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INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

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ABSTRACT

Background Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known.

Methods We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter and maintenance of glucose at a level between 180 and 200 mg per deciliter).

Results At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent ($P<0.04$, with adjustment for sequential analyses). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2 percent with conventional treatment, as compared with 10.6 percent with intensive insulin therapy; $P=0.005$). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care.

Conclusions Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit. (N Engl J Med 2001;345:1359-67.)

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CRITICALLY ill patients who require intensive care for more than five days have a 20 percent risk of death and substantial morbidity.[1] Critical-illness polyneuropathy and skeletal-muscle wasting prolong the need for mechanical ventilation.[2-5] Moreover, increased susceptibility to severe infections and failure of vital organs amplify the risk of an adverse outcome.

Hyperglycemia associated with insulin resistance[6-8] is common in critically ill patients, even those who have not previously had diabetes. It has been reported that pronounced hyperglycemia may lead to complications in such patients,[9-13] although data from controlled trials are lacking. In diabetic patients with acute myocardial infarction, therapy to maintain blood glucose at a level below 215 mg per deciliter (11.9 mmol per liter) improves the long-term outcome.[14-16] In nondiabetic patients with protracted critical illnesses, high serum levels of insulin-like growth factor–binding protein 1, which reflect an impaired response of hepatocytes to insulin, increase the risk of death.[17,18]

We hypothesized that hyperglycemia or relative insulin deficiency (or both) during critical illness may directly or indirectly confer a predisposition to complications,[11,19,20] such as severe infections, polyneuropathy, multiple-organ failure, and death. We performed a prospective, randomized, controlled trial at one center to determine whether normalization of blood glucose levels with intensive insulin therapy reduces mortality and morbidity among critically ill patients.

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METHODS

Study Population

All adults receiving mechanical ventilation who were admitted to our intensive care unit (which is dedicated primarily but not exclusively to surgical patients) between February 2, 2000, and January 18, 2001, were eligible for enrollment in the study after written informed consent had been obtained from the closest family member. Only 14 patients were excluded: 5 who were participating in other trials, and 9 who were moribund or for whom there were do-not-resuscitate orders. The protocol was approved by the institutional review board.

Four patients had renal failure requiring dialysis before admission. Among the patients who were admitted to the intensive care unit after cardiac surgery had been performed, 59 percent had undergone coronary bypass surgery, 27 percent valve replacement, and 14 percent a combined procedure. On admission, 13 percent of the patients had a history of diabetes, and 5 percent were receiving treatment with insulin (Table 1). The blood glucose level on admission exceeded the upper limit of the normal range after an overnight fast (110 mg per deciliter [6.1 mmol per liter]) in 75 percent of the patients but was in the nonfasting diabetic range (>200 mg per deciliter [11.1 mmol per liter]) in only 12 percent.[21,22]

Study Design

At the time of admission to the intensive care unit, patients were randomly assigned to receive either intensive or conventional insulin therapy. Assignments to the treatment groups were made with the use of sealed envelopes, with stratification according to the type of critical illness (Table 1), and were balanced with the use of permuted blocks of 10. In the conventional-treatment group, a continuous infusion of insulin (50 IU of Actrapid HM [Novo Nordisk, Copenhagen, Denmark] in 50 ml of 0.9 percent sodium chloride), with the use of a pump (Perfusor-FM, B. Braun, Melsungen, Germany), was started only if the blood glucose level exceeded 215 mg per deciliter,[8,9] and the infusion was adjusted to maintain the level at a value between 180 and 200 mg per deciliter (10.0 and 11.1 mmol per liter).

In the intensive-treatment group, an insulin infusion was started if the blood glucose level exceeded 110 mg per deciliter, and the infusion was adjusted to maintain normoglycemia (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]). The maximal dose of insulin was arbitrarily set at 50 IU per hour. When the patient was discharged from the intensive care unit, a conventional approach was adopted (maintenance of blood glucose at a level between 180 and 200 mg per deciliter).

Adjustments of the insulin dose were based on measurements of whole-blood glucose in undiluted arterial blood, performed at one- to four-hour intervals with the use of a glucose analyzer (ABL700, Radiometer Medical, Copenhagen). The dose was adjusted according to a strict algorithm by a team of intensive care nurses, assisted by a study physician who was not involved in the clinical care of the patients.

On admission, all patients were fed continuously with intravenous glucose (200 to 300 g per 24 hours). The next day, total parenteral, combined parenteral and enteral, or total enteral feeding was instituted according to a standardized schedule, with 20 to 30 nonprotein kilocalories per kilogram of body weight per 24 hours and a balanced composition (including 0.13 to 0.26 g of nitrogen per kilogram per 24 hours and 20 to 40 percent of nonprotein calories in the form of lipids).[23] Total enteral feeding was attempted as early as possible.

Data Collection

At base line, demographic and clinical information was obtained, including information necessary to determine the severity of illness and use of intensive care resources (Table 1). Scores were calculated for the Acute Physiology and Chronic Health Evaluation (APACHE II)[24] and the simplified Therapeutic Intervention Scoring System (TISS-28).[25,26] Higher scores indicate more severe illness and a higher number of therapeutic interventions, respectively. For the TISS-28 score, each therapeutic intervention is assigned 1 to 4 points, and the points are summed daily to obtain the overall score.

Because 17 percent of patients were admitted to intensive care after a median delay of 48 hours, APACHE II scores at the time of admission were artificially lowered. Moreover, zero points were usually assigned for the neurologic evaluation, since the majority

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)
Male sex — no. (%)	557 (71)	544 (71)
Age — yr	62.2±13.9	63.4±13.6
Body-mass index†	25.8±4.7	26.2±4.4
Reason for intensive care — no. (%)		
Cardiac surgery	493 (63)	477 (62)
Noncardiac indication	290 (37)	288 (38)
Neurologic disease, cerebral trauma, or brain surgery	30 (4)	33 (4)
Thoracic surgery, respiratory insufficiency, or both	56 (7)	66 (9)
Abdominal surgery or peritonitis	58 (7)	45 (6)
Vascular surgery	32 (4)	30 (4)
Multiple trauma or severe burns	35 (4)	33 (4)
Transplantation	44 (6)	46 (6)
Other	35 (4)	35 (5)
APACHE II score‡		
First 24 hr		
Median	9	9
Interquartile range	7–13	7–13
Second 24 hr		
Median	9	9
Interquartile range	6–13	6–13
Score >9 in first 24 hr — no. (%)	458 (58)	429 (56)
TISS-28 score§		
First 24 hr		
Median	43	43
Interquartile range	36–47	37–46
Second 24 hr		
Median	38	38
Interquartile range	32–44	31–43
Tertiary referral — no. (%)	135 (17)	126 (16)
History of cancer — no. (%)	119 (15)	122 (16)
History of diabetes — no. (%)	103 (13)	101 (13)
Treated with insulin	33 (4)	39 (5)
Treated with oral antidiabetic agent, diet, or both	70 (9)	62 (8)
Blood glucose — no. (%)¶		
>110 mg/dl	598 (76)	557 (73)
>200 mg/dl	101 (13)	81 (11)

*Plus–minus values are means ±SD.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡APACHE II denotes Acute Physiology and Chronic Health Evaluation. Higher scores reflect more severe critical illness. The scores in the first 24 hours were artificially lowered because of resuscitative interventions outside the intensive care unit and because of the assumption of normal consciousness in sedated patients.

§TISS-28 denotes Therapeutic Intervention Scoring System. Each therapeutic intervention is assigned 1 to 4 points, and the points are summed daily to obtain the overall score. Higher scores indicate a higher number of therapeutic interventions.

¶To convert the values for glucose to millimoles per liter, multiply by 0.05551.

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of patients were sedated. This approach was considered most objective, but it inevitably reduced the APACHE II scores.[27]

Blood was obtained on admission and subsequently every four hours. The blood glucose level was measured on admission and daily at 6 a.m., and daily maximal and minimal blood glucose levels were determined. Laboratory staff were unaware of the treatment assignments.

Blood cultures were obtained whenever the central body temperature exceeded 38.5°C,[28,29] and the results were interpreted by an investigator who was unaware of the treatment assignments. An episode of septicemia was defined by the first positive culture in a series. To identify bacteremia with coagulase-negative staphylococci, identical strains (compared by antibiogram) in two or more positive blood cultures were required.[28,29]

Weekly electromyographic screening for critical-illness polyneuropathy was performed among patients who remained in the intensive care unit for a week or more. The results were interpreted by one electrophysiologist, who was unaware of the treatment assignments.

For patients who died, the cause of death was confirmed by postmortem examination performed by a pathologist who was unaware of the treatment assignments.

Outcome Measures

The primary outcome measure was death from any cause during intensive care. Secondary outcome measures were in-hospital death; the number of days in the intensive care unit and the need for prolonged intensive care (more than 14 days) or readmission; the need for ventilatory support, renal replacement therapy, or inotropic or vasopressor support; critical-illness polyneuropathy; markers of inflammation (the C-reactive protein level, white-cell count, and body temperature); bloodstream infection and use of antibiotics for more than 10 days; transfusion requirements; and hyperbilirubinemia. To minimize the possibility of bias caused by delays in the transfer of patients to a regular ward because of the unavailability of beds, patients were considered to be ready for discharge when they no longer needed vital-organ support and were receiving at least two thirds of their caloric intake by the normal enteral route. Use of intensive care resources was assessed on the basis of cumulative TISS-28 scores (the sum of daily scores), indicating the total number of interventions per patient.[25]

Statistical Analysis

We planned to enroll 2500 patients in order for the study to have the capacity to detect an absolute difference in mortality between the treatment groups of 5 percent among patients who remained in the intensive care unit for more than five days, and of 2 percent among all patients in intensive care (two-sided alpha level, <0.05). Interim analyses of overall mortality in the intensive care unit were performed at three-month intervals, with stopping boundaries (two-sided alpha level, <0.01) designed to allow early termination of the study. The fourth interim analysis indicated that conventional treatment was inferior, and the study was stopped.

Base-line and outcome variables were compared with the use of Student's t-test, the chi-square test, and the Mann–Whitney U test. Adjustment for the sequential analysis of the primary outcome variable (death during intensive care) was performed according to the Lan and DeMets method.[30] Odds ratios were estimated on the basis of multivariate logistic-regression analysis. The effect of intensive insulin therapy on the time of death was assessed by Kaplan–Meier analysis and the Mantel–Cox log-rank test. Patients discharged alive from the hospital were considered to have survived. Data are presented as means ±SD or as medians with interquartile ranges, unless otherwise indicated. All analyses were performed on an intention-to-treat basis.

The sponsors of the study were not involved in the study design, data collection, analysis or interpretation of the data, or preparation of the manuscript.

RESULTS

Study Population

A total of 1548 patients were enrolled in the study. The clinical and demographic characteristics of the treatment groups were similar at randomization (Table 1), and there were no significant differences with respect to the delay in admission to the intensive care unit, the presence of renal failure, the type of cardiac surgery, or rates of preexisting diabetes and hyperglycemia at the time of admission.

The mean intake of nonprotein calories was 19.1±7.1 kcal per kilogram per 24 hours in the conventional-treatment group and 18.5±7.5 kcal per kilogram per 24 hours in the intensive-treatment group ($P=0.2$); the highest intake of nonprotein calories in both groups was 24±10 kcal per kilogram per 24 hours. The mean nitrogen intake was 0.15±0.06 g per kilogram per 24 hours in the conventional-treatment group and 0.14±0.06 g per kilogram per 24 hours in the intensive-treatment group ($P=0.3$), and the maximal nitrogen intake was 0.19±0.08 g per kilogram per 24 hours in both groups.

Blood Glucose Control

In the intensive-treatment group, almost all the patients required exogenous insulin, and the morning blood glucose level was maintained at a mean value of 103±19 mg per deciliter (5.7±1.1 mmol per liter) (Table 2). In the conventional-treatment group, the morning blood glucose level was maintained at a mean value of 153±33 mg per deciliter (8.5±1.8 mmol per liter). Only 39 percent of the patients treated with the

TABLE 2. INSULIN THERAPY AND CONTROL OF BLOOD GLUCOSE LEVELS.*

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Administration of insulin — no. (%)	307 (39.2)	755 (98.7)	<0.001
Insulin dose — IU/day‡			
Median	33	71	
Interquartile range	17–56	48–100	<0.001
Duration of insulin use — % of ICU stay			
Median	67	100	<0.001
Interquartile range	40–100		
Morning blood glucose — mg/dl§			
All patients	153±33	103±19	<0.001
Patients receiving insulin	173±33	103±18	<0.001

*Plus–minus values are means ±SD. ICU denotes intensive care unit.

†P values were determined with the use of Student's t-test, the Mann–Whitney U test, or the chi-square test, as appropriate.

‡Values were calculated only for days on which insulin was given.

§To convert the values for glucose to millimoles per liter, multiply by 0.05551.

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conventional approach received insulin; their mean blood glucose level was 173±33 mg per deciliter (9.6±1.8 mmol per liter), as compared with 140±25 mg per deciliter (7.8±1.4 mmol per liter) in the patients who did not receive insulin.

Hypoglycemia (defined as a blood glucose level of 40 mg per deciliter [2.2 mmol per liter] or less) occurred in 39 patients in the intensive-treatment group and in 6 patients in the conventional-treatment group. In two patients who received intensive insulin therapy, hypoglycemia was associated with sweating and agitation, but there were no instances of hemodynamic deterioration or convulsions.

Mortality

Thirty-five patients in the intensive-treatment group (4.6 percent) died during intensive care, as compared with 63 patients (8.0 percent) in the conventional-treatment group, representing an apparent risk reduction of 42 percent (95 percent confidence interval, 22 to 62 percent) (Table 3 and Fig. 1). However, after adjustment for repeated interim analyses,[30] the median unbiased estimate of the reduction in mortality was 32 percent (adjusted 95 percent confidence interval, 2 to 55 percent; $P<0.04$). Intensive insulin therapy also reduced in-hospital mortality; the greatest reduction involved deaths due to multiple-organ failure with a septic focus, documented on postmortem examination. The intervention was effective in almost all subgroups of patients defined according to the APACHE II and TISS-28 scores in the first 24 hours after admission (Fig. 2), and the results were similar in patients who had undergone cardiac surgery and those who had undergone other types of surgery.

The numbers of deaths during the first five days of intensive care were similar in the two treatment groups. The proportion of patients who required intensive care for more than five days was similar in the two groups (27 percent in the intensive-treatment group and 31 percent in the conventional-treatment group, $P=0.1$). Among these patients, the median APACHE II score for the first 24 hours of intensive care was the same in the two treatment groups (median score, 12); two thirds of patients in both groups were admitted to the intensive care unit for reasons other than cardiac surgery. The observed reduction in mortality with intensive insulin therapy occurred exclusively in this long-stay cohort (10.6 percent mortality in the intensive-treatment group vs. 20.2 percent in the conventional-treatment group, $P=0.005$).

In a multivariate logistic-regression model, the independent determinants of mortality were an APACHE II score of 9 or higher for the first 24 hours of intensive care, greater age, an indication for admission

TABLE 3. MORTALITY.

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE*
Death during intensive care — no./total no. (%)	63/783 (8.0)	35/765 (4.6)	<0.04 (adjusted)
During first 5 days of intensive care	14/783 (1.8)	13/765 (1.7)	0.9
Among patients receiving intensive care for >5 days	49/243 (20.2)	22/208 (10.6)	0.005
Reason for intensive care			
Cardiac surgery	25/493 (5.1)	10/477 (2.1)	
Neurologic disease, cerebral trauma, or brain surgery	7/30 (23.3)	6/33 (18.2)	
Thoracic surgery, respiratory insufficiency, or both	10/56 (17.9)	5/66 (7.6)	
Abdominal surgery or peritonitis	9/58 (15.5)	6/45 (13.3)	
Vascular surgery	2/32 (6.2)	2/30 (6.7)	
Multiple trauma or severe burns	3/35 (8.6)	4/33 (12.1)	
Transplantation	1/44 (2.3)	2/46 (4.4)	
Other	6/35 (17.1)	0/35	
No history of diabetes	57/680 (8.4)	31/664 (4.7)	
No history of diabetes and >5 days of intensive care	45/218 (20.6)	20/187 (10.7)	
History of diabetes	6/103 (5.8)	4/101 (4.0)	
History of diabetes and >5 days of intensive care	4/25 (16.0)	2/21 (9.5)	
Cause of death — no.			0.02
Multiple-organ failure with proven septic focus	33	8	
Multiple-organ failure without detectable septic focus	18	14	
Severe brain damage	5	3	
Acute cardiovascular collapse	7	10	
In-hospital death — no./total no. (%)			
All patients	85/783 (10.9)	55/765 (7.2)	0.01
Patients receiving intensive care for >5 days	64/243 (26.3)	35/208 (16.8)	0.01

*P values were determined with the use of the chi-square test. For the primary outcome variable (death during intensive care), the P value has been corrected for the repeated interim analyses, according to the method of Lan and DeMets[30]; the unadjusted P value is 0.005. Sequential interim analyses were not performed for the other variables, and nominal (unadjusted) P values are given for these comparisons.

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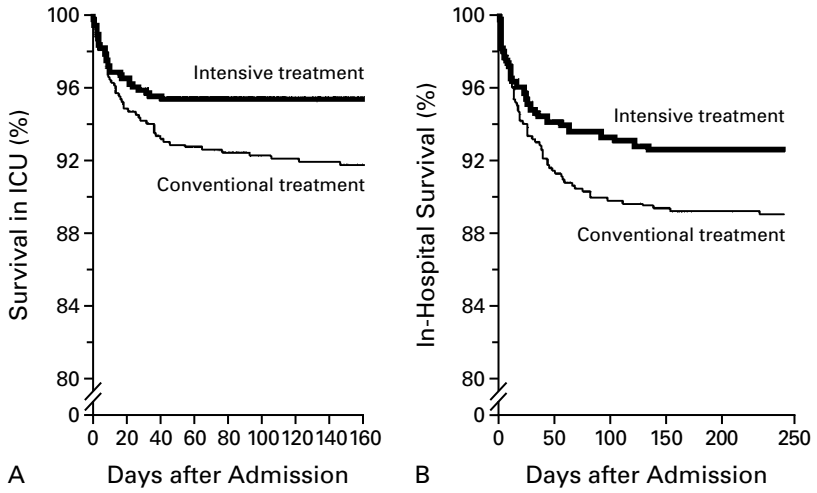

Figure 1. Kaplan–Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).

Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the differences between the treatment groups were significant (survival in ICU, nominal $P=0.005$ and adjusted $P<0.04$; in-hospital survival, nominal $P=0.01$). P values were determined with the use of the Mantel–Cox log-rank test.

other than cardiac surgery, tertiary referral, and conventional insulin treatment, but not a history of diabetes or hyperglycemia at the time of admission to the intensive care unit.

Morbidity

A history of diabetes or hyperglycemia at the time of admission did not affect measures of morbidity. Intensive insulin therapy reduced the duration of intensive care but not the overall length of stay in the hospital. The rate of readmission to the intensive care unit was the same in the two groups (2.1 percent). Significantly fewer patients in the intensive-treatment group than in the conventional-treatment group required prolonged ventilatory support and renal replacement therapy, whereas the proportion of patients who needed inotropic or vasopressor support was the same in the two groups (Table 4). The number of patients who had hyperbilirubinemia was also significantly smaller in the intensive-treatment group than in the conventional-treatment group.

Intensive insulin treatment reduced episodes of septicemia by 46 percent (95 percent confidence interval, 25 to 67 percent) (Table 4). Of the episodes of septicemia in the intensive-treatment group, 34 percent were polymicrobial as compared with 23 percent in the conventional-treatment group ($P=0.2$). Causative pathogens included coagulase-negative staphylococci (accounting for 31.3 percent of all episodes of septicemia), enterococcus species (14.7 percent), nonfermenting gram-negative bacilli (14.7 percent), inducible Enterobacteriaceae (12.6 percent), other Enterobacteriaceae (8.4 percent), and *Staphylococcus aureus* (7.7 percent).

Markers of inflammation were less frequently abnormal in the intensive-treatment group than in the conventional-treatment group ($P\leq0.02$). The patients who received intensive insulin therapy were less likely to require prolonged use of antibiotics than were the patients who received conventional treatment, an effect that was largely attributable to the lower rate of bacteremia in the intensive-treatment group (75 percent of patients who had bacteremia received antibiotics for more than 10 days, as compared with 10 percent of patients who did not have bacteremia; $P<0.001$). Among patients with bacteremia, those treated with intensive insulin therapy had a lower mortality rate than those treated conventionally (12.5 percent vs. 29.5 percent), although this difference was not statistically significant. The use of medications other than insulin or antibiotics did not differ significantly between the two treatment groups.

Because intensive insulin therapy reduced the length of stay in the intensive care unit among patients requiring intensive care for more than five days, fewer patients in the intensive-treatment group than in the conventional-treatment group were screened for polyneuropathy (20.5 percent vs. 26.3 percent, $P=0.007$). Among the patients who were screened, those receiving intensive insulin therapy were less likely to have critical-illness polyneuropathy than were those receiving conventional treatment, and the cases that did develop resolved more rapidly. In both groups, there was a positive, linear correlation between the risk of

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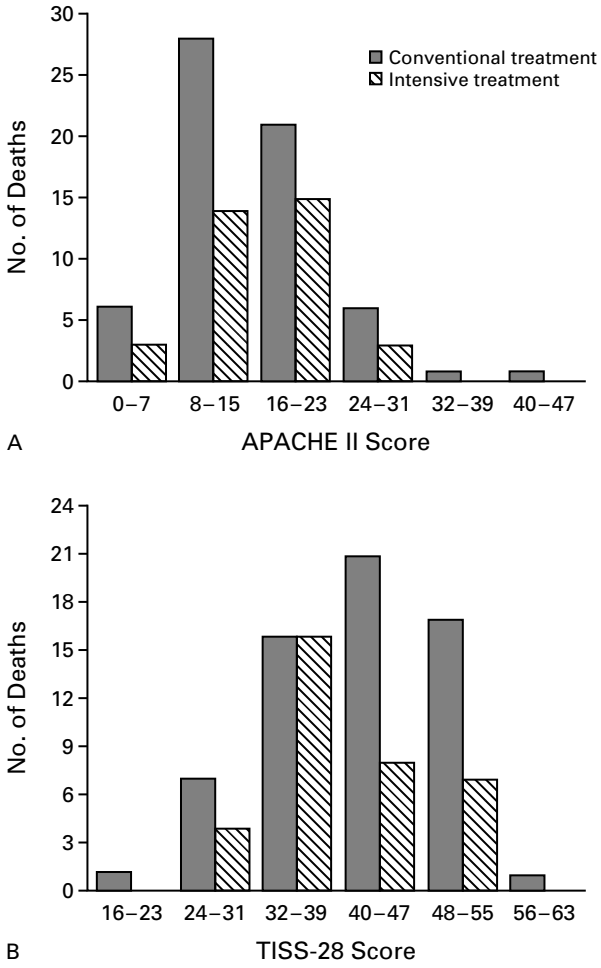

Figure 2. Number of Deaths in the Intensive Care Unit According to the Acute Physiology and Chronic Health Evaluation (APACHE II) Score (Panel A) and the Simplified Therapeutic Intervention Scoring System (TISS-28) Score (Panel B) in the First 24 Hours.

Higher APACHE II scores indicate more severe illness, and higher TISS-28 scores indicate a higher number of therapeutic interventions.

polyneuropathy and the mean blood glucose level. In a multivariate analysis, independent predictors of polyneuropathy were conventional insulin treatment (odds ratio, 2.6; 95 percent confidence interval, 1.6 to 4.2), vasopressor support for more than three days (odds ratio, 2.5; 95 percent confidence interval, 1.4 to 4.2), bacteremia (odds ratio, 2.3; 95 percent confidence interval, 1.3 to 4.1), and renal replacement therapy (odds ratio, 1.9; 95 percent confidence interval, 1.0 to 3.8).

The number of patients who received red-cell transfusions did not differ significantly between the two groups. However, the median number of transfusions in the intensive-treatment group was only half that in the conventional-treatment group. This difference was not due to more liberal use of transfusions in the conventional-treatment group, as indicated by the lower hemoglobin and hematocrit values in that group.

The TISS-28 score on the last day in the intensive care unit, an indication of how many therapeutic interventions were still needed when patients were sent to a regular ward, was the same in the two treatment groups (a median score of 30). However, intensive insulin treatment reduced the median cumulative TISS-28 score by 23 percent among patients who remained in the intensive care unit for more than five days.[25]

DISCUSSION

The use of intensive insulin therapy to maintain blood glucose at a level that did not exceed 110 mg per deciliter substantially reduced mortality in the intensive care unit, in-hospital mortality, and morbidity among critically ill patients admitted to our intensive care unit.

The limitations of this study should be noted. First, it was not feasible to conduct the study in a strictly blinded fashion because adjustment of the insulin dose requires blood glucose monitoring. To minimize bias, we assigned responsibility for adjustment of the insulin dose to a team of nurses and to a study physician who was not taking part in clinical decisions, with strictly blinded analysis of important outcome measures. Furthermore, the two treatment groups did not differ in the use of medications other than insulin and antibiotics, the latter most likely a consequence of the effect of intensive insulin therapy on septicemia. Second, since the study involved patients admitted to a surgical intensive care unit, the results cannot be extrapolated to patients in medical intensive care units or those with severe illnesses that were not present in the study population.

Intensive insulin treatment reduced the number of deaths from multiple-organ failure with sepsis, regardless of whether there was a history of diabetes or hyperglycemia.[31] Since the introduction of mechanical ventilation, few intensive care interventions have improved survival. Treatment of sepsis with activated protein C results in a 20 percent reduction in mortality at 28 days.[32] Glycemic control is a preventive approach that is more broadly applicable to critically ill patients and that reduced mortality during intensive care by more than 40 percent.

Intensive insulin therapy also reduced the use of intensive care resources and the risk of complications that are common among patients requiring intensive care, including episodes of septicemia and a corresponding need for prolonged antibiotic therapy. The higher risk in the conventional-treatment group may reflect the deleterious effects of hyperglycemia on macrophage or neutrophil function[33-36] or insulin-induced trophic effects on mucosal and skin barriers. Intensive insulin treatment also prevented acute renal failure.

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TABLE 4. MORBIDITY.*

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Duration of intensive care — days			
All patients			
Median	3	3	0.2
Interquartile range	2–9	2–6	
≤5 Days			
Median	2	2	0.2
Interquartile range	2–3	2–3	
>5 days			
Median	15	12	0.003
Interquartile range	9–27	8–20	
Patients requiring >14 days of intensive care — no. (%)	123 (15.7)	87 (11.4)	0.01
Duration of ventilatory support — days			
All patients			
Median	2	2	0.06
Interquartile range	1–6	1–4	
≤5 Days of intensive care			
Median	1	1	0.9
Interquartile range	1–2	1–2	
>5 Days of intensive care			
Median	12	10	0.006
Interquartile range	7–23	6–16	
Patients requiring >14 days of ventilatory support — no. (%)	93 (11.9)	57 (7.5)	0.003
Inotropic or vasopressor treatment — no. (%)	586 (74.8)	574 (75.0)	0.9
Renal impairment — no. (%)			
Peak plasma creatinine >2.5 mg/dl	96 (12.3)	69 (9.0)	0.04
Peak plasma urea nitrogen >54 mg/dl	88 (11.2)	59 (7.7)	0.02
Dialysis or continuous venovenous hemofiltration	64 (8.2)	37 (4.8)	0.007
Hyperbilirubinemia (peak bilirubin >2 mg/dl) — no. (%)	209 (26.7)	171 (22.4)	0.04
Bloodstream infection — no. (%)			
Septicemia during intensive care	61 (7.8)	32 (4.2)	0.003
Treatment with antibiotics for >10 days	134 (17.1)	086 (11.2)	<0.001
Electromyographic evidence of critical-illness polyneuropathy — no./total no. (%)			
At any time	107/206 (51.9)	45/157 (28.7)	<0.001
On more than 2 occasions	39/206 (18.9)	11/157 (7.0)	0.001
Red-cell transfusions			
Patients requiring transfusion — no. (%)	243 (31.0)	219 (28.6)	0.3
No. of transfusions/patient‡			
Median	2	1	<0.001
Interquartile range	1–3	1–2	
Cumulative TISS-28 score§			
All patients			
Median	108	105	0.2
Interquartile range	76–293	76–215	
≤5 Days of intensive care			
Median	84	85	0.3
Interquartile range	67–111	68–115	
>5 Days of intensive care			
Median	563	431	<0.001
Interquartile range	329–956	271–670	

*To convert the value for creatinine to micromoles per liter, multiply by 88.4. To convert the value for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the value for bilirubin to micromoles per liter, multiply by 17.1.

†P values were determined with the use of the Mann–Whitney U test or the chi-square test, as appropriate. Nominal (unadjusted) P values are given because sequential interim analyses were not performed for measures of morbidity.

‡The analysis of the number of transfusions did not take the day of admission into account.

§TISS-28 denotes the Simplified Therapeutic Intervention Scoring System. Higher scores indicate a higher number of therapeutic interventions.

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Aside from optimization of hemodynamic status, no other strategy to prevent renal failure has proved effective.[37-40] The reduced number of transfusions in the intensive-treatment group may reflect improved erythropoiesis or reduced hemolysis, since this benefit was associated with a lower incidence of hyperbilirubinemia. Alternatively, intensive insulin therapy may reduce the risk of cholestasis, since adequate provision of glucose and insulin to hepatocytes is crucial for normal choleresis.[41,42]

The exact cause of critical-illness polyneuropathy is unknown, but sepsis and the use of neuromuscular blocking agents, corticosteroids, and aminoglycosides are thought to have a role.[2-5] The reduction in the risk of polyneuropathy with intensive insulin therapy, regardless of the concomitant use of these medications, suggests that hyperglycemia, insulin deficiency, or both contribute to axonal dysfunction and degeneration.[43] The linear relation between blood glucose levels and the risk of polyneuropathy suggests that maintenance of the lowest possible level is necessary. The reduced need for mechanical ventilation in patients who received intensive insulin therapy is explained in part by the reduced rate of critical-illness polyneuropathy, though a direct anabolic effect of insulin on respiratory muscles[44] may also play a part. However, the exact mechanisms by which morbidity and mortality were reduced remain largely speculative, since the effects of glycemic control cannot be distinguished from those of increased insulin levels.

Prospective studies of the effect of strict blood glucose control in patients with type 1 or type 2 diabetes have not shown a reduction in mortality.[45,46] During pregnancy, however, this approach has been shown to prevent intrauterine and perinatal death.[47] The results of our study offer a possible explanation of the failure of growth hormone therapy as anabolic treatment in patients with prolonged critical illness.[1] Growth hormone substantially aggravates insulin resistance and hyperglycemia and doubles the mortality rate among critically ill patients, mainly because of multiple-organ failure and sepsis.

In conclusion, the use of exogenous insulin to maintain blood glucose at a level no higher than 110 mg per deciliter reduced morbidity and mortality among critically ill patients in the surgical intensive care unit, regardless of whether they had a history of diabetes.

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