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ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

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ABSTRACT

BACKGROUND

The role of intensive insulin therapy in patients with severe sepsis is uncertain. Fluid resuscitation improves survival among patients with septic shock, but evidence is lacking to support the choice of either crystalloids or colloids.

METHODS

In a multicenter, two-by-two factorial trial, we randomly assigned patients with severe sepsis to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch, a low-molecular-weight hydroxyethyl starch (HES 200/0.5), or modified Ringer's lactate for fluid resuscitation. The rate of death at 28 days and the mean score for organ failure were coprimary end points.

RESULTS

The trial was stopped early for safety reasons. Among 537 patients who could be evaluated, the mean morning blood glucose level was lower in the intensive-therapy group (112 mg per deciliter [6.2 mmol per liter]) than in the conventional-therapy group (151 mg per deciliter [8.4 mmol per liter], P<0.001). However, at 28 days, there was no significant difference between the two groups in the rate of death or the mean score for organ failure. The rate of severe hypoglycemia (glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was higher in the intensive-therapy group than in the conventional-therapy group (17.0% vs. 4.1%, P<0.001), as was the rate of serious adverse events (10.9% vs. 5.2%, P=0.01). HES therapy was associated with higher rates of acute renal failure and renal-replacement therapy than was Ringer's lactate.

CONCLUSIONS

The use of intensive insulin therapy placed critically ill patients with sepsis at increased risk for serious adverse events related to hypoglycemia. As used in this study, HES was harmful, and its toxicity increased with accumulating doses. (ClinicalTrials.gov number, NCT00135473.)

The authors' affiliations are listed in the Appendix. The investigators who participated in the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org. Address reprint requests to Dr. Reinhart at the Department of Anesthesiology and Intensive Care Medicine, Friedrich Schiller University of Jena, Erlanger Allee 101, 07747 Jena, Germany, or at konrad.reinhart@med.uni-jena.de.

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In a study by Van den Berghe et al. involving critically ill surgical patients, intensive insulin therapy to maintain euglycemia (glucose level, 80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) lowered in-hospital mortality from 10.9% to 7.2%, mostly by reducing deaths from multiple organ failure with a proven septic focus.[1] This beneficial effect occurred predominantly in cardiac surgical patients who received high glucose challenges immediately after surgery (8 to 12 g of glucose intravenously per hour) and was associated with an unusually high rate of death (5.1%) among controls.

Furthermore, in a follow-up study by Van den Berghe et al., involving critically ill patients who had not undergone surgery and had not received a high glucose challenge, intensive insulin therapy had no beneficial effect on survival rates. However, such therapy was associated with an increase in hypoglycemic events (mean glucose level, 31 mg per deciliter [1.7 mmol per liter]) by a factor of 5 to 6.[2] Although it is unknown whether intensive insulin therapy improves the outcome during critical illness with severe sepsis, such therapy has been widely advocated.[3]

Few data are available to guide the choice of either colloid or crystalloid for fluid resuscitation in patients with septic shock.[4] In animal models, hydroxyethyl starch (HES), as compared with crystalloids, improved microcirculation during endotoxemia[5] and lessened tissue damage.[6] On the other hand, HES was associated with serious side effects, including coagulopathy and acute renal failure.[7,8] We assessed the safety and efficacy of intensive insulin therapy as compared with conventional insulin therapy (on the basis of the Leuven titration protocol) as well as the safety and efficacy of HES as compared with Ringer's lactate in patients with severe sepsis or septic shock.

METHODS

STUDY DESIGN

In this multicenter, randomized study, called the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, we compared intensive insulin therapy with conventional insulin therapy and HES with Ringer's lactate, using a two-by-two factorial, open-label design. There was no a priori reason to expect interactions between the two types of treatment.

STUDY PATIENTS

From April 2003 to June 2005, we recruited patients in multidisciplinary intensive care units (ICUs) at 18 academic tertiary hospitals in Germany. Patients with severe sepsis or septic shock who were at least 18 years of age were eligible to enroll in the study. Severe sepsis and septic shock were defined according to criteria reported previously (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org).[9] Patients were deemed to be eligible if the onset of the syndrome was less than 24 hours before admission to the ICU or less than 12 hours after admission if the condition developed in the ICU. The treatment period was ended at 21 days after randomization or at discharge from the ICU or at the time of death (see the Supplementary Appendix).

The trial was approved by the ethics committee at each participating institution. Written informed consent was obtained from all patients or their legal representatives. In cases in which previous consent could not be obtained from the patient because of critical illness or the use of sedatives or anesthetic drugs and in order to permit early resuscitation, the ethics committee approved a provision for delayed consent. In such cases, a surrogate decision maker was fully informed as soon as possible. Consent was then obtained or the patient was removed from the study and all study procedures were ended.

The study's sponsors — B. Braun, Novo Nordisk, and HemoCue — provided drugs and glucometers but had no role in the design of the study, the gathering or analysis of data, or the preparation of the manuscript. The sponsors also had no responsibility for the conduct of the trial, had no access to the data, and did not control the decision to publish the results. The authors accept full responsibility for the conduct of the trial, had complete and unrestricted access to the data, and vouch for the completeness and accuracy of the data.

INSULIN THERAPY

In the conventional-therapy group, a continuous insulin infusion (50 IU of Actrapid HM, Novo Nordisk) in 50 ml of 0.9% saline solution was delivered through a perfusion pump when the blood glucose level exceeded 200 mg per deciliter (11.1 mmol per liter); the insulin level was then adjusted to maintain a blood glucose level of

180 mg per deciliter (10.0 mmol per liter) to 200 mg per deciliter. In the intensive-therapy group, infusion of insulin was started when blood glucose levels exceeded 110 mg per deciliter; the insulin level was then adjusted to maintain euglycemia (80 to 110 mg per deciliter).

The insulin dose was adjusted to whole-blood glucose levels, which were measured at intervals of 1 to 4 hours with the use of either arterial or capillary blood samples and a glucometer (HemoCue). ICU nurses calculated insulin adjustments with the use of the Leuven titration guidelines.[10]

FLUID RESUSCITATION

Patients were not eligible to participate in the study if they had received more than 1000 ml of HES in the 24 hours before randomization. (For details on fluid composition and hemodynamic management, see the Supplementary Appendix.) Renal-replacement therapy was instituted, regardless of the study-group assignment, in the case of acute renal failure or in the presence of another indication, such as volume overload or hyperkalemia.[11]

OUTCOME MEASURES AND SAFETY END POINTS

The coprimary end points were the rate of death from any cause at 28 days and morbidity, as measured during the intervention by the mean score on the Sequential Organ Failure Assessment (SOFA), on a scale ranging from 0 to 4 for each of six organ systems, with an aggregate score of 0 to 24 and higher scores indicating more severe organ dysfunction. Secondary end points were the rate of acute renal failure (defined as a doubling of the baseline serum creatinine level or the need for renal-replacement therapy), the time to hemodynamic stabilization, the frequency of vasopressor therapy, mean SOFA subscores, the need for red-cell transfusion, the duration of mechanical ventilation, the length of stay in the ICU, and mortality at 90 days. The occurrence of severe hypoglycemia (≤40 mg of glucose per deciliter [2.2 mmol per liter]) was defined as a safety end point. Serious adverse events were reported according to standard definitions.[12] One safety analysis was planned and performed before the first interim analysis.

STATISTICAL ANALYSIS

The study was designed to detect a reduction in mortality from 40% to 30% at 28 days. Such an effect was expected to reduce the mean SOFA score by 1.2 points.[13] To permit early termination of the study in case of futility or unexpectedly large effects, as well as modifications of the sample size and end points on the basis of interim results, we used a two-stage adaptive design with mortality and the mean SOFA score as coprimary end points.[14] To detect a difference of 1.2 in the mean SOFA score with a power of 80%, we needed to enroll 600 patients in the first stage of the adaptive study design. Therefore, the first interim efficacy analysis was performed after inclusion of 600 patients. We used the chi-square test and the t-test to assess differences in mortality at 28 days and the mean SOFA score, respectively, in the intention-to-treat population. Details on the stopping strategy, as well as the analyses of secondary end points, are described in the Supplementary Appendix. Cox regression analysis with time-dependent covariates was used to identify risk factors for the time to death. All reported P values are two-sided. Statistical analyses were performed with the use of SAS software, version 9.13.

RESULTS

TRIAL SUSPENSION

After the first safety analysis, involving 488 patients,[15] intensive insulin therapy was terminated early by the data and safety monitoring board, owing to an increased number of hypoglycemic events, as compared with conventional insulin therapy; hypoglycemia was reported in 30 of 247 patients in the intensive-therapy group (12.1%) and in 5 of 241 patients in the conventional-therapy group (2.1%, $P<0.001$). The comparison between HES and Ringer's lactate was continued with all patients receiving conventional insulin therapy until the planned interim analysis involving 537 patients. The additional 49 patients, who underwent randomization after the first safety analysis, were not different with respect to baseline characteristics or the conduct of insulin treatment.

The planned interim analysis after the enrollment of 600 patients showed a significantly greater incidence of renal failure and a trend toward higher 90-day mortality among patients who received HES than among those who received Ringer's lactate. The study was suspended by the data and safety monitoring board, and the second stage of the adaptive design was aborted.

Enrollment and outcomes are shown in Figure 1 of the Supplementary Appendix.

ANALYSES OF INTERACTION

There were no significant interactions between the two study interventions with respect to the rate of death at 28 days (P=0.55) and the rate at 90 days (P=0.71). However, we found a suggestion of an interaction for the mean SOFA score (P=0.07) and the development of acute renal failure (P=0.06). There was no interaction for the mean SOFA score if the renal subscore was excluded (P=0.11). Comparisons between single study groups suggested that the risk of acute renal failure in the intensive-therapy group was higher among patients who received HES than among

Table 1. **Baseline Characteristics of the Patients.***

Variable		Insulin Therapy			Fluid Resuscitation		
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†	Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Age — yr	64.6±13.7	65.2±13.2	64.0±14.3	0.35	64.9±14.1	64.4±13.3	0.72
Male sex — no. (%)	322 (60.0)	171 (59.0)	151 (61.1)	0.61	164 (59.6)	158 (60.3)	0.87
Body-mass index§	27.3±5.5	27.5±5.3	26.9±5.8	0.22	27.2±5.5	27.3±5.6	0.74
APACHE II score¶	20.2±6.7	20.3±6.8	20.2±6.6	0.84	20.3±6.7	20.1±6.7	0.72
Preexisting condition — no. (%)‖							
Hypertension	249 (46.4)	144 (49.7)	105 (42.5)	0.10	134 (48.7)	115 (43.9)	0.26
Diabetes mellitus							
Either type	163 (30.4)	91 (31.4)	72 (29.1)	0.58	83 (30.2)	80 (30.5)	0.93
Type 1	73 (13.6)	41 (14.1)	32 (13.0)	0.69	37 (13.5)	36 (13.7)	0.92
Type 2	90 (16.8)	50 (17.2)	40 (16.2)	0.75	46 (16.7)	44 (16.8)	0.98
Heart failure	80 (14.9)	44 (15.2)	36 (14.6)	0.85	34 (12.4)	46 (17.6)	0.09
Renal dysfunction	44 (8.2)	23 (7.9)	21 (8.5)	0.81	30 (10.9)	14 (5.3)	0.02
COPD	82 (15.3)	44 (15.2)	38 (15.4)	0.95	46 (16.7)	36 (13.7)	0.34
Liver cirrhosis	12 (2.2)	7 (2.4)	5 (2.0)	0.76	6 (2.2)	6 (2.3)	0.93
Cancer							
Previous disease	49 (9.1)	27 (9.3)	22 (8.9)	0.87	26 (9.5)	23 (8.8)	0.79
Current disease	34 (6.3)	23 (7.9)	11 (4.5)	0.10	23 (8.4)	11 (4.2)	0.05
Immunosuppression	10 (1.9)	7 (2.4)	3 (1.2)	0.36	5 (1.8)	5 (1.9)	1.00
Site of infection — no. (%)‖							
Lung	221 (41.2)	123 (42.4)	98 (39.7)	0.58	124 (45.1)	97 (37.0)	0.04
Abdomen	207 (38.5)	112 (38.6)	95 (38.5)	0.93	103 (37.5)	104 (39.7)	0.64
Bone or soft tissue	61 (11.4)	34 (11.7)	27 (10.9)	0.79	29 (10.5)	32 (12.2)	0.55
Surgical wound	42 (7.8)	21 (7.2)	21 (8.5)	0.58	23 (8.4)	19 (7.3)	0.62
Urogenital	47 (8.8)	29 (10.0)	18 (7.3)	0.27	18 (6.5)	29 (11.1)	0.07
Primary bacteremia	22 (4.1)	10 (3.4)	12 (4.9)	0.41	11 (4.0)	11 (4.2)	0.92
Other	23 (4.3)	10 (3.4)	13 (5.3)	0.29	10 (3.6)	13 (5.0)	0.45
Recent surgical history — no. (%)				0.47			0.04
Elective surgery	86 (16.0)	49 (16.9)	37 (15.0)		50 (18.2)	36 (13.7)	
Emergency surgery	198 (36.9)	100 (34.5)	98 (39.7)		88 (32.0)	110 (42.0)	
No history of surgery	252 (46.9)	140 (48.3)	112 (45.3)		137 (49.8)	115 (43.9)	
Missing data	1 (0.2)	1 (0.3)	0		0	1 (0.4)	

Table 1. (Continued.)

Variable		**Insulin Therapy**			**Fluid Resuscitation**		
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†	Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Laboratory values							
Blood glucose — mg/dl				0.05			0.13
Median	134	138	130		136	133	
Interquartile range	110–178	111–184	108–167		112–184	106–168	
Glycated hemoglobin — %				0.04			0.58
Median	5.9	6.0	5.9		6.0	5.8	
Interquartile range	5.3–6.3	5.4–6.4	5.2–6.2		5.3–6.3	5.3–6.3	
Plasma C-reactive protein — mg/liter				0.99			0.97
Median	200	204	198		199	203	
Interquartile range	127–290	126–289	131–290		127–307	127–280	
Serum creatinine — mg/dl				0.45			0.68
Median	1.43	1.44	1.40		1.39	1.47	
Interquartile range	0.96–2.13	0.95–2.20	0.96–2.07		0.94–2.20	0.96–2.07	
Creatinine clearance — ml/min				0.72			0.77
Median	51.8	51.7	51.9		52.3	51.7	
Interquartile range	32.8–83.3	31.0–84.6	35.3–81.0		30.7–86.5	34.7–76.7	
Lactate — mmol/liter				0.14			0.93
Median	2.2	2.4	2.1		2.2	2.2	
Interquartile range	1.5–4.0	1.6–4.0	1.4–3.8		1.5–4.3	1.5–3.8	
Hemodynamic variables							
Heart rate — bpm				0.95			0.82
Median	104	104	104		104	103	
Interquartile range	90–118	90–118	90–118		90–117	90–118	
Central venous pressure — mm Hg				0.30			0.32
Median	12.0	12.0	12.0		12.0	12.0	
Interquartile range	8.0–15.0	8.0–15.0	8.0–15.0		8.0–14.5	8.0–15.0	
Mean arterial pressure — mm Hg				0.82			0.64
Median	75.0	75.0	77.0		75.0	75.5	
Interquartile range	68.0–85.0	68.0–84.0	67.0–85.0		68.0–85.0	67.0–85.0	
Central venous oxygen saturation — %				0.88			0.20
Median	75.0	75.0	75.0		74.0	75.0	
Interquartile range	68.0–80.0	68.0–80.0	68.0–81.0		68.0–79.0	69.0–81.0	

* Plus–minus values are means ±SD. P values were calculated with the t-test or the Mann–Whitney test and the chi-square test or Fisher's exact test, as appropriate. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. COPD denotes chronic pulmonary obstructive disease, and HES hydroxyethyl starch (pentastarch).

† P values are for the comparison between conventional insulin therapy and intensive insulin therapy.

‡ P values are for the comparison between Ringer's lactate and HES.

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

¶ Missing subscores on the Acute Physiology and Chronic Health Evaluation (APACHE II) were counted as 0. This scale ranges from 0 to 71, with higher scores indicating a greater severity of illness.

‖ Multiple responses per patient were possible.

those who received Ringer's lactate (odds ratio, 2.65; 95% confidence interval [CI], 1.51 to 4.68). However, the risk was also increased among patients in the HES group who received intensive insulin therapy, as compared with those who received conventional therapy (odds ratio, 1.69; 95% CI, 1.01 to 2.83).

INSULIN THERAPY

The characteristics of the patients and indicators of the severity of disease were well balanced between the intensive-therapy group and the conventional-therapy group (Table 1, and Table 1 of the Supplementary Appendix). The numbers of patients were also well balanced with respect to the receipt of concomitant medications relevant to hyperglycemia (Table 2 of the Supplementary Appendix).

Nutrition and Blood Glucose Control

Data regarding nutritional intake and blood glucose levels are shown in Figure 1 and in Table 4 of the Supplementary Appendix. In the intensive-therapy group, 243 of 247 patients (98.4%) received insulin on at least one study day for glucose values above the target range (>110 mg per deciliter), whereas only 215 of 290 patients (74.1%) in the conventional-therapy group needed insulin because glucose values were outside the target range (≥200 mg per deciliter) (P<0.001). During the study period, mean morning blood glucose levels were lower in the intensive-therapy group (mean, 112 mg per deciliter [6.2 mmol per liter]; 95% CI, 110 to 114 [6.1 to 6.3]) than in the conventional-therapy group (mean, 151 mg per deciliter [8.4 mmol per liter]; 95% CI, 148 to 155 [8.2 to 8.6]; P<0.001). The median insulin dose that was administered per patient per day was higher in the intensive-therapy group (32 IU; interquartile range, 20 to 50) than in the conventional-therapy group (5 IU; interquartile range, 0 to 22; P<0.001).

Mortality

The rate of death did not differ significantly between the intensive-therapy group and the conventional-therapy group at 28 days (24.7% vs. 26.0%, P=0.74) or at 90 days (39.7% vs. 35.4%, P=0.31) (Table 2 and Fig. 2A). In a Cox regression analysis, intensive insulin therapy was not an independent risk factor for death (hazard ratio, 0.95; 95% CI, 0.70 to 1.28; P=0.72). However, identified risk factors were the patient's score on the Acute Physiology and Chronic Health Evaluation (APACHE II, ranging from 0 to 71, with higher scores indicating a greater severity of illness) with the exclusion of the age subscore (hazard ratio, 1.07; 95% CI, 1.05 to 1.09; P<0.001), an age of at least 60 years (hazard ratio, 2.45; 95% CI, 1.68 to 3.57; P<0.001), and hypoglycemia (hazard ratio, 3.31; 95% CI, 2.23 to 4.90; P<0.001).

In unplanned subgroup analyses that evaluated the APACHE II score before randomization, the reasons for ICU admission, the presence or absence of diabetes, and the presence or absence of empirical or appropriate antimicrobial therapy, there was no significant difference in survival between the intensive-therapy group and the conventional-therapy group. In addition, an analysis that excluded all patients who were discharged from the ICU before the 3rd, 5th, or 10th day did not show significant differences between the two study groups (Table 3A of the Supplementary Appendix).

Exploratory analyses that stratified data according to the mean morning blood glucose level (<110 mg per deciliter, 110 to 150 mg per deciliter, or >150 mg per deciliter) did not show significant differences in survival rates between the two study groups (Fig. 2 of the Supplementary Appendix).

Morbidity

There was no significant difference between the intensive-therapy group and the conventional-therapy group in mean SOFA scores (7.8 and 7.7 points, respectively; P=0.88). Likewise, SOFA subscores were similar in both groups. There were also no significant differences between the two study groups in secondary end points, including the rate of acute renal failure, the need for renal-replacement therapy, the use of vasopressors, and the number of ventilator-free days. Patients in the intensive-therapy group tended to have longer stays in the ICU than did patients in the conventional-therapy group (Table 2).

Safety End Points

At least one episode of severe hypoglycemia occurred in 42 patients in the intensive-therapy group (17.0%) and in 12 patients in the conventional-therapy group (4.1%, P<0.001). Significantly more serious hypoglycemic episodes were reported in the intensive-therapy group (in 19 patients)

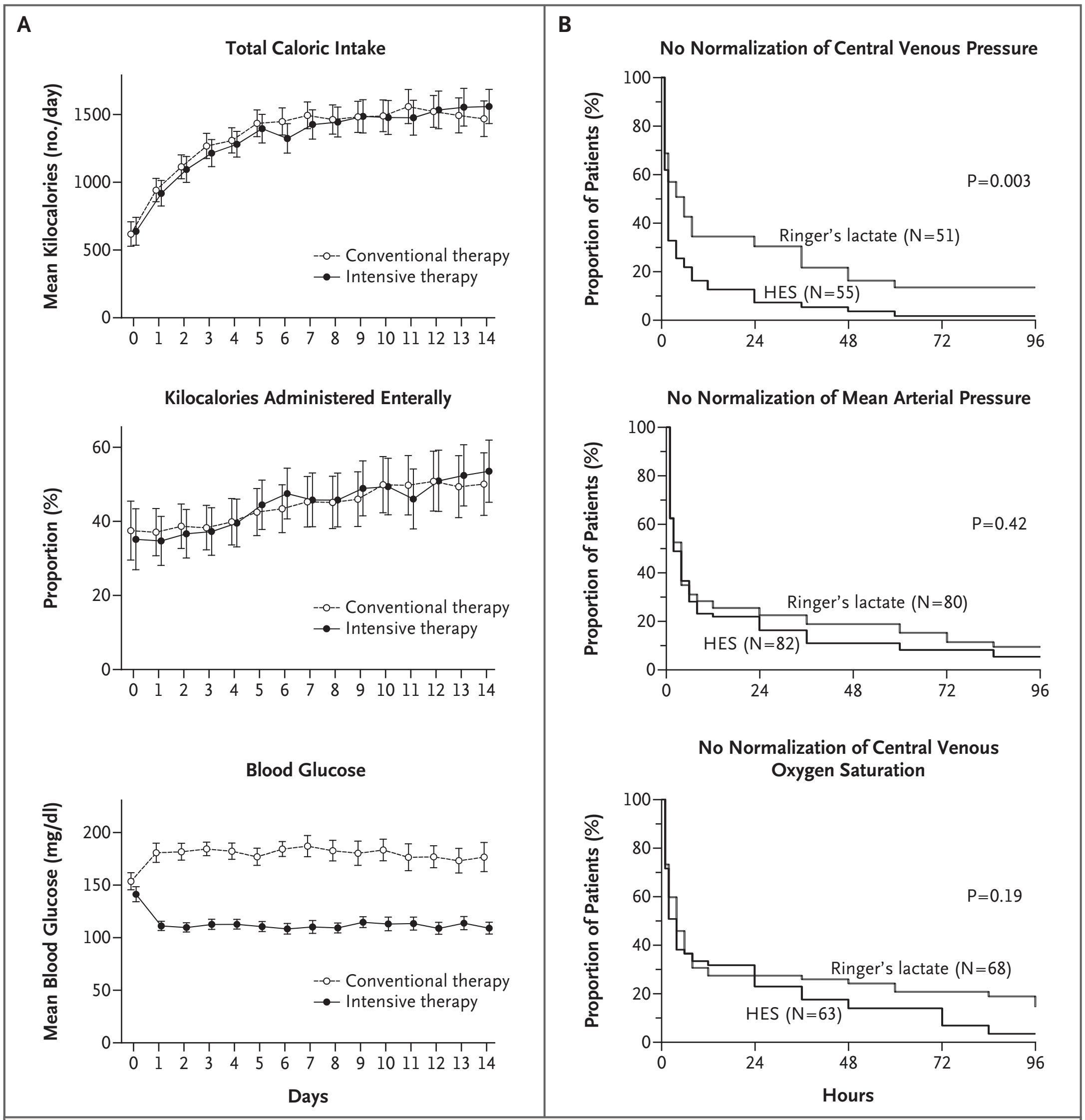

Figure 1. Nutrition, Blood Glucose, Systemic Pressures, and Central Venous Oxygen Saturation, According to the Type of Insulin and Fluid Therapy.

Panel A shows caloric intake and daily morning blood glucose levels in all 537 patients during the first 14 days of the study, according to whether patients received intensive insulin therapy or conventional insulin therapy. Day 0 represents the time at randomization until the start of the next full 24-hour study day; I bars denote 95% confidence intervals. The mean daily caloric intake (both parenteral and enteral) and the fraction of kilocalories administered by the enteral route, respectively, were calculated only for days on which nutrition was given. The type of nutrition was similar in the two study groups. The mean morning blood glucose level in both study groups was calculated only for patients receiving insulin therapy on the respective study day ($P<0.001$). Panel B shows the results of volume resuscitation in patients receiving either 10% pentastarch, a low-molecular-weight hydroxyethyl starch (HES), or Ringer's lactate, with P values calculated by the log-rank test. Indicated are the proportions of patients who did not have normalization of hemodynamic values for central venous pressure, mean arterial pressure, and central venous oxygen saturation.

than in the conventional-therapy group (7 patients), a difference of 7.7% versus 2.4% ($P=0.005$). Although no serious adverse event was found to result directly in death, the hypoglycemic episodes were more often classified as life-threatening in the intensive-therapy group than in the conventional-therapy group (in 13 vs. 6 patients; 5.3% vs. 2.1%; $P=0.05$) and as requiring prolonged hospitalization (6 patients vs. 1 patient; 2.4% vs. 0.3%; $P=0.05$) (Table 3).

FLUID RESUSCITATION

Before randomization, the characteristics of patients were well balanced between the group that received HES and the group that received Ringer's lactate (Table 1, and Table 1 of the Supplementary Appendix). Patients in the two study groups received similar fluids in the 12 hours before randomization (Table 5 of the Supplementary Appendix).

Patients in the Ringer's lactate group received significantly more total resuscitation fluid than did patients in the HES group. The ratio of total fluid in the Ringer's lactate group to that in the HES group was 1.32 for the entire study period (1.58 on day 1 and 1.44 on days 1 to 4). Patients in the HES group received a median cumulative dose of 70.4 ml per kilogram of body weight (interquartile range, 33.4 to 144.2). The median central venous pressure was 11.8 mm Hg (interquartile range, 9.5 to 14.2) in the HES group and 10.7 mm Hg (interquartile range, 8.6 to 12.7) in the Ringer's lactate group (P<0.001); the median

Table 2. Primary and Secondary Outcomes.*

Variable	Insulin Therapy				Fluid Resuscitation		
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†	Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Death							
At 28 days§				0.74			0.48
No./total no.	136/536	75/289	61/247		66/274	70/262	
Percent (95% CI)	25.4 (21.7–29.1)	26.0 (20.9–31.0)	24.7 (19.3–30.1)		24.1 (19.0–29.2)	26.7 (21.4–32.1)	
At 90 days				0.31			0.09
No./total no.	200/535	102/288	98/247		93/274	107/261	
Percent (95% CI)	37.4 (33.3–41.5)	35.4 (29.9–40.9)	39.7 (33.6–45.8)		33.9 (28.3–39.6)	41.0 (35.0–47.0)	
SOFA score§¶				0.88			0.16
Mean	7.8	7.7	7.8		7.5	8.0	
95% CI	7.4–8.1	7.3–8.2	7.3–8.3		7.1–8.0	7.5–8.5	
SOFA subscores							
Cardiovascular				0.96			0.51
Median	1.78	1.75	1.82		1.76	1.80	
Interquartile range	1.00–2.67	1.00–2.67	1.00–2.74		1.00–2.71	0.86–2.67	
Respiratory				0.24			0.58
Median	2.53	2.57	2.50		2.57	2.50	
Interquartile range	2.00–2.89	2.17–2.92	2.00–2.86		2.00–2.89	2.00–2.90	
Coagulation				0.90			<0.001
Median	0.21	0.21	0.21		0.11	0.46	
Interquartile range	0–1.00	0–1.00	0–1.08		0–0.83	0–1.30	
Renal				0.90			0.02
Median	0.50	0.50	0.53		0.42	0.67	
Interquartile range	0–1.60	0–1.60	0–1.59		0–1.33	0–1.94	
Hepatic				0.74			1.00
Median	0.10	0.08	0.11		0.11	0.09	
Interquartile range	0–0.87	0–0.88	0–0.85		0–0.90	0–0.85	
Central nervous system				0.82			0.50
Median	1.00	1.00	1.00		1.00	1.00	
Interquartile range	0.08–2.10	0–2.00	0.10–2.33		0.05–2.00	0.09–2.43	

Table 2. (Continued.)

Variable	Insulin Therapy				Fluid Resuscitation		
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†	Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Hypoglycemia (≤40 mg/dl)				<0.001			0.85
No. of patients/total no.	54/537	12/290	42/247		27/275	27/262	
Percent (95% CI)	10.1 (7.5–12.6)	4.1 (1.9–6.4)	17.0 (12.3–21.7)		9.8 (6.3–13.3)	10.3 (6.6–14.0)	
Acute renal failure				0.25			0.002
No. of patients/total no.	153/533	77/289	76/244		62/272	91/261	
Percent (95% CI)	28.7 (24.9–32.6)	26.6 (21.6–31.7)	31.1 (25.3–37.0)		22.8 (17.8–27.8)	34.9 (29.1–40.7)	
Renal-replacement therapy				0.19			0.001
No. of patients/total no.	132/533	65/289	67/244		51/272	81/261	
Percent (95% CI)	24.8 (21.1–28.4)	22.5 (17.7–27.3)	27.5 (21.9–33.1)		18.8 (14.1–23.4)	31.0 (25.4–36.7)	
Red-cell transfusion				0.02			0.06
No. of patients/total no.	388/537	197/290	191/247		189/275	199/262	
Percent (95% CI)	72.3 (68.5–76.0)	67.9 (62.6–73.3)	77.3 (72.1–82.6)		68.7 (63.3–74.2)	76.0 (70.8–81.1)	
No. of red-cell transfusion units				0.95			<0.001
Median	5	5	5		4	6	
Interquartile range	2–10	3–10	2–10		2–8	4–12	
Length of stay in ICU (days)				0.06			0.32
Median	14	14	16		14	16	
Interquartile range	8–28	7–25	8–30		7–28	8–28	
Vasopressor-free (days)‖				0.24			0.52
Median	17	18	16		17	17	
Interquartile range	7–20	8–20	6–20		8–20	6–20	
Ventilator-free (days)‖				0.83			0.06
Median	3	3	3		3	2	
Interquartile range	1–6	1–6	1–7		1–7	1–6	

* P values were calculated with the t-test or the Mann–Whitney test and the chi-square test or Fisher's exact test, as appropriate. HES denotes hydroxyethyl starch (pentastarch), and SOFA Sequential Organ Failure Assessment.

† P values are for the comparison between conventional insulin therapy and intensive insulin therapy.

‡ P values are for the comparison between Ringer's lactate and HES.

§ This category is a coprimary outcome of the study. All other categories are secondary outcomes.

¶ Subscores on SOFA range from 0 to 4 for each of six organ systems, with an aggregate score of 0 to 24 and with higher scores indicating more severe organ dysfunction.

‖ This category applies to days during the study period.

central venous oxygen saturation was 73.6% (interquartile range, 70.0 to 76.9) in the HES group and 72.4% (interquartile range, 69.3 to 75.9) in the Ringer's lactate group (P=0.04). The use of nonstudy colloid fluids is discussed in the Supplementary Appendix.

Among patients who entered the study with values for central venous pressure that were below the hemodynamic target values (≥8 mm Hg), the target values were achieved faster in patients receiving HES than in those receiving Ringer's lactate (P=0.003) (Fig. 1B).

Mortality

The rate of death at 28 days did not differ significantly between the HES group and the Ringer's lactate group (26.7% and 24.1%, respectively; P=0.48). However, there was a trend toward a

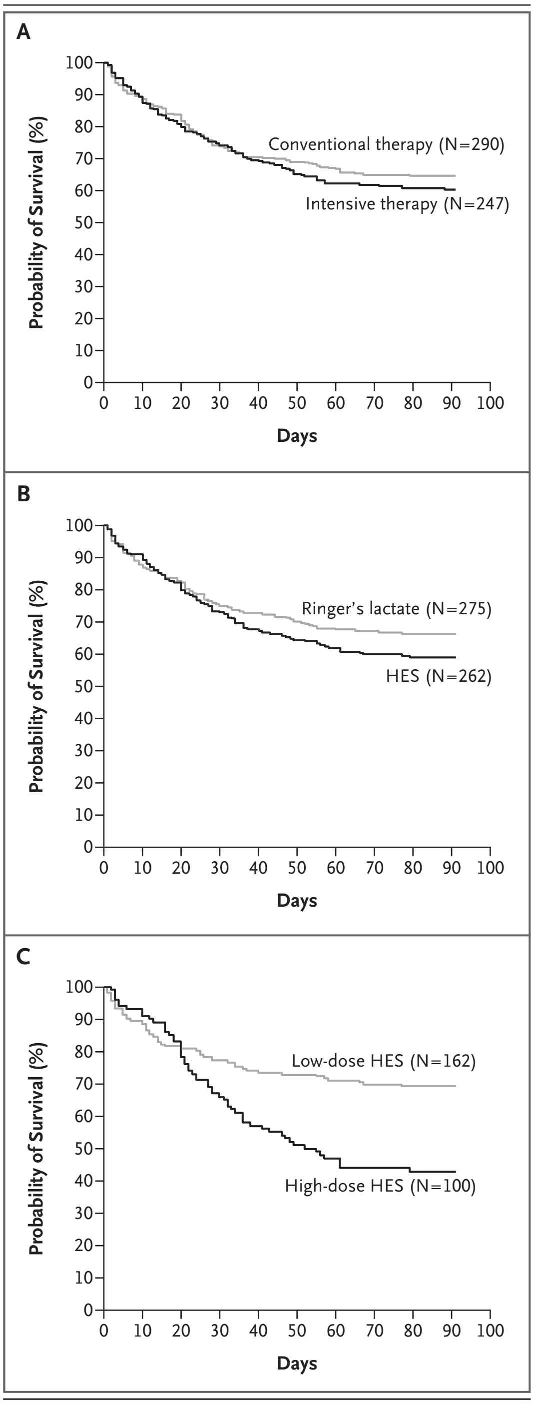

Figure 2. Kaplan–Meier Curves for Overall Survival.

Panel A shows the comparison of overall survival between patients receiving intensive insulin therapy and those receiving conventional insulin therapy (P=0.36 by the log-rank test). Panel B shows the comparison between patients receiving pentastarch (HES) for volume resuscitation and those receiving Ringer's lactate (P=0.14 by the log-rank test). Panel C shows the comparison between patients in the low-dose HES subgroup (≤22 ml per kilogram of body weight per day), who received a median cumulative dose of 48.3 ml per kilogram (interquartile range, 21.9 to 96.2), and those in the high-dose subgroup (>22 ml per kilogram for at least 1 day during the study period), who received a median cumulative dose of 136.0 ml per kilogram (interquartile range, 79.0 to 180.0) (P<0.001 by the log-rank test).

rate of death at 90 days that was higher in the HES group than in the Ringer's lactate group (41.0% vs. 33.9%, P=0.09) (Table 2 and Fig. 2B).

Morbidity

The mean SOFA scores did not differ significantly between the HES group and the Ringer's lactate group (8.0 and 7.5 points, respectively; P=0.16) (Table 2). However, the HES group had a significantly higher rate of acute renal failure (34.9% vs. 22.8%, P=0.002) and more days on which renal-replacement therapy was required (650 of 3554 vs. 321 of 3471 total days; 18.3% vs. 9.2%). Patients in the HES group had a lower median platelet count (179,600 per cubic millimeter; interquartile range, 122,000 to 260,000) than did those in the Ringer's lactate group (224,000 per cubic millimeter; interquartile range, 149,800 to 314,800; P<0.001) and received more units of packed red cells than did patients in the Ringer's lactate group (Table 2).

SUBGROUP AND MULTIVARIATE ANALYSES

In post hoc univariate analysis, there was a direct correlation between the cumulative dose of HES and both the need for renal-replacement therapy and the rate of death at 90 days; there was no corresponding correlation with the cumulative dose of Ringer's lactate (Fig. 3). The dose limit for HES (20 ml per kilogram per day) was exceeded by more than 10% on at least 1 day in 100 of 262 patients in the HES group. In 74 of these 100 patients, the dose escalation occurred within the first 24 hours. Before randomization, the median APACHE II scores and ages of these patients were similar to those of patients who did not receive a dose escalation; however, patients who received a dose escalation had lower initial values for central venous pressure (median, 11.0 mm Hg; interquartile range, 6.0 to 15.0) than did patients who did not receive a dose escalation (median, 12.0 mm Hg; interquartile range, 9.0 to 15.0; P=0.03). They also received more crystalloid

Table 3. Adverse and Serious Adverse Events.*

Variable	Insulin Therapy				Fluid Resuscitation		
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†	Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Adverse event							
Patients with at least one adverse event				<0.001			0.81
No. of patients	80	25	55		40	40	
Percent (95% CI)	14.9 (11.9–17.9)	8.6 (5.4– 11.9)	22.3 (17.1–27.5)		14.5 (10.4–18.7)	15.3 (10.9–19.6)	
Hypoglycemia (≤40 mg/dl)				<0.001			0.85
No. of patients	54	12	42		27	27	
Percent (95% CI)	10.1 (7.5–12.6)	4.1 (1.9–6.4)	17.0 (12.3–21.7)		9.8 (6.3–13.3)	10.3 (6.6–14.0)	
Bleeding				0.30			0.45
No. of patients	23	10	13		10	13	
Percent (95% CI)	4.3 (2.6–6.0)	3.4 (1.4–5.6)	5.3 (2.5–8.1)		3.6 (1.4–5.9)	5.0 (2.3–7.6)	
Other§				1.0			0.11
No. of patients	10	5	5		8	2	
Percent (95% CI)	1.9 (0.7–3.0)	1.7 (0.2–3.2)	2.0 (0.3–3.8)		2.9 (0.9–4.9)	0.8 (0–1.8)	
Serious adverse event							
Patients with at least one serious adverse event				0.01			0.63
No. of patients	42	15	27		20	22	
Percent (95% CI)	7.8 (5.6–10.1)	5.2 (2.6–7.7)	10.9 (7.0–14.8)		7.3 (4.2–10.3)	8.4 (5.0–11.8)	
Hypoglycemia (≤40 mg/dl)¶							
Any				0.005			0.90
No. of patients	26	7	19		13	13	
Percent (95% CI)	4.8 (3.0–6.7)	2.4 (0.7–4.2)	7.7 (4.4–11.0)		4.7 (2.2–7.2)	5.0 (2.3–7.6)	
Life-threatening				0.05			0.90
No. of patients	19	6	13		10	9	
Percent (95% CI)	3.5 (2.0–5.1)	2.1 (0.4–3.7)	5.3 (2.5–8.1)		3.6 (1.4–5.9)	3.4 (1.2–5.6)	
Resulting in prolonged hospitalization				0.05			0.72
No. of patients	7	1	6		3	4	
Percent (95% CI)	1.3 (0.3–2.3)	0.3 (0– 1.0)	2.4 (0.5– 4.4)		1.1 (0–2.3)	1.5 (0–3.0)	
Bleeding				0.99			0.14
No. of patients	13	7	6		4	9	
Percent (95% CI)	2.4 (1.1–3.7)	2.4 (0.7–4.2)	2.4 (0.5–4.4)		1.5 (0–2.9)	3.4 (1.2– 5.6)	
Other§				0.19			0.37
No. of patients	5	1	4		4	1	
Percent (95% CI)	0.9 (0.1–1.7)	0.3 (0–1.0)	1.6 (0–3.2)		1.5 (0–2.9)	0.4 (0–1.1)	

* P values were calculated with the chi-square test or Fisher's exact test, as appropriate. Definitions of all adverse events are listed in the Supplementary Appendix.

† P values are for the comparison between conventional insulin therapy and intensive insulin therapy.

‡ P values are for the comparison between Ringer's lactate and HES.

§ Other conditions included acute worsening of oxygenation, ventricular fibrillation, cardiac arrest, hyperosmolarity, hyperkalemia, and hypernatremia.

¶ Severe hypoglycemia did not result directly in death or in persistent or substantial disability or incapacity in any patient.

in the 12 hours preceding study entry (median, 2400 ml; interquartile range, 1000 to 3500) than did those who did not receive a dose escalation (median, 1135 ml; interquartile range, 500 to 2560; P=0.002). The rate of death at 90 days was significantly increased among patients who received a higher dose of HES, as compared with those who received a lower dose (57.6% vs. 30.9%, P<0.001) (Fig. 2C). Detailed analyses of antimicrobial therapy showed no imbalances that could

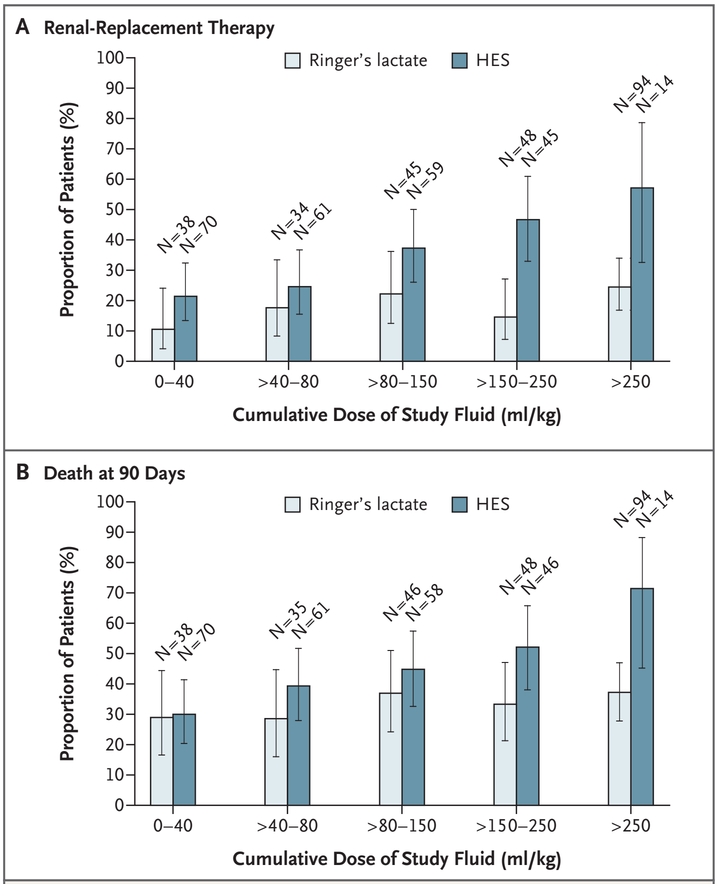

Figure 3. Cumulative Effect of Volume Resuscitation on the Need for Renal-Replacement Therapy and the Rate of Death at 90 Days.

Panel A shows the relationship between the cumulative dose of either pentastarch (HES) or Ringer's lactate and the percentage of patients who needed renal-replacement therapy (Panel A) and the rate of death at 90 days (Panel B). The need for renal-replacement therapy and 90-day mortality were significantly correlated with the cumulative dose of HES (P<0.001 and P=0.001, respectively) but not with the dose of Ringer's lactate (P=0.11 and P=0.31, respectively). All P values were calculated with the Cochran–Armitage test for trend. I bars denote 95% confidence intervals.

easily explain these study results (Table 3B and Table 7 of the Supplementary Appendix).

In a multivariate post hoc logistic-regression model that was adjusted for insulin therapy, the total dose of Ringer's lactate, baseline creatinine clearance, mean arterial pressure, and total dose of colloids administered 12 hours before the start of therapy, the total dose of HES was a significant independent predictor of both the need for renal-replacement therapy and the rate of death at 90 days (Table 6 of the Supplementary Appendix). At 90 days, patients who had received a lower dose of HES were more likely to have renal failure than those who had received Ringer's lactate (30.9% vs. 21.7%, P=0.04) and were more likely to need renal-replacement therapy (25.9% vs. 17.3%, P=0.03).

DISCUSSION

In 537 patients with septic shock, we found no beneficial effect of intensive insulin treatment (administered according to the Leuven protocol) with respect to the rate of death at 28 days and the mean SOFA score; we also found no benefit with respect to any of the secondary end points. Moreover, our study was stopped early, at the first planned safety analysis, because intensive insulin therapy was associated with a significantly increased rate of severe hypoglycemic events and a trend toward a prolonged stay in the ICU.

Cox regression analysis identified the occurrence of hypoglycemia as an independent risk factor for death from any cause. Hypoglycemia may be only a marker of a poor outcome, independently of insulin therapy. On the other hand, it is possible that unrecognized adverse effects of hypoglycemia on the brain or heart offset potential beneficial effects of intensive insulin therapy.[16] The full extent of hypoglycemic events in our study is unknown, since the usual clinical warning signs and symptoms of hypoglycemia in the patients we studied may have been masked by critical illness and sedation.

Our findings are similar to those of the second study by Van den Berghe et al.,[2] which assessed the use of intensive insulin therapy in maintaining euglycemia in critically ill patients in a medical ICU. In our study, the nonsignificant differences in the rates of death at 28 days and at 90 days in the intensive-therapy group and the conventional-therapy group were similar to those in the study by Van den Berghe et al., as was the magnitude of the significant increase in hypoglycemic episodes in the intensive-therapy group, as compared with the conventional-therapy group (18.7% vs. 3.1% in the study by Van den Berghe et al. and 17.0% vs. 4.1% in our study). The mean blood glucose levels during hypoglycemia in the intensive-therapy group and the conventional-therapy group were also similar in the study by Van den Berghe et al. (32 mg and 31 mg per deciliter, respectively; P=0.50) and in our study (31 mg and 28 mg per deciliter, respectively; P=0.30). Moreover, in the study by Van den Berghe et al., mean morning blood glucose levels in the intensive-therapy group and in the conventional-therapy group (111±29 mg and 153±31 mg per deciliter, respectively) were similar to the levels in our study (112±18 mg and 151±33 mg per deciliter, respectively). In their second study of medical ICU patients, Van den Berghe et al. performed exploratory subgroup analyses regarding the length of the ICU stay and the resolution of organ injury. The beneficial effects that were shown in these subgroup analyses were not confirmed in our study.

Taken together, our study and the medical ICU study by Van den Berghe et al. establish that intensive insulin therapy has no measurable, consistent benefit in critically ill patients in a medical ICU, regardless of whether the patients have severe sepsis, and that such therapy increases the risk of hypoglycemic episodes. The results of these two studies are in marked contrast to the results of the first study by Van den Berghe et al.,[1] which showed a beneficial effect of intensive insulin therapy on postoperative survival rates among critically ill surgical patients. In that study, the beneficial effect was predominantly seen in cardiac surgical patients (accounting for 62% of the study population) who were given intravenous glucose loads (200 to 300 g per 24 hours) on admission to the ICU. It is possible that intensive insulin therapy was beneficial in these patients because it decreased the adverse effect of this high glucose load.

In sedated, severely ill patients with sepsis, the benefits of intensive insulin therapy (administered according to the Leuven protocol) are unproven, but the risk of hypoglycemia is increased by a factor of 5 to 6. We cannot exclude the possibility that patients with sepsis may benefit from other less strict insulin protocols,[17] given that variability in the glucose level was a stronger independent predictor of death in the ICU than was the mean glucose concentration.[18]

After the first planned interim analysis, our trial was suspended because of increased rates of renal failure and death at 90 days in the group receiving HES. Adverse effects of HES on renal function have been reported in patients who have undergone renal transplantation and in critically ill patients.[19,20] Schortgen et al.[21] reported adverse renal effects associated with a starch solution that had a higher degree of molar substitution (0.6) than that used in our study (0.5). Other studies did not detect adverse effects except for impaired coagulation, even with large doses of starch solutions; however, these studies were limited by their design, small size, and short observation periods.[22-27] Even though we used a "modern" HES solution[28] that was designed to have fewer side effects, we found an even higher incidence of acute renal failure than that reported by Schortgen et al. Our study showed that HES was associated with an increased need for renal-replacement therapy in patients with sepsis, even when it was administered at recommended daily doses, and that higher cumulative doses were associated with an increased rate of death at 90 days. Our results should not be used to address the effect of rapid volume expansion on the outcome in patients with sepsis, nor should our findings be extrapolated to other volume expanders.

The differences between the hemodynamic effects of HES and those of Ringer's lactate were minor (e.g., a more rapid return to normal central venous pressure in the HES group). However, we observed marked adverse effects of HES therapy on kidney function, coagulation, transfusion requirements, and survival. The ability of HES to interfere with coagulation has already prompted warning labels and dose limitations.[29,30] Furthermore, long-term storage of the colloid is potentially toxic and may be responsible (beyond the adverse effects on renal function) for the observed increase in the rate of death at 90 days, particularly with higher doses.[21,31-36]

Fluid resuscitation with 10% HES 200/0.5 is harmful in patients with severe sepsis. At recommended doses, it causes renal impairment, and at high doses, it impairs long-term survival. Since adverse effects have been attributed to various HES solutions,[37] until long-term studies with adequate numbers of patients show that a particular HES solution is safe in critically ill patients, HES solutions should be avoided.

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APPENDIX

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