperglycemia (≥150 mg/dL) was a necessary inclusion criterion in the present trial.

In spite of the lower risk of hypoglycemia in CAIP group compared with Leuven group, the risk was still considerable. In comparison with other studies [1,5,20,21], the frequency of hypoglycemia observed in this study was higher. The incidence of hypoglycemia was 21.4% in the CAIP group and 41.4% in the Leuven group, whereas in other studies, which used the Leuven protocol, the incidence varied between 5.1% and 18.7%. We believe that the higher incidence of hypoglycemia observed in this study was attributable to (1) the longer ICU stay of patients enrolled in this study (median, 7 vs 3 days in the first study by Van den Berghe et al [1]). Assuming that the risk of hypoglycemia is relatively constant while patients are on an insulin drip, patients in this study would have approximately double the chance of experiencing an episode of hypoglycemia. In fact, the mean proportion of hypoglycemic measurements per patient was low in CAIP group (0.43%). (2) The eligibility criteria in this study, with the need of one episode of hyperglycemia and presence of SIRS or mechanical ventilation, leads to the selection of patients with a higher risk of hypoglycemia [8,22]. In fact, different samples will have a remarkably different risk as evidenced by the 5.1% and 18.7% incidence of hypoglycemia in the intensive insulin arms of the surgical and medical Leuven trials, respectively. Therefore, estimates of hypoglycemic risk may not be comparable between studies; instead, different insulin protocols should be submitted to a randomized comparison, as we did. (3) The ICU that enrolled most of the patients in this study had a low nurse-to-patient ratio and high staff turnover (Hospital Mário Covas, Santo André, SP, Brazil). Compliance with all protocols was sometimes inadequate, in special at night (eg, omission of glucose measurements with unchanged insulin infusion). Therefore, many hypoglycemic episodes arose because of protocol noncompliance and might have been avoided.

4.4. Interpretation of study findings and clinical implications

The CAIP group had approximately half the incidence of hypoglycemia (≤40 mg/dL) compared with the Leuven group. We think the following features of CAIP reduced the risk of hypoglycemia: (1) higher target range (100-130 mg/dL); (2) insulin infusion and next BG measurement are indicated by the microcomputer software, which may have facilitated its implementation; (3) insulin is adjusted not only according to current BG level, but also according to the rate of change since the last measurement, which allows a smoother BG control. We believe that the incidence of hypoglycemia observed with CAIP might be further lowered by the following: (1) strict adherence to protocol orders, (2) use of arterial blood for glucose measurement instead of fingerstick blood, and (3) use of hemogasometers within ICU to measure BG instead of point-of-care glucometers.

Good acceptance of the insulin protocol by the nursing staff is critical for a smooth implementation of strict glucose control [9]. We evaluated the nurses' perception regarding the feasibility of the insulin protocols and also which of those the nurses would prefer to use in their ICU. Between the 2 continuous insulin infusion protocols, the CAIP was considered easier to use than the Leuven protocol. Also, CAIP was considered as easy as the conventional protocol. Most nurses chose CAIP as the protocol they would like to see implemented in their ICUs. We believe that the easy use of the computer program was an important determinant for turning CAIP into a more practical protocol than Leuven. Also, CAIP displays the exact dose of insulin to be infused; therefore, as opposed to Leuven protocol, CAIP did not require decisions to be made by the nurses, allowing them to concentrate on other aspects of patient care.

Recently, several randomized controlled trials [2-5] have had results conflicting with those obtained in the very influential study of Van den Berghe et al [1]. Most of the newer studies found a similar mortality with the strict or the liberal glucose control strategies [2,3,5]. More remarkably, NICE-SUGAR, the largest multicenter trial evaluating intensive vs conventional glucose control in critically ill patients, observed an increase in the risk of death at day 90th associated with the intensive glucose control strategy (81-108 mg/dL) compared with a conventional strategy (<180 mg/dL) [4]. Our study did not aim and was not powered to evaluate the effect of different BG goals on patients' outcomes. However, based on the available evidence, it is sensible to conclude that BG ranges below 180 mg/dL, but not very strict targets, are probably safe and effective goals for critically ill patients.

We conclude that CAIP protocol may be used to achieve glucose control within 100 to 130 mg/dL in critically ill

patients with a lower risk of hypoglycemia than the Leuven protocol and may have better acceptance by the nursing staff.

4.5. Future research

In line with the available evidence showing that BG levels just below 180 mg/dL are probably superior to very strict levels, protocols such as CAIP may be adapted and tested to target higher BG levels. On the other side, development of glucose control devices, which integrate continuous or very frequent glucose measurement with insulin infusion (closed loop), may greatly improve glucose control in critically ill patients while virtually avoiding hypoglycemia.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcrc.2009.05.005.

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