

The efficacy and safety of glucose control algorithms in intensive care

A pilot study of the Survival Using Glucose Algorithm Regulation (SUGAR) trial

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KEY WORDS

critical care, insulin, mortality

ABSTRACT

INTRODUCTION The benefits, harms and feasibility of intensive insulin therapy in critically ill patients remain unclear. Several single center studies have attempted to demonstrate the benefit of intensive insulin therapy in critically ill patients with variable results.

OBJECTIVES We conducted a pilot randomized trial to assess the feasibility, safety and clinical outcomes of preprinted glucose management algorithms before the initiation of a large multicenter trial.

PATIENTS AND METHODS Within 48 hours of admission to the intensive care unit, we randomized mechanically ventilated patients to either the "high" group (target serum glucose concentration 9–11 mmol/l) or the "low" group (target serum glucose concentration 5–7 mmol/l). To assess feasibility we measured the time to reach target glucose range, time in target range, morning glucose concentrations, average daily glucose concentrations, and number of cross-overs. To assess safety, we measured the number of hypoglycemic events (serum glucose <2.2 mmol/l), and other serious adverse events such as cardiac arrests and seizures.

RESULTS Sixty-eight patients were enrolled (35 in the high group and 33 in the low group). During the first week, the median proportions of time spent in the target range were 35.7% and 53.0% for the high and low groups, respectively ($p = 0.0001$). Morning glucose concentrations were 8.3 ± 1.6 mmol/l and 6.2 ± 1.2 mmol/l. One (2.9%) and 8 (24.2%) episodes of hypoglycemia (<2.2 mmol/l) occurred in the high and low groups, reflecting 0.002 and 0.03 hypoglycemic events per patient-day, respectively.

CONCLUSIONS This pilot trial of intensive insulin therapy identified numerous challenges that helped in the preparation of an international multicenter randomized trial of intensive insulin therapy to evaluate benefits and harms.

INTRODUCTION The incidence of hyperglycemia in the intensive care unit (ICU) ranges from 20–90%.^{1–3} However, based on the findings of prospective observational cohort studies^{4,5} and randomized clinical trials^{1,6–9} the utility

of tight glucose control remains controversial. In a landmark trial, Van den Berghe¹ randomized 1548 critically ill patients (mostly cardiac surgical) to receive either intensive insulin therapy or conventional insulin therapy. Compared

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to the conventional group, hospital mortality in the intensive insulin therapy group was reduced by 3.4%, and by 9.6% among the subset of patients who spent >5 days in the ICU. These investigators conducted a second study of intensive insulin therapy in critically ill medical patients⁶ and found no difference in hospital mortality between the two groups. After adjustment for baseline imbalances, intensive insulin therapy was associated with a trend toward lower mortality ($p = 0.05$). However, in an *a priori* subgroup of patients treated in the ICU for ≥ 3 days, there was a significant reduction in mortality ($p < 0.001$).⁶

The German Competence Sepsis Network (VISEP trial)⁷ found no difference in 28 day (21.9% vs. 21.6%, $p = 1.0$) and 90 day mortality (32.8% vs. 29.5%, $p = 0.43$) but an increased risk of hypoglycemia (12.1% vs. 2.1%) in the intensive insulin group vs. control group. In the absence of a mortality benefit, the trial was discontinued early after enrolling 488 patients after a safety analysis.

Similarly, the Glucontrol study was discontinued after the first interim analysis due to futility.^{8,9} This trial was designed to enroll 3500 patients, but was stopped in May 2006 after 1101 patients in 21 ICUs had completed the study, because of the occurrence of adverse events in patients randomized to intensive insulin therapy. Severe hypoglycemia (defined as a blood glucose concentration of less than 40 mg/dl or 2.2 mmol/l) occurred in 8.6% of the intensive insulin therapy group compared with only 2.4% ($p < 0.001$) in the less strictly controlled group. Multivariate analysis confirmed that aggressive blood glucose targets significantly increased the risk of hypoglycemia. However, there was no difference in all-cause mortality (17% vs. 15%, $p =$ nonsignificant) between groups and the risk of death was not increased in patients who experienced severe hypoglycemia.

Numerous authors¹⁰⁻¹⁵ have called for trials involving more diverse populations, and better understanding of the role of nutritional strategies, glucose exposure, and the effect of large insulin doses. A recently published editorial¹⁶ states "tight glycemic control recommendations are grade C at present" and that further randomized trials are required. A recent meta-analysis of 8432 randomized trials showed no effect of intensive insulin therapy on mortality in critically ill patients.¹⁷ In this pilot randomized trial, we assessed the feasibility and safety of intensive insulin therapy, in preparation for a multicenter prospective trial of intensive insulin therapy that was designed to evaluate potential benefits and harms in a mixed medical/surgical ICU population.

PATIENTS AND METHODS Three overall aims

We had three overall aims for this pilot trial: to evaluate feasibility, safety and clinical outcomes. This pilot trial was specifically undertaken to evaluate the feasibility of preprinted

paper-based glucose management algorithms in anticipation of a multicenter trial of glucose control in critically ill populations. To assess feasibility, we measured the time to reach target glucose range, time in target range, mean morning glucose concentrations, mean daily glucose concentrations, and number of crossovers. Second, to assess safety, we recorded hypoglycemic events (blood glucose < 2.2 mmol/l), and serious adverse events such as cardiac arrests and seizures. Third, to assess clinical outcomes we recorded mortality (both in ICU and in hospital), length of ICU stay, need for renal replacement therapy, and incidence of bacteremia.

Study population We chose a convenience sample of 65 patients and estimated that we would require 24 months to enroll this number of patients in a single study center. Patients were considered for enrollment if they were ≥ 16 years old and had been admitted to the ICU within the last 48 hours. Exclusion criteria were lack of informed consent, pregnancy, severe head injury (Glasgow Coma Score < 8 at the time of hospital admission), fulminant hepatic failure (as defined by the King's College criteria)¹⁸, enrollment in another interventional trial, a clinical situation where therapeutic hyperglycemia may be indicated (e.g. acetylsalicylic acid overdose), myocardial infarction/ischemia as the reason for this hospital admission, or history of insulin-dependent diabetes. Patients not expected to be in the ICU for more than 24 h (due to imminent death, withdrawal of life support, or discharge) were also excluded (FIGURE).

The SUGAR (Survival Using Glucose Algorithm Regulation) pilot trial was a single center study involving human subjects. The trial protocol was approved by the Institutional Review Board at the Vancouver Hospital and Health Sciences Centre. Informed consent was obtained for eligible patients or legal proxy decision makers before enrollment.

Intervention After obtaining informed consent from the patient or their surrogate, patients were allocated to groups by a computerized random number generator. Allocation arm was recorded in sealed, opaque envelopes, which were opened by a hospital staff member who was not one of the study investigators. Patients were randomized to receive an insulin regimen to control blood glucose concentrations in one of two specified ranges, controlled by the bedside nurse using a preprinted algorithm. Patients randomized to conventional insulin therapy ("high" group) had a target glucose concentration of 9–11 mmol/l while those randomized to intensive insulin therapy ("low" group) had a target glucose concentration of 5–7 mmol/l. After enrollment of 14 patients, we found that the glucose concentrations in the low group were higher than the desired range; therefore, for the last 18 patients in this group, we revised the algorithm to achieve a target glucose concentration of 4–6 mmol/l.

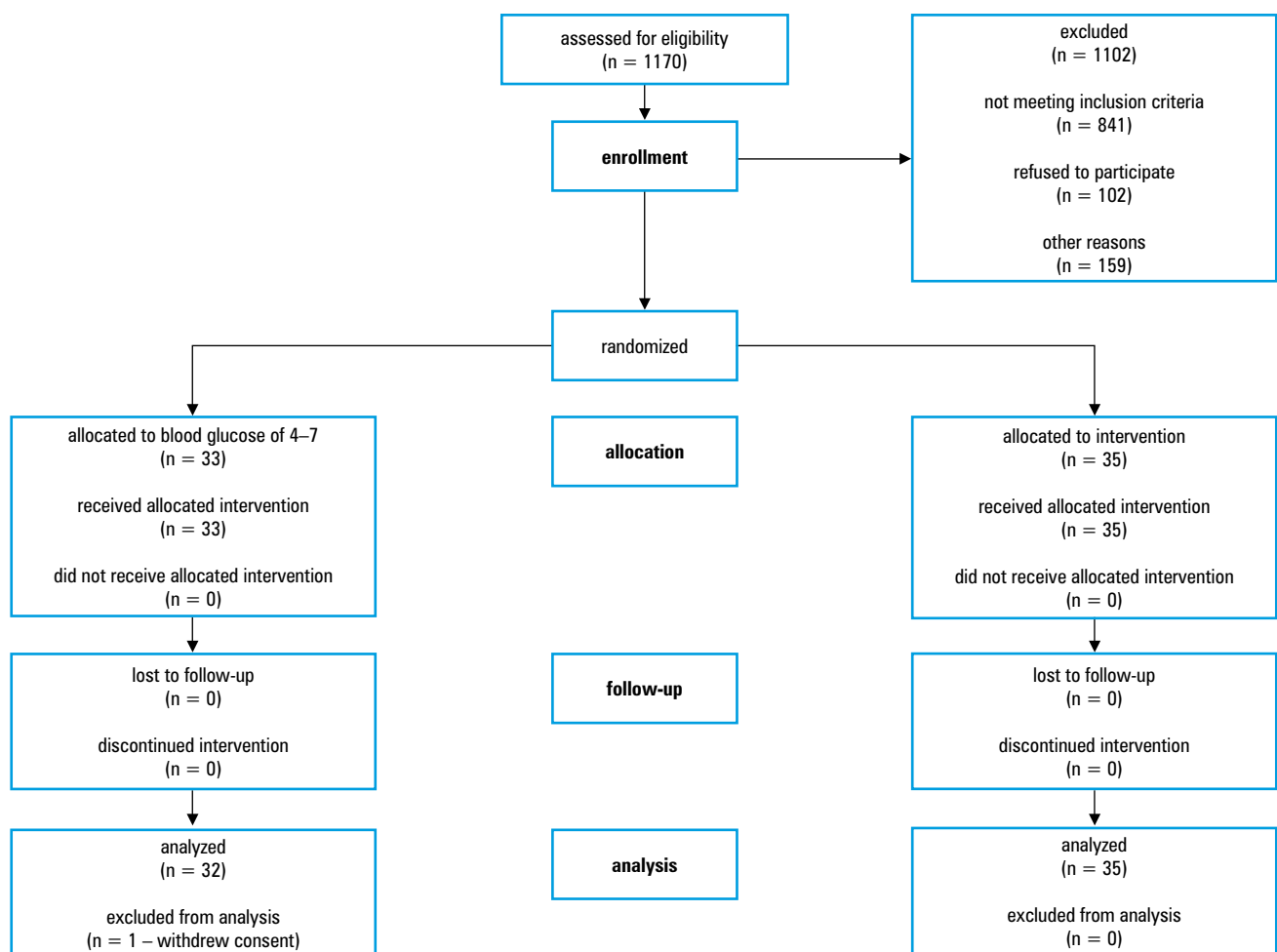


FIGURE Diagram of patient enrollment

In the high group, a continuous intravenous infusion of insulin (50 IU Humulin R in 50 ml of 0.9% sodium chloride) was started if the blood glucose concentration exceeded 11.0 mmol/l. The infusion rate was adjusted to keep the blood glucose concentration less than 11.0 mmol/l and titrated when needed to maintain the glucose concentration between 9–11 mmol/l. If, without insulin, the patient's glucose concentration was <9.0 mmol/l, intravenous dextrose was not administered unless serum glucose concentrations fell below 4.0 mmol/l. Initially, in the low group, a continuous intravenous infusion of insulin (50 IU Humulin R in 50 ml of 0.9% sodium chloride) was started if the blood glucose concentration exceeded 7.0 mmol/l and the infusion rate was adjusted to maintain the glucose concentration between 5.0–7.0 mmol/l. If, without insulin, the glucose concentration was <5.0 mmol/l, intravenous dextrose was not administered unless serum glucose concentrations fell below 3.5 mmol/l.

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the last 18 patients in the low group, a continuous intravenous infusion of insulin (50 IU Humulin R in 50 ml of 0.9% sodium chloride) was started if the glucose concentration exceeded 6.0 mmol/l and the infusion rate was adjusted to maintain the glucose concentration between 4.0–6.0 mmol/l. If, without insulin, the glucose concentration was <4.0 mmol/l, intravenous dextrose was not administered unless serum glucose concentrations fell below 2.5 mmol/l. For the analysis, all of the low group patients were treated as one group.

Blood samples were taken from arterial catheters. Adjustments to the insulin dose were made based on the values from bedside glucose measurement devices (Accu-Chek, Boehringer-Mannheim, Laval, PQ, Canada) on undiluted arterial blood done initially at hourly intervals. The frequency of blood glucose measurements was determined by a predefined algorithm that depended on insulin dose and the current measurement. If these concentrations were within the assigned range, glucose concentrations were measured less frequently than if they were either above or below the target range. Before this pilot trial began, bedside nurses and physicians were formally trained in the use of the insulin regimens by a Research Coordinator.

After discharge from the ICU, blood glucose management occurred at the discretion of the patients' attending physician.

Data collection and outcome measures Upon enrollment, we recorded detailed demographic information including age, sex, admission diagnosis, co-morbidities, and Acute Physiology and Chronic Health Evaluation (APACHE II) score during the first 24 hours of ICU admission. We documented dates of admission to and discharge from the ICU and the hospital.

The primary outcome of feasibility was assessed by measuring time to reach target glucose range, time in target range, mean morning glucose concentration, mean daily glucose concentration, and crossover time. Crossover time was defined as the percentage of total study time that patients spent in the target range of the group to which they were not assigned. Morning glucose concentrations were recorded and mean daily glucose concentrations were calculated. Safety was assessed by measuring the number of episodes of serum glucose concentration ≤ 2.2 mmol/l (a conventional threshold used in previous similar trials) and serious adverse events such as cardiac arrests and seizures. The clinical outcomes were mortality (both in ICU and in hospital), length of ICU stay, need for renal replacement therapy, and episodes of bacteremia. We collected data on daily caloric intake from all sources in all subjects every day.

Data analysis The two groups were compared using descriptive statistics. The feasibility of glucose control was determined by recording the median time to reach target glucose range, percentage of time in target range, mean morning glucose concentrations and mean daily glucose concentrations and number of crossovers. Due to the variable numbers of glucose measurements in each patient throughout the day, linear interpolation from recorded values was used to generate hourly mean glucose values. We tested for

significant differences with the Student's t-test, the Mann-Whitney U test, or the χ^2 test, as appropriate. We compared mortality rates in the two groups using relative risk and 95% confidence intervals. We used repeated measures ANOVA to analyze differences in the daily caloric intake between the two groups.

RESULTS Study population Between September 2002 and September 2004, 1170 patients were screened and 329 patients met inclusion criteria. Of these, 102 patient surrogates refused consent and 159 were excluded for other reasons. Therefore, 68 patients were enrolled and randomized to the high or low groups; 35 patients were assigned to a target glucose concentration of 9–11 mmol/l (high group), and 33 were assigned to the low group (14 to be maintained between 5 and 7 mmol/l, and subsequently 19 to be maintained between 4–6 mmol/l; **FIGURE**). One patient in the low group withdrew consent before the trial intervention began. All remaining 67 patients were included in the intention-to-treat analyses. There were no differences between the groups in any of the recorded baseline characteristics (**TABLE 1**).

Feasibility: glucose control and insulin use

The high group spent 24.6% of the study period within, 62.5% below, and 12.9% above the targeted glucose range (**TABLE 2**). The low group spent 56.3% of study time within, 9.7% below, and 34.1% above the targeted glucose range. In the first 7 days, the high group spent less time in their target range (a median of 35.7% of the time vs. 53.0% in the low group; $p = 0.0001$). The mean morning glucose concentration was significantly higher in the high group than the low group (8.3 mmol/l vs. 6.2 mmol/l,

TABLE 1 Baseline characteristics

	Low group (n = 32)	High group (n = 35)
age in years (\pm SD)	56.7 (\pm 18.7)	56.4 (\pm 16.0)
APACHE II score (\pm SD)	21.75 (\pm 6.1)	23 (\pm 6.3)
male gender (%)	23 (71.9)	20 (57.1)
congestive heart failure (%)	4 (12.5)	2 (6.3)
ischemic heart disease (%)	4 (12.5)	5 (14.3)
non insulin dependent diabetes mellitus (%)	4 (12.5)	2 (5.7)
liver disease (%)	1 (3.1)	0 (0)
chronic renal failure (%)	0 (0)	0 (0)
chronic obstructive pulmonary disease (%)	6 (18.8)	8 (22.9)
cancer (%)	5 (15.6)	6 (17.1)
transplant (%)	2 (6.3)	1 (2.9)
immunocompromised (%)	6 (18.8)	3 (8.6)
recent surgery (%)	19 (59.4)	17 (48.6)
trauma (%)	11 (34.4)	13 (37.1)
steroids prior to ICU (%)	3 (9.4)	3 (8.6)

Abbreviations: APACHE – Acute Physiology and Chronic Health Evaluation, ICU – intensive care unit, SD – standard deviation

TABLE 2 Feasibility of glucose control

	Low group (n = 32)	High group (n = 35)	p
received insulin (% of patients)	32 (100%)	20 (57.1%)	<0.0001
insulin units per day (\pm SD)	78.9 \pm 66.3	25.2 \pm 45.6	0.0002
08:00 hours glucose concentration (\pm SD)	6.2 \pm 1.2	8.3 \pm 1.6	<0.0001
daily average glucose concentration (\pm SD)	6.3 \pm 1.0	8.4 \pm 1.7	<0.0001
time in range (median % of time in study)	53.0%	35.7%	<0.0001
number of hypoglycemic events (number of patients) while in study	8 (7)	1 (1)	0.0233

Abbreviations: see TABLE 1

respectively, $p < 0.0001$). The percentage of total study time that patients spent in the target range of the group that they were not assigned to (crossover time) was a median of 19.9% for the high group and a median of 1.7% for the low group ($p < 0.0001$).

Fifty-seven percent of patients in the high group received insulin during their ICU stay whereas all patients in the low group received insulin. The average daily dose of insulin in the high group was 25.2 IU (± 45.6 IU) compared to 78.9 IU (± 66.3 IU) in the low group ($p = 0.0002$).

Safety One episode of hypoglycemia occurred in the high group (2.9% of patients), and 8 episodes occurred in the low group (24.2% of patients). These occurred out of a total of 2802 and 2313 glucose measurements in the high and low groups, respectively. There were 0.002 and 0.03 hypoglycemic events per patient-day in the high and low groups ($p = 0.0233$). We detected no untoward consequences or serious adverse events such as seizures or cardiac arrests associated with these episodes of hypoglycemia. No patients were withdrawn from their assigned intervention by their physicians.

Clinical outcomes There was no difference in 28 day mortality between groups. Five (14.3%) patients in the high group and four (12.5%) patients in the low group died (relative risk 1.14 (95% CI from 0.34–3.89, $p = 0.83$)).

In the high and low groups, respectively, the median lengths of ICU stay (see TABLE 3) were 11.5 and 7.43 days ($p = 0.013$). The median lengths of hospital stay were 33 days and 22 days in the high and low groups ($p = 0.079$). The median duration of mechanical ventilation was 228.2 h in the high group and 132.2 h in the low group ($p = 0.019$). Two patients (9.4%) in the high group and two

patients (8.6%) in the low group required renal replacement therapy ($p = 0.93$). Nine patients (28.1%) in the high group and 3 (8.6%) in the low group developed bacteremia, but there was no difference in time-adjusted bacteremia rates.

Average daily calories were 2256 kcal/day in the high group and 2299 kcal/day in the low group ($p = 0.46$). Patients received most of their nutrition via the enteral route ($85 \pm 0.65\%$ in the low group and $83 \pm 5.1\%$ in the low group, $p = 0.59$).

DISCUSSION In this pilot randomized trial we examined the feasibility, safety, and clinical outcomes of two intensive insulin therapy regimens. Several important lessons were learned that assisted in the development and management of the subsequent multicenter trial.

With respect to feasibility, we found that our initial preprinted low group algorithm did not achieve the desired target range. After 14 patients were enrolled in the low group we found that the glucose concentrations in the low group were higher than the desired range. Therefore, we revised the algorithm for the last 18 patients in this group to achieve lower average glucose levels.

We did find that our preprinted algorithms successfully created a statistically significant difference between the two groups in mean daily blood glucose concentrations. However, patients randomized to the high group spent the majority of the study period with glucose levels below their target range. This may have been because the study protocol did not include directions to increase the glucose concentrations unless they were considered to be dangerously low. This distinction is important, as the algorithms studied in this pilot trial allowed a large overlap in blood glucose levels between the high and the low groups. In a trial assessing clinical outcomes this overlap

TABLE 3 Clinical outcomes

	Low group (n = 32)	High group (n = 35)	p
median ICU length of stay (days, interquartile range)	7.43 (5.12–12.72)	11.5 (7.39–20.95)	0.013
median hospital length of stay (days, interquartile range)	22 (13–40.5)	33 (21–66)	0.079
median duration of mechanical ventilation (hours, interquartile range)	132.24 (89.88–227.76)	228.24 (139.68–458.4)	0.019
renal replacement therapy (number of patients)	2	2	0.9263
episodes of bacteremia or fungemia (number of patients)	4	17	NS

Abbreviations: NS – nonsignificant, others – see TABLE 1

might hinder the ability to detect meaningful outcomes. This finding allowed us to modify our glucose management algorithm prior to the subsequent multicenter trial.

In terms of safety, we found that hypoglycemia occurred more commonly in the low group than the high group (8 vs. 1 episode, or 24.2% vs. 2.9% of patients). Our protocol was associated with a higher rate of hypoglycemia than that in a recent report of intensive insulin therapy in a medical ICU⁶ but is consistent with rates of hypoglycemia seen in a similar study in a surgical ICU¹. Hypoglycemic events in critically ill patients may be associated with increased mortality, which requires careful evaluation in studies with larger sample sizes.¹⁹ We did not document any seizures or cardiac arrests associated with these short-lived hypoglycemic episodes.

This pilot trial was not powered to detect differences in clinical outcomes between groups, and any differences observed must be interpreted cautiously. We found no difference in mortality between patients treated with insulin to maintain blood glucose concentrations between 4–7 mmol/l and those treated to maintain these concentrations between 9–11 mmol/l. The low target group had a short median duration of mechanical ventilation and a shorter median duration of ICU stay, but no difference in median length of hospital stay. The rates of fungemia and bacteremia were not different between the two groups when adjusted for time.

Patients studied in the first trial by van den Berghe et al. were substantially different from those whom we enrolled. The patients in the van den Berghe et al. trial were primarily cardiac surgical patients (62.7% of all patients), a population in which the benefit of strict glucose control has previously been demonstrated.^{20–22} In their second trial⁶, van den Berghe and colleagues enrolled patients who had an average APACHE II score of approximately 23 and who had mostly medical illnesses. Despite the similar level of illness seen in our population, 57.1% of patients in our high group (9–11 mmol/l) required insulin as compared to 70.4% in the conventional treatment arm of the second trial by van den Berghe et al. We speculate that this difference is explained by differences in nutritional practices between our study and van den Berghe's studies. Both studies by van den Berghe et al. used large amounts of intravenous carbohydrate, which is not typical of North American practice.^{23,24} In our study there was no difference between the groups in the average amount of daily calories received, and most calories were provided enterally.

Interpreting any trial of intensive insulin therapy and glucose control requires understanding nutritional strategies employed. In critically ill patients an infusion of dextrose may worsen the neurohormonal environment. This occurs via the activation of pro-inflammatory cytokines, the impairment of neutrophil function, and

the promotion of inappropriate thrombosis.²⁵ It is therefore possible that the use of insulin in previous trials may have partly been as a "rescue therapy" for severe hyperglycemia and that the use of insulin to achieve a target blood glucose of 4.4–6.1 mmol/l helped mitigate the harm of the dextrose infusions.

Our study has several limitations. Of the 329 eligible screened patients, 68 (20.7%) were enrolled. This low rate of enrollment was primarily due to difficulty in achieving timely informed consent. It is possible that this may have introduced a bias into the type of patients enrolled, which may affect the generalizability of our results. As a single centre trial, the generalizability of our findings is limited to ICUs with practices and algorithms similar to ours. Although the randomization of patients was concealed and blinded, treatment was not, so like other unblinded intensive insulin therapy trials, it is possible that patient management may have influenced outcomes. However, our pilot trial was not designed to assess short- or long-term mortality and morbidity endpoints; furthermore, the small sample size makes any inferences about these outcomes speculative.

In conclusion, we have examined the feasibility and safety of two glucose control algorithms in critically ill patients, illustrating how pilot trials can help to prepare for future large trials. Our results demonstrate how difficult it can be, even under study conditions, to maintain a narrow range of glucose concentrations in critically ill patients.

In another pilot randomized trial (LOGIC – the Lowering Of Glucose In Critical Care), glucose values were in the two target ranges only 40% of the time despite using well accepted insulin infusion algorithms.²⁶ We documented more hypoglycemic events in the low target range group, but this trial is too small to draw conclusions about the consequences of such events, or the effect of intensive insulin therapy on clinical outcomes. Recently, a large collaborative randomized trial powered to detect differences in clinically important outcomes was completed in Australia, New Zealand, Canada, and the USA.²⁷ The success of NICE-SUGAR trial was in part due to the lessons learned in our preparatory pilot trial.

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Skuteczność i bezpieczeństwo stosowania algorytmów kontroli stężenia glukozy w intensywnej terapii

Survival Using Glucose Algorithm Regulation (SUGAR) – badanie pilotowe

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SŁOWA KLUCZOWE

insulina, intensywna terapia, śmiertelność

STRESZCZENIE

WPROWADZENIE Korzyści, zagrożenia i możliwość przeprowadzenia intensywnej terapii insulinowej u pacjentów w stanie krytycznym pozostają niejasne. W kilku jednośrodkowych badaniach podjęto próbę wykazania korzyści płynących z intensywnej terapii insulinowej u pacjentów w stanie krytycznym, otrzymując niespójne wyniki.

CELE Przed rozpoczęciem dużego badania wielośrodkowego przeprowadzono pilotowe badanie z randomizacją w celu oceny wykonalności, bezpieczeństwa oraz efektów klinicznych stosowania z góry ustalonych algorytmów kontroli stężenia glukozy.

PACJENCI I METODY W ciągu 48 godzin od przyjęcia na oddział intensywnej terapii randomizowano pacjentów mechanicznie wentylowanych, przydzielając ich losowo do grupy „dużego stężenia” (docelowe stężenie glukozy w surowicy 9–11 mmol/l) albo „małego stężenia” (docelowe stężenie glukozy w surowicy 5–7 mmol/l). Aby dokonać oceny wykonalności badania, zmierzono czas potrzebny do osiągnięcia docelowego zakresu stężeń glukozy, czas kontynuacji badania przy osiągnięciu docelowego zakresu stężeń, poranne stężenia glukozy, średnie dobowe stężenia glukozy oraz liczbę przejść pacjentów z jednej grupy do drugiej. W celu przeprowadzenia oceny bezpieczeństwa zmierzono liczbę epizodów hipoglikemii (stężenie glukozy w surowicy <2,2 mmol/l) oraz liczbę innych ciężkich zdarzeń niepożądanych, takich jak zatrzymanie krążenia, drgawki.

WYNIKI Do badania włączono 68 pacjentów (35 z grupy „dużego stężenia” oraz 33 z grupy „małego stężenia”). W pierwszym tygodniu badania mediana odsetka czasu badania, w którym wyniki pomiaru glukozy mieściły się w zakresie stężeń docelowych, wynosiła 35,7% w grupie „wysokiego stężenia” oraz 53% w grupie „niskiego stężenia” ($p = 0,0001$). Poranne stężenia glukozy wynosiły odpowiednio $8,3 \pm 1,6$ mmol/l i $6,2 \pm 1,2$ mmol/l. W grupie „wysokiego stężenia” miał miejsce jeden (2,9%) epizod hipoglikemii (<2,2 mmol/l), a w grupie „niskiego stężenia” odnotowano 8 takich epizodów (24,2%), co przekłada się odpowiednio na 0,002 i 0,03 zdarzeń hipoglikemicznych na pacjenta/dobę.

WNIOSKI Niniejsze badanie pilotowe dotyczące intensywnej insulinoterapii pokazało liczne problemy, które okazały się pomocne w przygotowaniu międzynarodowego, wielośrodkowego badania z randomizacją nad intensywną insulinoterapią w celu oceny korzyści i ryzyka związanych z tą metodą.

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