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A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study

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Abstract *Purpose:* An optimal target for glucose control in ICU patients remains unclear. This prospective randomized controlled trial compared the effects on ICU mortality of intensive insulin therapy (IIT) with an intermediate glucose control. *Methods:* Adult patients admitted to the 21 participating medico-surgical ICUs were randomized to group 1 (target BG 7.8–10.0 mmol/L) or to group 2 (target BG 4.4–6.1 mmol/L). *Results:* While the required sample size was 1,750 per group, the trial was stopped early due to a high rate of unintended protocol violations. From 1,101 admissions, the outcomes of 542 patients assigned to group 1 and 536 of group 2 were analysed. The groups were well balanced. BG levels averaged in group 1 8.0 mmol/L (IQR 7.1–9.0) (median of all values) and 7.7 mmol/L (IQR 6.7–8.8) (median of morning BG) versus 6.5 mmol/L (IQR 6.0–7.2) and 6.1 mmol/L (IQR 5.5–6.8) for group 2 ($p < 0.0001$ for both comparisons). The percentage of patients treated with insulin averaged 66.2 and 96.3%, respectively. Proportion of time spent in target BG was similar, averaging 39.5% and 45.1% (median (IQR) 34.3 (18.5–50.0) and 39.3 (26.2–53.6)%) in the groups 1 and 2, respectively. The rate of hypoglycaemia was higher in the group 2 (8.7%) than in group 1 (2.7%, $p < 0.0001$). ICU mortality was similar in the two groups (15.3 vs. 17.2%). *Conclusions:* In this prematurely stopped and therefore underpowered study, there was a lack

of clinical benefit of intensive insulin therapy (target 4.4–6.1 mmol/L), associated with an increased incidence of hypoglycaemia, as compared to a 7.8–10.0 mmol/L target. (ClinicalTrials.gov # NCT00107601, EUDRA-CT Number: 200400391440).

Keywords Insulin therapy · Insulin resistance · Stress hyperglycaemia · Hypoglycaemia · Critical illness

Introduction

The interest in the management of stress related hyperglycaemia was renewed by one landmark study [1] which reported an improved outcome in critically ill patients when insulin therapy was dosed to lower blood glucose level (BG) to a 4.4–6.1 mmol/L tight range (intensive insulin therapy, IIT), as compared to hyperglycaemia up to the classical renal threshold (12 mmol/L). Since the release of these results, recommendations to implement tight glucose control in intensive care units have been rapidly issued by several health care agencies (Joint Commission on Accreditation of Healthcare Organization, the Institute for Healthcare Improvement and the Volunteer Hospital Organization) and by the American Diabetes Association. The occurrence of adverse events in patients randomized in the IIT group was not a reason to prematurely stop the study.

Even though IIT is easily accessible and inexpensive, this technique is labour-intensive. Several issues might limit the external validity of the benefits of IIT [2, 3]. Firstly, a large amount of glucose was administered intravenously for nutritional purposes to all patients included in both trials performed in Leuven [1], yielding a high incidence of sustained hyperglycaemias. Secondly, associated risks of IIT included hypoglycaemia, implying increases in workload and stress [4], and potential complications [5]. Thirdly, the results suggest that the benefit of IIT may be restricted to some subsets of patients (for instance, cardiac surgery and patients without diabetes who stayed at least 3 days in the ICU) [1] but not to others such as medical ICU patients [6] or patients with severe sepsis, as recently reported [7]. Whether the observations made in a highly experienced centre may translate to others is presently unknown [3].

The present study was undertaken to test the hypothesis that IIT improves survival of patients treated in medico-surgical intensive care units (ICU), as compared with a glucose control target of 7.8–10.0 mmol/L, lower than in the Leuven trials [1, 6]. The control target was selected to prevent the adverse effects of severe hyperglycaemia, while reducing the risks of hypoglycaemia. Specifically, this study was designed to detect whether IIT was associated with a 4% decrease of the absolute ICU mortality.

Parts of this work were presented as an abstract at the 20th Congress of the European Society of Intensive Care Medicine [8].

Patients and methods

The Glucontrol study was launched in 2002 by the working group on metabolism and nutrition of the European Society of Intensive Care Medicine and was endorsed by the European Critical Care Research Network. Twenty-one intensive care units (Appendix 1) participated: their characteristics were recorded in a survey [9] including their usual management of glucose control during the year before the implementation of the study (Table 1). There was no financial incentive, nor defrayment of costs related to the study. The study sponsor had no role in the conduct of the study or the interpretation of data.

The recruitment of patients was started in November 2004. Adult patients (older than 18 years) admitted to the participating ICUs were eligible. The study was approved by the institutional review board of each participating hospital. The investigators followed the respective national standards for informed consent. Signed informed consent was obtained when required, from patients or the next-of-kin, in conformity with national and local regulations. Exclusion criteria included a life expectancy lower than 24 h, and the absence of consent. The primary endpoint was all-cause ICU mortality. The expected mortality in the "control" group (group 1) was based on the data recorded in the preliminary survey (Table 1) [8]

Table 1 Data recorded from the participating units

Characteristics	Value
Median number of beds (range)	12 (5–44)
Median nursing staff (bed/nurse) (range)	2.0 (0.5–3.0)
Median number of admission/year (range)	600 (188–3745)
Median number of glucometers/ICU (IQR)	2 (1–37)
Median number of glucometer/bed (IQR)	0.32 (0.09–1.00)
Median APACHE II score (IQR)	15 (11–21)
Median ICU LOS (days) (IQR)	6.0 (3–13)
Median ICU mortality (%) (range)	16.0 (10.0–21.3)
Usual threshold of blood glucose (mmol/L) to start iv insulin (number of ICUs)	
5.0	1
5.5	1
6.7	2
8.3	14
10.0	2
11.1	1

APACHE Acute Physiological and Chronic Health Evaluation, *LOS* Length of Stay, *ICU* Intensive Care Unit, *IQR* InterQuantile Range

and was used to calculate the sample size needed to detect a 4% decrease in mortality with an alpha error rate of 5% and beta error rate of 20% ($n = 1{,}496$ patients in each group). A total of 1,750 patients per group were deemed necessary to account for drop-outs. Interim analyses by an independent data safety monitoring board (DSMB) were planned after every 100 deaths.

Study design

Upon ICU admission, patients were randomised to a BG target of 7.8–10.0 mmol/L (group 1), or to a BG target 4.4–6.1 mmol/L (group 2). The protocol was applied from the time of admission until ICU discharge or death. The central computerised randomisation (blocks of eight patients) was stratified by centre and concealed. The central data manager and the statistician were blinded to treatment assignment.

Regular human insulin (Actrapid, Novo-Nordisk, DK, 1 IU/mL NaCl 0.9%) was administered by continuous intravenous infusion (algorithm in electronic supplemental material) via the pumps available at each site. There was no standardised policy for ICU discharge, nutrition, or for the weaning of mechanical ventilation. After discharge from the ICU or when the patient was on full oral feeding, intravenous insulin was shifted to subcutaneous administration, according to the standard local practice. There was no restriction for any other treatment including nutritional support (enteral or parenteral) or intravenous glucose. The vital outcome of the patients was recorded until discharge from the hospital or until the 28th day after ICU admission if the patient was discharged before this day. In case of readmission for a second ICU stay, only the outcome data of the last stay was used.

BG was measured in arterial or central venous samples when indwelling catheter were in place, or in samples drawn from the fingertip. The centres were asked to use a blood gas analyser, or a specific glucometer (Accu-Chek Inform, Roche Diagnostics, Mannheim, Germany) to measure the glucose concentration and to check BG hourly until the achievement of the target and at least every 4 h thereafter. Built-in checks of quality parameters were left under the responsibility of the local laboratories. At least one BG value per day was measured by the hospital central laboratory on a morning sample ("morning value") and recorded. The other BG values measured by a blood gas analyser or by a glucose reader on plasma samples were recorded and used uncorrected for the adaptation of the insulin infusion rate. Hypoglycaemia, defined as a BG concentration below 2.2 mmol/L, was treated according to a predefined algorithm (electronic supplemental material). The rate of hypoglycaemia was defined as the proportion of patients that experienced at least one episode of hypoglycaemia. The quality of glucose control was assessed from the percentage of BG readings within, below and above the assigned range of each group. The areas under the curve of BG values above (AUChigh) and below (AUClow) the desired ranges were calculated and expressed in hour mmol/L. The hyperglycaemic and hypoglycaemic indices and the duration of hypoglycaemia were calculated as the area under the curve (AUC) above the upper limit or below the lower limit of the group target divided by the length of observation (mmol/L) [10]. For the purpose of comparability with other trials, the percentage of morning BG values within assigned range was also calculated. Glucose variability was assessed by the standard deviation of BG values and by minimal and maximal values calculated from all values and from the means of BG recorded by patient (patient-averaged glycemia). The time from admission to the start of insulin drip, the duration of insulin therapy, and the number of insulin-free days (i.e. number of days alive in the ICU without intravenous insulin) were calculated.

Baseline characteristics and outcome measures

Upon admission, the patients were categorised as medical, scheduled surgery, emergency surgery and/or trauma, and further subcategorised according to the predominantly failing organ system(s). The Acute Physiological and Chronic Health Evaluation (APACHE II) on admission [11] and the daily Sequential Organ Failure Assessment (SOFA) [12] scores and the presence of diabetes were recorded. The primary outcome variable was the all-cause absolute mortality during the ICU stay. Secondary outcome variables included hospital and 28-day mortality, ICU and hospital, Length of stay (LOS), incidence of organ failures assessed by the daily SOFA score, rate of hypoglycaemia and the SOFA score on the day of hypoglycaemia, duration of mechanical ventilation, inotrope/vasopressor and renal replacement therapy, number of packed red blood cells transfusion (PRBC), febrile days and days with therapeutic anti-infective agents.

Statistical analysis

Continuous variables not normally distributed (Shapiro–Wilk test) are reported as medians and inter-quartile ranges (IQR) and were compared using the Wilcoxon Mann Whitney test. When normality was demonstrated, the continuous variables were presented as mean and standard deviation (SD) and were compared using the Student's t test for independent samples. When median and quartiles were equal to zero, the non-Gaussian data were presented as mean $\pm$ SD and as median (IQR). Categorical variables were compared using Chi^2 tests. To minimise the influence of variations in sampling intervals and the potential weight of outlying measures, the

proportion of time spent in the various BG ranges were calculated by the trapeze method. Average standard deviation was used to compare the variability of the BG. A uni-variable followed by a multivariable logistic regression using a backward elimination procedure was performed to identify possible independent factors associated with hypoglycaemia and mortality. The list of possible factors included age, gender, APACHE II score, pre-existing diabetic, ICU LOS, treatment group (IIT or LIT) and occurrence of hypoglycaemia (for mortality only). The results are presented in odds ratios (OR) with their 95% confidence interval (95% CI). All the analyses were performed on an intent-to-treat basis, with a p value <0.05 considered as statistically significant.

Results

From 3 November 2004 to 30 May 2006, 7,747 patients were admitted, 1,108 patients were assessed from inclusion, of which 1,101 (14.2%) consented to participate and had been randomised, including 23 readmitted patients (Fig. 1). The groups were well matched, as the characteristics of the patients did not differ between groups at the time of inclusion, except for a higher incidence of diabetes in group 1 (Table 2). Following the first interim analysis performed after the 100th death, the DSMB recommended to stop the inclusion of patients. Specifically, the proportion of BG values in the assigned range calculated from the BG readings available at the time of the interim analysis [54.8% (group 1) and 27.8% (group 2) (39.2% after exclusion of day 1 data)] were deemed as a high rate of unintended protocol violation rate. The increased rate of hypoglycaemia in the IIT group was not considered as a safety concern by the DSMB.

Outcome measures (Table 3)

ICU, 28-day and hospital mortality were similar in both groups. ICU and hospital LOS were identical. ICU mortality did not differ when stratifying the patients according to the ICU LOS, less or equal to 3 days (short-stayers) versus more than 3 days (long-stayers) (Table 3). The ICU mortality rate of patients did not differ between patients who were "in-target" and of those who were not : for group 1, the mortality of patients "in-target" (221/542) was 14.5 vs. 15.9% ($p = 0.655$); for group 2 the mortality of patients "in-target"(139/536) was 12.9 vs. 18.6% ($p = 0.126$). Similarly, the mortality rate did not differ between the patients in whom mean BG was below 6.1 mmol/L (8.6% for group 1 and 13.5% for group 2) and those in whom mean BG was higher than 6.1 mmol/L (13.9% for group 1 vs. 19.2% for group 2) ($p > 0.05$ for both comparisons). The power of the sample size of 1,078 patients to detect a 4% difference in ICU mortality with an alpha error rate of 5% and beta error rate of 20% was 32%. The overall severity of organ failures assessed by daily SOFA scores were similar in both groups as were the other severity indices of illness, the number of febrile days and the number of days with anti-infective agents, except for the number of patient days with vasopressors/inotropes which was higher in the group 2 (Table 3).

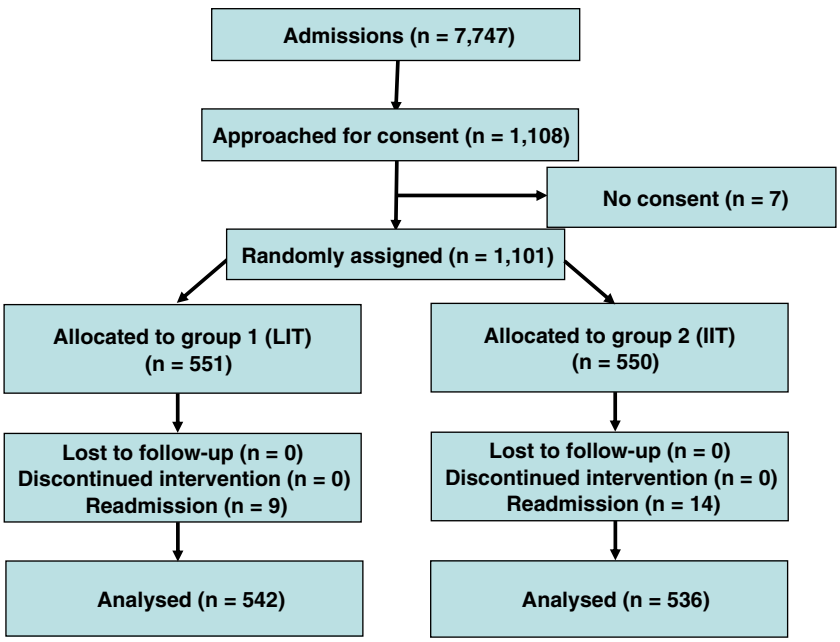

Fig. 1 Study flow chart

Table 2 Characteristics of the patients upon admission

	Group 1 BG target 7.8–10.0 mmol/L $N = 542$	Group 2 BG target 4.4–6.1 mmol/L $N = 536$	p Value
Age (median, IQR)	64.5 (51.1–74.1)	64.8 (50.8–74.0)	0.856
Male patients (%)	333 (61.4)	345 (64.4)	0.339
Type of patients (% of each)			0.881
Medical	219 (40.4)	226 (42.2)	
Scheduled surgery	174 (32.1)	162 (30.2)	
Emergency surgery	96 (17.7)	89 (16.6)	
Trauma	43 (7.9)	41 (7.6)	
Category of diagnosis (% of each)			0.751
Cardiac	178 (32.8)	170 (31.7)	
Respiratory	99 (18.3)	96 (17.9)	
Gastroenterological	79 (14.6)	88 (16.4)	
Neurological	68 (12.6)	74 (13.8)	
Vascular	18 (3.3)	9 (1.7)	
Renal	14 (2.6)	11 (2.1)	
Orthopaedic	34 (6.3)	36 (6.7)	
Haematological	4 (0.7)	2 (0.4)	
Other	48 (8.9)	50(9.3)	
APACHE II score (median, IQR)	15 (11–22)	15 (11–21)	0.807
SOFA score (mean ± SD (range))	6.7 ± 3.3 (0–16)	6.9 ± 3.1 (0–19)	0.454
Glasgow coma score (median, IQR)	15 (9–15)	15 (8–15)	0.787
Respiratory support (% of patients)			0.444
Invasive ventilation	386 (71.2)	363 (67.7)	
Non invasive ventilation	28 (5.2)	33 (6.2)	
Spontaneous breathing	128 (23.6)	140 (26.1)	
Vasopressors/inotropes (% of patients)	218 (40.2)	201 (37.5)	0.359
Proportion of patients with T° > 38.5°C (%)	51 (9.4)	52 (9.7)	0.741
Pre-existing diabetes (% of patients)	116 (21.4)	87 (16.2)	0.029

APACHE, Acute Physiological and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment

Adherence to assigned blood glucose target (Fig. 2)

A total of 62,548 BG values were recorded. Median values of BG (Table 3) (Fig. 2a, b) were higher in group 1 than in group 2 for all study days starting from day 1. BG variability assessed from the min–max values and from SD (Table 3) was similar in the two groups. The proportion of time spent in the assigned range calculated from all readings was higher in the group 2 than in the group 1 (Table 3). The rate of achievement of the targets was stable over time in each centre (data not shown). The amount and duration of insulin therapy was higher in group 2 than in group 1, while the total amount of glucose administered intravenously (including non-nutritional solutions) was similar in both groups (Table 3).

The rate of hypoglycaemia was higher in group 2 (8.7%) than in group 1 (2.7%) (Table 3). Twenty out of the 111 episodes of hypoglycaemia were likely due to the inappropriate continuation of insulin infusion (two patients in group 1, nine patients in group 2). The multivariable logistic regression analysis identified the allocation to group 2, and each 1-point increase in the admission APACHE II score as independent factors associated with hypoglycaemia [adjusted OR, 4.49 (95% CI 2.49–8.12) $p < 0.001$, and 1.07 (95% CI 1.04–1.11) $p < 0.001$), respectively]. The factors identified as associated with mortality by the multivariable logistic regression analysis included the occurrence of hypoglycaemia and APACHE II score [adjusted OR, 1.91 (95% CI 1.07–3.42), and 1.13 (95% CI 1.10–1.16), both $p < 0.01$]. Patients of both groups having experienced hypoglycaemic episodes exhibited higher mortality and mean SOFA scores (calculated as the average of the daily SOFA scores recorded during the ICU stay), compared to patients who did not (32.2% and 7.0 ± 3.1 vs. 13.6% and 6.8 ± 3.2, both $p < 0.01$). The SOFA scores recorded on the days with hypoglycaemia were higher than during the days without hypoglycaemia (7.3 vs. 6.1, $p < 0.01$).

Discussion

The main findings of this multi-centre study performed in medical and surgical critically ill patients were the lack of clinical benefits of IIT targeting a BG of 4.4–6.1 mmol/L, associated with an increased rate of hypoglycaemia, as compared with a less strict glucose control targeting a BG of 7.8–10.0 mmol/L. Because of the premature stop of the

Table 3 Outcome data, treatment-related variables, nutritional management and therapeutic variables glucose control

	Group 1 BG target 7.8–10.0 mmol/L $N = 542$	Group 2 BG target 4.4–6.1 mmol/L $N = 536$	p Value
Outcome data			
ICU mortality (%)	83 (15.3)	92 (17.2)	0.410
Short-stayers (LOS $\leq$3 days) $n = 281$	17/154 (11.0)	17/127 (13.4)	0.5483
Long-stayers (LOS >3 days) $n = 787$	66/388 (17.0)	75/399 (18.8)	0.5135
28-day mortality (%)	83 (15.3)	100 (18.7)	0.1438
Patients still in ICU at D28 (n):	33	34	
Hospital mortality (%)	105 (19.4)	125 (23.3)	0.1136
ICU LOS (days) [median (IQR)]	6 (3–13)	6 (3–13)	0.238
Total ICU stay (LOS)	5,433	5,090	
Hospital LOS (days) [median (IQR)]	16 (11–29)	16 (11–29)	0.708
Number of febrile days (patient days)	384	392	0.980
Mean SOFA score (during ICU stay) (mean $\pm$ SD)	5.9 $\pm$ 3.1	6.0 $\pm$ 2.9	0.583
Treatment-related variables			
Mechanical ventilation (patient days)	1,179	1,155	0.562
Renal replacement therapy (patient days)	523	519	0.753
Vasopressors/inotropes (patient days)	1,350	1,521	<0.0001
Number of PRBC (units) (median (IQR)	0 (0–2)	0 (0–2)	0.607
Number of days with therapeutic anti infective agents [median (IQR)]	0 (0–5)	0 (0–5)	0.573
Nutritional management			
No of days with enteral or parenteral nutrition/total ICU stay	2,549	2,594	
Caloric intake (Kcal per day with nutrition support)			
Enteral (mean $\pm$ SD)	482 $\pm$ 676	488 $\pm$ 676	0.884
Median (IQR)	0 (0–1,081)	0 (0–1,112)	
Parenteral (mean $\pm$ SD)	255 $\pm$ 551	275 $\pm$ 561	0.556
Median (IQR)	0 (0–0)	0 (0–0)	
Proportion of time (% days) with (mean $\pm$ SD)			
Enteral nutrition	49 $\pm$ 50	48 $\pm$ 50	0.786
Parenteral nutrition	27 $\pm$ 44	26 $\pm$ 44	0.758
Total IV glucose (g/day) (mean $\pm$ SD)	71.8 $\pm$ 78.7	73.7 $\pm$ 79.7	0.701
Median (IQR)	50.0 (19.8–83.3)	50.0 (16.3–87.9)	
IV glucose in non-nutrition solutions (g/day)			
Mean $\pm$ SD	38.1 $\pm$ 30.9	36.6 $\pm$ 30.4	0.446
Median (IQR)	37.9 (0–60)	37.5 (0–58.3)	
Glucose control and insulin therapy			
Blood glucose concentrations calculated from all readings (mmol/L) [median (IQR)]	8.0 (7.1–9.0)	6.5 (6.0–7.2)	<0.0001
Blood glucose concentrations calculated from morning readings (mmol/L) [median (IQR)]	7.7 (6.7–8.8)	6.1 (5.5–6.8)	<0.0001
Rate of hypoglycaemia calculated from BG % (n)	2.7 (13)	8.7 (44)	<0.0001
Estimated duration of hypoglycaemia (min) in patients presenting hypoglycaemic episode [median (IQR)]	59 (37–76)	52 (13–135)	0.887
Proportion of time in range			
(% of all BG readings)	34.7 (164)	42.8 (196)	0.0118
(% of morning BG)	39.5 (187)	45.1 (207)	0.0856
p value (difference between all readings and morning BG)	NS	NS	
Median of the proportion of time in range (%) (IQR)	34.3 (18.5–50.1)	39.3 (26.2–53.6)	
Proportion of time below the range			
(% of all BG readings)	50.3 (238)	5.9 (27)	<0.0001
(% of morning BG)	51.2 (242)	5.2 (24)	
p value (difference between all readings and morning BG)	NS	NS	<0.0001
Median of the proportion of time below range (%) (IQR)	44.7 (24.3–75.8)	5.1 (1.1–9.2)	
Proportion of time above the range			
(% of all BG readings)	14.9 (71)	51.3 (236)	<0.0001
(% of morning BG)	9.3 (44)	49.7 (228)	
p value (difference between all readings and morning BG)	0.0072	NS	<0.0001
Median of the proportion of time above range (%) (IQR)	7.6 (0.0–25.3)	52.6 (39.2–67.4)	
AUChigh (hour mmol L^{-1}) [median(IQR)]	4.1 (0–40.2)	79.3 (25.9–181.1)	<0.0001
AUClow (hour mmol L^{-1}) [median(IQR)]	42.3 (12.8–125.9)	2.1 (0.2–6.1)	<0.0001
Hyperglycaemic index (mmol L^{-1}) [median(IQR)]	0.06 (0.00–0.33)	0.78 (0.39–1.39)	<0.0001
Hypoglycaemic index (mmol L^{-1}) [median (IQR)]	0.44 (0.22–0.94)	0.33 (0.03–0.85)	<0.0001

Table 3 coninued

	Group 1 BG target 7.8–10.0 mmol/L $N = 542$	Group 2 BG target 4.4–6.1 mmol/L $N = 536$	p Value
Minimum–Maximum BG values (mmol L^{-1})			
All BG	1.1–33.2	1.1–30.7	
Patient averaged BG	4.1–14.6	4.1–13.3	
Standard deviation of BG (mmol L^{-1})	1.9	2.0	0.071
Time from admission to start of insulin drip, hours [median(IQR)]	0 (0–10)	0(0–12)	0.312
Patients treated with IV insulin, % (n)	66.2 (313)	96.3 (442)	<0.0001
Rate of insulin infusion (IU/h) [median(IQR)]	0.32 (0–1.27)	1.30 (0.65–2.3)	<0.0001
Duration of insulin treatment in hours median (IQR)	10 (0–43)	36 (13–96)	<0.0001
Days on insulin [median (IQR)]	2 (0–5)	5 (2–9)	<0.0001
Insulin-free days [median (IQR)]	2 (0–5)	0 (0–1)	<0.0001
Duration of insulin treatment in hours [median(IQR)] while			
Glycaemia in range	6 (0–27)	22 (8–64)	<0.0001
Below range	1 (0–7)	2 (0–6)	0.0203
Above range	1 (0–6)	11 (3–26)	<0.0001
Duration of insulin treatment in minutes (mean ± SD) during hypoglycaemic episode	0.3 ± 3.3	3.5 ± 20.9	0.0014

Results are presented as mean (± standard deviation, SD) or median (inter-quartile range, IQR)
ICU Intensive Care Unit, *LOS* Length of Stay, *SOFA* Sequential Organ Failure Assessment, *PRBC* Packed Red Blood Cells, *BG* blood glucose, *AUChigh* area under the curve of readings above the desired BG range, *AUClow* area under the curve of readings below the desired BG range

study, we were unable to test the hypothesis as anticipated.

Effect of intensive insulin therapy

The present findings contrast with the benefits of insulin therapy targeting a BG of 4.4–6.1 mmol/L reported in other prospective trials [1, 13], but confirm the findings by others [7, 14–19], who failed to show any benefit from IIT. They are also in agreement with the data of two recent meta-analyses [20, 21], which included the data of this study [8]. Several factors may explain these discrepant findings, including differences in BG targets, in study designs, glucose supply, case mix, centre experience, staffing and equipment.

In the present study, BG target for group 1 (intermediate target) was lower than in the pioneering studies [1, 6], but identical than in a more recent and larger trial [19]. The toxic effects of hyperglycaemia reported from retrospective trials are thought to occur when BG exceeds 10.0 mmol/L but toxic effects of moderate hyperglycaemia during critical illness are conflicting [22, 23]. A recent observational study in a surgical ICU reports important decreases in mortality when BG was lowered by IIT from 12.8 to 10.0 mmol/L [24], but no further effect when BG is decreased to lower values, consistently with other recent findings [14, 25].

Secondly, in the present study the amount of intravenous glucose administered during the first day after admission was about 50% compared to the Leuven studies [1, 6]. Similarly, the average dose of insulin was lower, reflecting the marked hyperglycaemic effect of parenteral glucose [26, 27]. As a result, the proportion of caloric intake brought via the enteral route was higher than in the Leuven studies, thereby reducing the insulin requirements [26].

Thirdly, patient case mix and severity of illness were different in Glucontrol (medical and surgical critically ill patients with APACHE II median of 15) than in the two Leuven studies as shown by the diagnostic categories and the APACHE II scores (means of 9 and 23 for the surgical [1] and for the medical [6] studies, respectively), although the APACHE II scores can be inaccurate to characterise the severity of cardiac surgery patients. The effects of IIT might indeed differ according to the type of patients (medical vs. surgical), as suggested by the comparison of the results of the two Leuven studies [1, 6]. The effect of IIT on the need for vasopressors or inotropes may be related to the endothelium-dependent relaxing effects of insulin [28].

Hypoglycaemia

The increase in the incidence of hypoglycaemia in the intensive insulin treatment group of 8.7% (vs. 2.7% in group 1) was similar to other studies with a 4-6 fold increase, ranging from 5.1% to 28.6% in the other trials [1, 6, 7, 14, 18, 19]. Other factors that might have influenced the rate and duration of hypoglycaemic episodes include the frequency of BG checks [29] and the degree

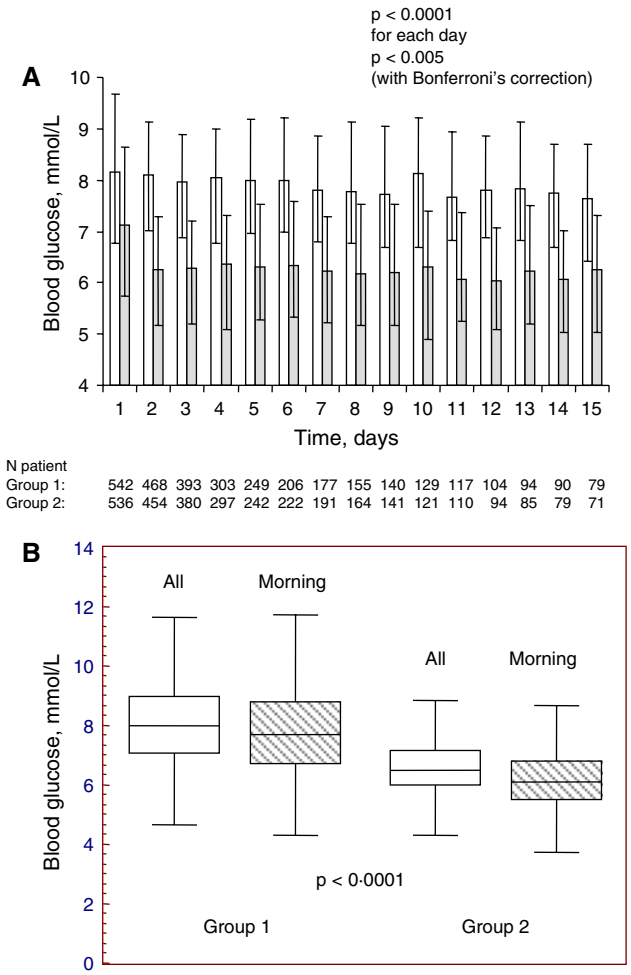

Fig. 2 Blood glucose values (BG) recorded in patients randomised to group 1 (target BG 7.8–10.0 mmol/L) and group 2 (target BG 4.4–6.1 mmol/L). *Left panel* **a** median BG and ranges measured during the first 15 days of the ICU stay in the group 1 (*white bars*) and in the group 2 (*light grey bars*). The differences between group 1 and 2 are highly significant ($p < 0.0001$ for each day, $p < 0.005$ with Bonferroni's correction). *Right panel* **b** box–plot of the median values and inter-quartile ranges of BG calculated from all BG readings (*empty bars*) or from morning BG values (*hatched bars*) in the groups 1 et 2 during the ICU stays. Both differences between group 1 and 2 are highly significant ($p < 0.0001$)

of adherence to insulin algorithms. The increased SOFA scores on the days with hypoglycaemia as well as the higher mortality of patients experiencing hypoglycaemia consistently supported the higher risk of hypoglycaemia in the most severely ill patients. Of course, these data do not imply that hypoglycaemia per se is life-threatening, but rather that sicker patients are at higher risk [30–32] consistently with the other data, showing a direct relationship between the risk of hypoglycaemia and the risk of death [5]. The design of Glucontrol did not allow for addressing the issue of the hypoglycaemia-related risks of neuroglycopaenia [30], although these were unlikely to occur, as the mean duration of hypoglycaemia was low in both groups.

Strengths of the study

A major strength of the present study is the randomisation of patients and the immediacy of initiation of insulin therapy from the time of admission. The quality of glucose control in this study was also assessed in more detailed way than in other trials [1, 6, 7, 14, 18], including the use of each BG recorded to calculate the average BG, and not only the morning BG value and the calculation of the time in the targeted range by the trapeze method and proportion of time spent within, above and below the BG target. The proportion of time in range calculated from morning BG values was not lower than in the most of the other studies [6, 7, 13, 17].

Thereby, accurate assessment of time in target allowed, more precisely than by the use of morning values only [1, 6, 7, 14, 18, 33–36]. To avoid excessive heterogeneity and inaccuracy in the measurement of glucose concentration, only a validated model of glucose analyser was allowed [37]. The use of a single method for BG measurement would have been ideal, but was unrealistic in the conditions of the present study. The assessment of outcome and the statistical analysis were performed blindly.

Limitations of the study

Inherently related to the intervention under investigation, the study was not blinded, however. The variations in the number of patients recruited in each centre [38], differences in the experience of glucose control and of discharge policy, therapeutic limitations and/or prolongations of ICU stays for non-medical reasons potentially influenced the results, like many several studies performed in ICUs. The material used for insulin infusion was not standardised, thereby bringing a possibility of inaccuracies in the actual rate of infusion. Potential reasons for hypoglycaemia, such as discontinuation or lowering of the infusion rate of enteral or parenteral nutrition solutions were not recorded. The possibility for the centres to use different devices to measure blood glucose represents another potential source of inaccuracy, though it reflects the actual practice. The septic morbidity was roughly assessed from the number of febrile days and the days with anti-infective agents. The variations in the number of patients recruited in each centre [35], potentially influenced the results: after exclusion of the patients from the three centres which enrolled the lowest number of patients (less than 15), the outcome was not different (data not shown). The slight overlap in the BG concentrations (Fig. 2a) is mostly related to the fact that the

targets were closer than in other studies [1, 6, 7, 14, 18]. The same reason explains the low statistical power of the present study, as a result of its premature interruption following the recommendation of the DSMB. This decision was eagerly debated, as reflected by the long and tough discussions between the members of the DSMB. Nevertheless, the mortality was slightly and not significantly increased in the group 2, consistently with other recent prospective trials [7, 14, 18, 19].

Conclusions

Even though the premature interruption of this study precludes definitive conclusions to be drawn, the data of this multi-centre randomized controlled study comparing two targets for blood glucose control in critically ill patients pointed out that there was no measurable clinical benefit of a BG target 4.4–6.1 mmol/L versus 7.8–10.0 mmol/L, but an increased risk of hypoglycaemia.

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The members of the independent Data and Safety monitoring board were Christian Mélot, Peter Radermacher and Greet Van den Berghe.

Appendix 1: list of participants

Austria

University Clinic of Innsbruck (M Joannidis)

13 patients

Belgium

Regional Centre Hospital of Citadelle, Liege (F Damas, V Fraipont)

40 patients

University Hospital Centre, Liege (JL Canivet, P Damas, B Lambermont, D Ledoux)

4 units: 141 + 158 + 16 + 110 patients

France

Raymond Poincaré Hospital, Garches (D Annane)

74 patients

Gustave-Roussy Institute, Villejuif (G Nitenberg)

12 patients

Israel

Rabin Medical Centre, Petah Tiqva (P Singer)

85 patients

The Netherlands

Free University Medical Centre, Amsterdam (J Groeneveld)

10 patients

Slovenia

University Medical Centre, Ljubljana (A Stecher, L Kompan)

112 patients

Spain

University General Hospital, Alicante (J Acosta Escribano, S Almanza; R Carrasco Moreno, M Fernández Vivas, V Ortolá Vercher)

15 patients

University Hospital Germans Trias i Pujol, Badalona (ML Bordejé, P Marcos Neira, S Martínez Vega, H Pérez Moltó)

53 patients

Dr Josep Trueta University Hospital, Girona (A Bonet Sarís, N López de Arbina, P Ortiz Ballugera)

28 patients

Dr. Negrín University Hospital, Las Palmas de Gran Canaria (S Ruiz-Santana, P Saavedra, Hípola Escalada, MA Hernández Viera, R Manzanedo Velasco, JJ Díaz Díaz)

101 patients

Hospital Severo Ochoa, Leganés (J López Martinez, R Díaz Abad)

35 patients

University Hospital 12 October, Madrid (JC Montejo, T Grau Carmona, C García Fuentes)

2 units: 15 + 40 patients

Provincial Hospital of Toledo (B García Vila, ML Rodríguez Blanco, MC Martín Parra)

19 patients

Dr Peset Hospital, Valencia (M Cervera Montes, C Campos, A Castillo, S Sancho, JM Simón)

24 patients

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