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Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock
A Randomized Clinical Trial

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IMPORTANCE High-dose intravenous administration of sodium selenite has been proposed to improve outcome in sepsis by attenuating oxidative stress. Procalcitonin-guided antimicrobial therapy may hasten the diagnosis of sepsis, but effect on outcome is unclear.

OBJECTIVE To determine whether high-dose intravenous sodium selenite treatment and procalcitonin-guided anti-infectious therapy in patients with severe sepsis affect mortality.

DESIGN, SETTING, AND PARTICIPANTS The Placebo-Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT), a multicenter, randomized, clinical, 2 × 2 factorial trial performed in 33 intensive care units in Germany, was conducted from November 6, 2009, to June 6, 2013, including a 90-day follow-up period.

INTERVENTIONS Patients were randomly assigned to receive an initial intravenous loading dose of sodium selenite, 1000 µg, followed by a continuous intravenous infusion of sodium selenite, 1000 µg, daily until discharge from the intensive care unit, but not longer than 21 days, or placebo. Patients also were randomized to receive anti-infectious therapy guided by a procalcitonin algorithm or without procalcitonin guidance.

MAIN OUTCOMES AND MEASURES The primary end point was 28-day mortality. Secondary outcomes included 90-day all-cause mortality, intervention-free days, antimicrobial costs, antimicrobial-free days, and secondary infections.

RESULTS Of 8174 eligible patients, 1089 patients (13.3%) with severe sepsis or septic shock were included in an intention-to-treat analysis comparing sodium selenite (543 patients [49.9%]) with placebo (546 [50.1%]) and procalcitonin guidance (552 [50.7%]) vs no procalcitonin guidance (537 [49.3%]). The 28-day mortality rate was 28.3% (95% CI, 24.5%-32.3%) in the sodium selenite group and 25.5% (95% CI, 21.8%-29.4%) (P = .30) in the placebo group. There was no significant difference in 28-day mortality between patients assigned to procalcitonin guidance (25.6% [95% CI, 22.0%-29.5%]) vs no procalcitonin guidance (28.2% [95% CI, 24.4%-32.2%]) (P = .34). Procalcitonin guidance did not affect frequency of diagnostic or therapeutic procedures but did result in a 4.5% reduction of antimicrobial exposure.

CONCLUSIONS AND RELEVANCE Neither high-dose intravenous administration of sodium selenite nor anti-infectious therapy guided by a procalcitonin algorithm was associated with an improved outcome in patients with severe sepsis. These findings do not support administration of high-dose sodium selenite in these patients; the application of a procalcitonin-guided algorithm needs further evaluation.

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Patients with severe sepsis have oxidative stress that may contribute to multiorgan failure and death.[1] Depleted plasma selenium levels are associated with excess mortality.[2,3] Intravenous administration of selenium has been proposed as adjunctive sepsis therapy since it restores activity of glutathione peroxidase, attenuates oxidative stress,[4,5] and may improve survival.[6,7] However, a cocktail of antioxidants and vitamins comprising 800 µg of selenium did not reduce 28-day mortality in patients receiving mechanical ventilation.[8] Current guidelines[9] do not recommend intravenous administration of selenium for sepsis but highlight the lack of large multicenter studies to further evaluate the effectiveness of this therapeutic approach in this patient population.

Numerous studies[10-13] suggest that measurement of serum procalcitonin may contribute to hasten and improve the diagnosis of sepsis by differentiating infectious from noninfectious causes of systemic inflammation. Theoretically, this differentiation may translate into better clinical outcomes. A recent study[14] in critically ill patients showed a reduction in mortality when a procalcitonin algorithm was applied to determine when antimicrobial therapy should be discontinued. This hypothesis was contradicted by a study[15] in which procalcitonin-guided therapy was associated with increased use of broad-spectrum antimicrobials and potential harm. Thus, evidence to support procalcitonin-guided anti-infectious therapy is contradictive.

The objective of the present trial was to assess the efficacy of high-dose intravenous sodium selenite treatment and of procalcitonin-guided anti-infectious therapy in patients with severe sepsis. Because we did not expect an interaction between the 2 factors, we designed a 2 × 2 factorial trial. Our hypothesis was that both sodium selenite therapy and implementation of procalcitonin guidance would reduce 28-day mortality.

Key Points

Question Does high-dose selenium therapy or procalcitonin-guided anti-infective therapy affect survival in patients with severe sepsis or septic shock?

Findings In this randomized clinical trial of 1089 adults, 28-day mortality did not differ significantly between the sodium selenite and placebo groups as well as between the procalcitonin guidance and nonguidance group.

Meaning These findings do not support high-dose selenium-administration in patients with severe sepsis; the application of this procalcitonin-guided algorithm needs further evaluation.

Methods

Study Design

The Placebo-Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT) was an investigator-initiated, multicenter randomized clinical trial (protocol available in Supplement 1). It was conducted in 33 multidisciplinary intensive care units (ICUs) across Germany from November 6, 2009, until June 6, 2013. The study protocol was approved by the ethics board of Jena University Hospital. Written informed consent was obtained from all patients or their legal representatives.

Study Patients

Adults with severe sepsis or septic shock (termed *severe sepsis*) beginning not later than 24 hours before randomization were eligible for this study; definitions were reported previously.[16] Briefly, *severe sepsis* was defined as systemic inflammatory response syndrome caused by infection combined with acute organ dysfunction. *Septic shock* was defined as sepsis in combination with arterial hypotension or need for vasopressor therapy despite adequate fluid resuscitation. Pregnant or lactating women, patients with selenium intoxication, individuals with infections for which guidelines recommend a longer duration of antimicrobial therapy, immunocompromised patients, and those without commitment for full therapy or where death was imminent owing to coexisting diseases were excluded from the trial (eMethods in Supplement 2). As stated, written informed consent was obtained from all patients or their legal representatives. If this was not possible before enrollment, the ethics committees approved a deferred consent process where the inability to provide consent was confirmed by an independent physician. As soon as the legal representative of the patient was available, written informed consent was immediately obtained; otherwise, the patient was withdrawn from the study and all study procedures were ended. No financial compensation was given.

Study Interventions

Using a 2 × 2 factorial design, we randomly assigned patients to receive intravenous sodium selenite or placebo as well as antimicrobial therapy guided by a procalcitonin algorithm or conventional antimicrobial therapy without procalcitonin guidance with an allocation ratio of 1:1:1:1 by use of a central randomization web server. Randomization was stratified by study center, sex, and sepsis severity.[17] Assignment to the placebo or sodium selenite group was concealed with identical vial labels by the drug provider. Because of the nature of the procedure, the procalcitonin guidance group and related conventional therapy group were treated in an unblinded fashion.

Patients randomized to the sodium selenite group received an initial intravenous loading dose of 1000 µg (biosyn Corporation) followed by a continuous intravenous infusion of sodium selenite, 1000 µg/d, until discharge from the ICU, but not longer than 21 days. The control group received placebo (sodium chloride, 0.9%; biosyn Corporation) intravenously following the same schedule.

In patients randomized to the procalcitonin guidance arm, procalcitonin was measured locally on days 0, 1, 4, 7, 10, and 14 after randomization if the patient was still in the ICU. Procalcitonin concentration was assessed at each study site with time-resolved amplified cryptate-emission technology with a measurement range of 0.1 to 200 ng/mL, a functional assay sensitivity of at least 0.06 ng/mL, and a lower detection limit of at least 0.1 ng/mL. Procalcitonin concentration on day

0 or day 1 served as the baseline value. Depending on the procalcitonin results, an algorithm provided recommendations to change or discontinue antimicrobial therapy or trigger diagnostic procedures to optimize source control. On day 4, no change in antimicrobial therapy was recommended if the procalcitonin level dropped by at least 50% compared with the baseline value. Otherwise, change or optimization of antimicrobial therapy or interventions regarding source control were recommended. On the other days, stopping antimicrobial therapy was recommended if the procalcitonin level was 1 ng/mL or lower or if the procalcitonin level dropped by at least 50% compared with the previous value. Otherwise, change or optimization of antimicrobial therapy or interventions regarding source control were recommended (eTable 1 in Supplement 2).

Upon study initiation, personnel at each site were trained to request the decisions from the treating physicians at the times indicated in the study design. The treating physician was allowed to overrule the algorithm recommendation. In the group without procalcitonin guidance, no procalcitonin measurements were obtained until day 14; changes in antimicrobial therapy were made at the discretion of the treating physician. Investigators agreed to treat all patients according to the Guidelines of the Germany Sepsis Society,[18] which included recommendations to reevaluate antimicrobial therapy after 48 to 72 hours and to restrict duration of antimicrobial therapy to no more than 10 days. Costs of antimicrobial therapy were calculated by multiplying the dosages of individual prescriptions by the price taken from a large purchaser community of German hospitals. After the trial, selenium plasma concentrations were measured in retained samples by atomic absorption spectrometry (ZEEnit 60; Analytik Jena AG) at days 0, 1, 4, 10, and 14. Procalcitonin plasma concentrations of all patients were measured on the same days. All samples were stored at −80°C at the central study laboratory in Jena, Germany.

Statistical Analysis

The primary outcome of the study was death from any cause by 28 days after inclusion. The study was planned to detect an absolute difference of 10% in the primary end point with a significance level of .05 and a power of 0.9 for both factors. Assuming 40% mortality in the standard treatment arm (placebo with no procalcitonin guidance), 248 evaluable patients per arm were required. Accounting for an expected dropout rate of 15%, we decided to include 295 patients per arm (1180 in total). Secondary end points were 90-day all-cause mortality, mean total Sequential Organ Failure Assessment (SOFA) score and its subscores, duration of ICU and hospital stay, and ventilator-, vasopressor-, and dialysis-free days until day 90. Additional secondary end points for the procalcitonin vs conventional group were duration and costs of antimicrobial therapy, duration until change of antimicrobial therapy, antimicrobial exposure days, days free of antimicrobial therapy, frequency of surgical source control, frequency of diagnostic procedures for localization of the infection focus, clinical and microbiologic treatment response, secondary infections, and emergence of antibiotic-resistant bacteria (definitions available in eTable 2 in Supplement 2). A statistical analysis plan specified the tests for the end points and planned subgroup analyses (medical vs surgical patients, Acute Physiology and Chronic Health Evaluation [APACHE] II score <25 points vs ≥25 points, severe sepsis vs septic shock, <3 vs ≥3 organ dysfunctions at inclusion, and pneumonia vs abdominal infection). Imputations were performed for missing variables of the SOFA, Simplified Acute Physiology Score, and APACHE II scores; other missing values were treated as such. One interim analysis was conducted after recruitment of half of the planned sample size and presented to the data monitoring committee.

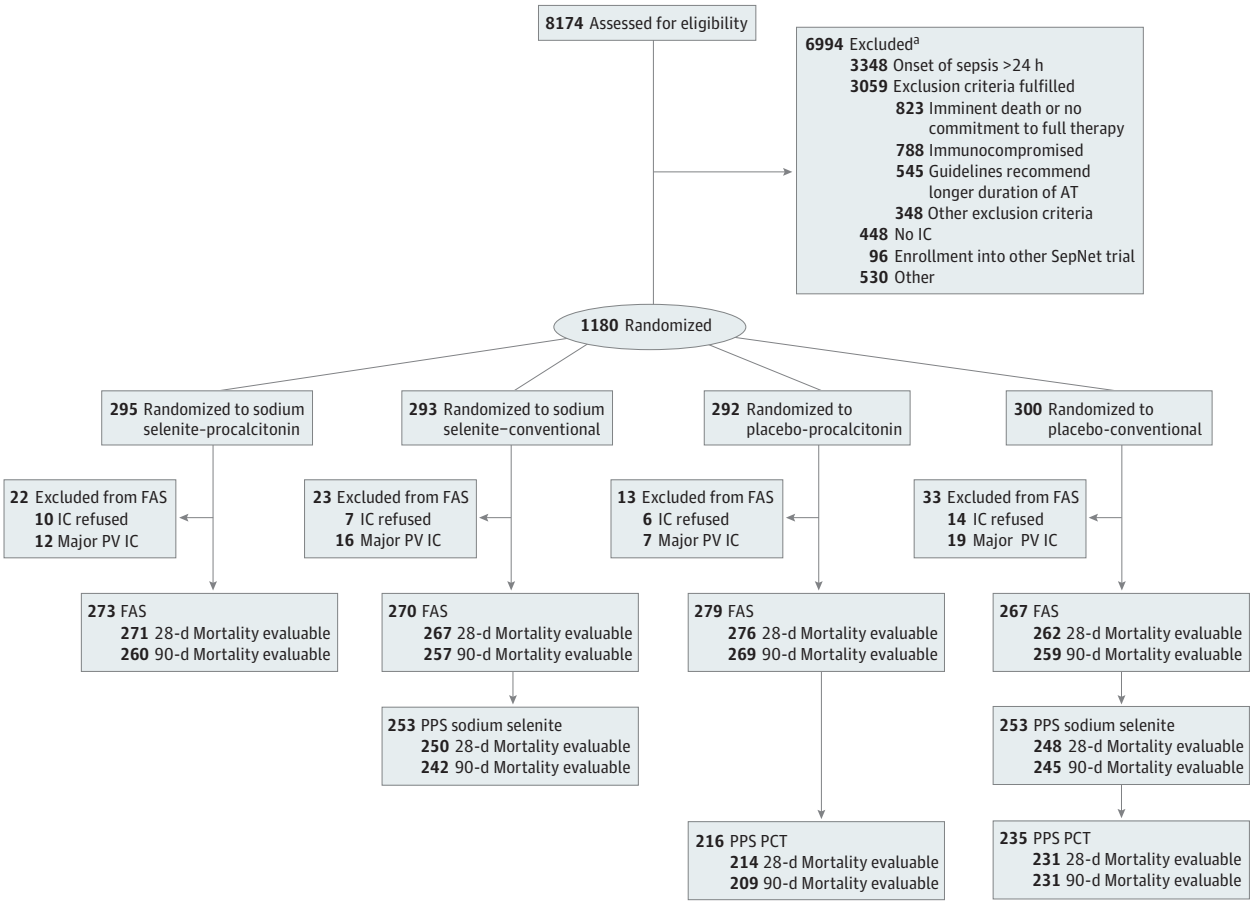
The significance level for the primary end point was adjusted by the α spending method[19,20] resulting in a significance level of $P = .006$ in the interim analysis and $P = .04$ for the final analysis. All other tests were conducted on the nominal level of $P = .05$ because these statistical comparisons were performed with exploratory intention. The interaction was assessed by a logistic regression model for the 28-day mortality adjusting for age, sex, SOFA score at baseline, renal replacement at baseline, and treatment with sodium selenite before randomization. If the interaction term was statistically significant, the analysis plan recommended comparison of only patients randomized either to the placebo and procalcitonin guidance arm or to the sodium selenite and no procalcitonin guidance arm with the standard arm. To further investigate the nature of a possible interaction, longitudinal blood concentration profiles of selenium were compared to see whether they differed between the procalcitonin arms and whether procalcitonin plasma concentrations differed between the sodium selenite arms. The statistical analysis was conducted consistent with the intention-to-treat principle.

The primary end point 28-day mortality was assessed by the χ^2 test for each factor. Secondary end points were analyzed by the χ^2 test, exact χ^2 test, t test, Wilcoxon rank sum test, Kaplan-Meier product limit estimate, or log-rank test, as appropriate. The cumulative number of days of antimicrobial exposure per cumulative number of ICU days were compared using a rate ratio test. All reported P values are 2-sided. Statistical analyses were performed with SAS, version 9.2 (SAS Institute Inc); SPSS, version 22.0 (SPSS Inc); and R, version 3.1.0 (R Foundation). Data analysis was performed from February 10 to October 20, 2014.

Results

Between November 6, 2009, and March 8, 2013, a total of 8174 patients were screened and 1180 patients were randomized; 91 patients were excluded from the final analysis because informed consent was not obtainable in the deferred consent process, resulting in 1089 patients with evaluable data (**Figure 1**). Of these, 947 patients (87.0%) had septic shock. Overall, the baseline characteristics of the 4 study groups were well balanced. However, requirement for renal replacement ranged from 13.2% to 22.2%; age and the disease severity marker mid-regional proadrenomedullin plasma concentrations differed considerably among the 4 groups (**Table 1** and eTable 3 in Supplement 2). We found a statistically significant interaction between the 2 study interventions regarding the primary end point ($P = .03$) (**Table 2**, eTable 4 in Supplement 2, and

Figure 1. CONSORT Diagram



Patients were randomized both to a selenium vs placebo group and to a procalcitonin-guided vs no procalcitonin (conventional) group. Differences between the number of patients in the final analysis set (FAS) or per-protocol set (PPS) and the number available for assessing 28- and 90-day mortality resulted from loss to follow-up or withdrawal of informed consent (IC). AT indicates antimicrobial therapy; PV, protocol violation.

[a] Multiple reasons possible.

Figure 2C). Because there was no indication that selenium influenced the plasma procalcitonin levels or that procalcitonin guidance influenced the plasma selenium levels (eFigure 1 and eFigure 2 in Supplement 2), we decided to accept the observed statistical interaction as a chance finding and proceed with the factorial analysis as originally planned. However, we also report the data in consideration of the significant interaction.

Sodium Selenite Therapy

Study treatment with sodium selenite led to a significant increase of selenium plasma concentrations into the upper reference range compared with the placebo arm (eFigure 1 in Supplement 2). Good adherence to the study protocol was observed (eTable 5 in Supplement 2). Patients received the study medication within 15.8 hours (interquartile range, 10.2-20.5 hours) after onset of sepsis-induced organ failure. Concomitant medications possibly interacting with sodium selenite treatment did not differ significantly between the groups (eTable 6 in Supplement 2).

Of 538 patients, there was no statistically significant difference in the 28-day mortality between the sodium selenite group (152 patients [28.3%]) and the placebo group (137 [25.5%]) (P = .30) (Table 2) nor did the survival curves differ significantly between the 2 groups (Figure 2A). There were no significant differences in 28-day mortality in any of our a priori-specified subgroup analyses in the intention-to-treat analysis (eFigure 3A in Supplement 2). Secondary outcomes are reported in **Table 3.** Patients in the sodium selenite group had fewer renal replacement–free days (by 1 day) than the placebo group; hospital length of stay was significantly shorter by 3 days in the sodium selenite group. Frequency of adverse and serious adverse events did not differ markedly between the placebo and the sodium selenite group (eTable 7 in Supplement 2).

Procalcitonin-Guided Therapy

The procalcitonin time course was known in 91.8% of the patients in the procalcitonin guidance group. In 21.0% of the patients in the procalcitonin guidance group, at least 1 protocol deviation was detected (eTable 6 in Supplement 2). The most frequent deviations were additional procalcitonin measurements not scheduled by the algorithm. Adherence to the recommendation of the algorithm dropped to 40.9%

Table 1. Baseline Characteristics

Variable	Total (N = 1089)	Sodium Selenite		Placebo	
		Procalcitonin Guidance (n = 273)	No Procalcitonin Guidance (n = 270)	Procalcitonin Guidance (n = 279)	No Procalcitonin Guidance (n = 267)
Age, mean (SD), y	65.7 (13.7)	63.9 (14.9)	65.8 (14.3)	67.3 (12.4)	65.6 (12.7)
Male sex, No. (%)	691 (63.5)	175 (64.1)	170 (63.0)	177 (63.4)	169 (63.3)
BMI, mean (SD)	27.9 (6.9)	27.7 (7.8)	28.0 (7.5)	27.8 (5.7)	27.9 (6.7)
APACHE II score, mean (SD), points[a]	24.2 (7.6)	23.6 (7.9)	24.7 (7.6)	24.2 (7.2)	24.4 (7.7)
Septic shock, No. (%)	947 (87.0)	239 (87.5)	237 (87.8)	240 (86.0)	231 (86.5)
SOFA score, mean (SD), points[b]	10.0 (3.3)	9.8 (3.4)	10.3 (3.3)	10.0 (3.3)	9.9 (3.3)
Charlson comorbidity index, median (IQR)	2 (1-4)	2 (0-3)	2 (0-4)	2 (1-4)	2 (1-4)
Site of infection, No. (%)[c]					
Lung	494 (45.4)	135 (49.5)	119 (44.1)	126 (45.2)	114 (42.7)
Thoracic	44 (4.0)	13 (4.8)	7 (2.6)	14 (5.0)	10 (3.7)
Abdomen	418 (38.4)	101 (37.0)	113 (41.9)	97 (34.8)	107 (40.1)
Bones/soft tissue	80 (7.3)	21 (7.7)	15 (5.6)	21 (7.5)	23 (8.6)
Surgical wound	41 (3.8)	7 (2.6)	13 (4.8)	6 (2.2)	15 (5.6)
Urogenital	100 (9.2)	20 (7.3)	30 (11.1)	27 (9.7)	23 (8.6)
Primary bacteremia	32 (2.9)	12 (4.4)	4 (1.5)	9 (3.2)	7 (2.6)
Other[d]	66 (6.1)	23 (8.4)	16 (5.9)	16 (5.7)	11 (4.1)
Unknown	41 (3.8)	6 (2.2)	10 (3.7)	14 (5.0)	11 (4.1)
Recent surgical history, No. (%)					
Elective	122 (11.2)	25 (9.2)	24 (8.9)	37 (13.3)	36 (13.5)
Emergency	494 (45.4)	135 (49.5)	128 (47.4)	128 (45.9)	103 (38.6)
None	473 (43.4)	113 (41.4)	118 (43.7)	114 (40.9)	128 (47.9)
Laboratory values, median (IQR)					
White blood cell count, /µL	15 800 (10 300-22 700)	15 300 (10 600-21 800)	16 000 (10 100-22 600)	15 400 (10 100-23 200)	16 100 (11000-22 800)
C-reactive protein, mg/L	188.0 (120.0-282.0)	208.5 (123.1-283.0)	180.4 (118.5-267.5)	206.0 (129.0-288.0)	182.0 (115.0-282.0)
Procalcitonin, ng/mL	7.37 (1.59-26.59)	6.43 (1.33-21.98)	8.15 (1.91-30.83)	7.18 (1.48-28.24)	7.30 (1.69-22.60)
Lactate, mmol/L	2.7 (1.6-4.7)	2.6 (1.6-4.2)	2.8 (1.7-5.4)	2.8 (1.7-4.7)	2.7 (1.7-4.7)
Selenium concentration, µg/L	39.4 (29.9-52.8)	40.9 (30.7-56.7)	38.6 (30.7-50.4)	38.6 (29.9-50.4)	39.4 (30.7-50.4)
Midregional proadrenomedullin, nmol/L	4.9 (2.6-8.8)	4.3 (2.2-7.9)	5.5 (2.8-9.0)	5.4 (3.0-9.4)	4.6 (2.7-8.2)
Sodium selenite therapy before inclusion, No. (%)[e]	124 (11.4)	30 (11.0)	30 (11.1)	32 (11.5)	32 (12.0)
Total dose of sodium selenite before inclusion, median (IQR), µg[e]	1042 (500-1426)	1000 (280-1151)	1099 (300-1352)	936 (509-1654)	1119 (814-1538)
Supportive therapy at inclusion, No. (%)					
Required mechanical ventilation	794 (72.9)	200 (73.3)	200 (74.1)	213 (76.3)	181 (67.8)
Required renal replacement therapy	178 (16.4)	36 (13.2)	60 (22.2)	39 (14.0)	43 (16.1)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

SI conversion factors: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; lactate to milligrams per deciliter, divide by 0.111; selenium to micromoles per liter, multiply by 0.0127; and white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] Missing subscores counted as 0.

[b] Missing subscores imputed by values at day 0 or day 1.

[c] Multiple responses per patient possible.

[d] Other infection sources included catheter, central nervous system, and cardiovascular.

[e] Up to 7 days before study inclusion.

commencing by day 7 (eTable 8 in Supplement 2). The treating physicians justified nonadherence to the algorithm by the presence of fever, microbiologic findings, and the course of the white blood cell count. The recommendations to stop antimicrobial therapy were overruled by the treating physicians in 50.4% of the cases. Procalcitonin plasma levels were equally elevated in both groups and decreased in both groups independent of the type of intervention (eFigure 2 in Supplement 2).

There was no statistically significant difference in 28-day mortality between the procalcitonin guidance (140 of 547 patients [25.6%]) and no procalcitonin guidance group (149 of 529

Table 2. Primary End Point[a]

Variable	No./Total No. (%) [95% CI]			*P* Value for Sodium Selenite vs Placebo	
	Placebo	Sodium Selenite	Total	Unadjusted	Adjusted
No procalcitonin guidance	60/262 (22.9) [18.0-28.5]	89/267 (33.3) [27.7-39.3]	149/529 (28.2) [24.4-32.2]	.008[b]	.03[b]
Procalcitonin guidance	77/276 (27.9) [22.7-33.6]	63/271 (23.2) [18.4-28.7]	140/547 (25.6) [22.0-29.5]	.21	.30
Total	137/538 (25.5) [21.8-29.4]	152/538 (28.3) [24.5-32.3]	289/1076 (26.9) [24.2-29.6]	.30[c]	
P value for procalcitonin guidance vs no guidance					
Unadjusted	.18[d]	.009	.34[e]		
Adjusted	.44[d]	.04			

[a] Primary end point was 28-day mortality. The significance level was adjusted by the α spending method[19] resulting in a significance level of .044.

[b] Sodium selenite vs placebo in only the no procalcitonin guidance group. Analysis was conducted under consideration of interaction (unadjusted and adjusted): variables for multivariate regression were defined a priori in the analysis plan. Midregional proadrenomedullin and lactate were also selected because they showed a clinically relevant imbalance at baseline.

[c] Sodium selenite vs placebo regardless of allocation to procalcitonin guidance or no guidance.

[d] Procalcitonin guidance vs no guidance only in the placebo group. Midregional proadrenomedullin and lactate were also selected because they showed a clinically relevant imbalance at baseline. Analysis was conducted under consideration of interaction (unadjusted and adjusted).

[e] Procalcitonin guidance vs no procalcitonin guidance regardless of the allocation to the sodium selenite or placebo group.

patients [28.2%]; *P* = .34) (Table 2), nor did the survival curves differ between the 2 groups (Figure 2B). No significant differences in the primary outcome were observed in any of the a priori subgroup analyses in the intention-to-treat analysis (eFigure 3B in Supplement 2). Secondary outcomes reported in Table 3 did not differ significantly between the 2 groups. The frequency of procedures for infection source control or diagnosis of the source of sepsis remained unaffected by the procalcitonin algorithm. Antibiotic exposure per 1000 ICU days was reduced by 4.5% from 862 days in the conventional group to 823 days in the procalcitonin guidance group (*P* = .02). Procalcitonin guidance was associated with an increase in antimicrobial-free days in the ICU (Figure 2D) (*P* = .03), but median antimicrobial-free days in the ICU were zero in both groups (Table 3). Procalcitonin guidance was not associated with a reduction of costs of antimicrobial therapy (Table 3). Clinical and microbiologic cure of infection were not different between the groups, and procalcitonin guidance did not affect the occurrence of multiresistant pathogens (eTables 9 and 10 in Supplement 2).

Effects of Procalcitonin-Selenium Interaction on Primary Outcome

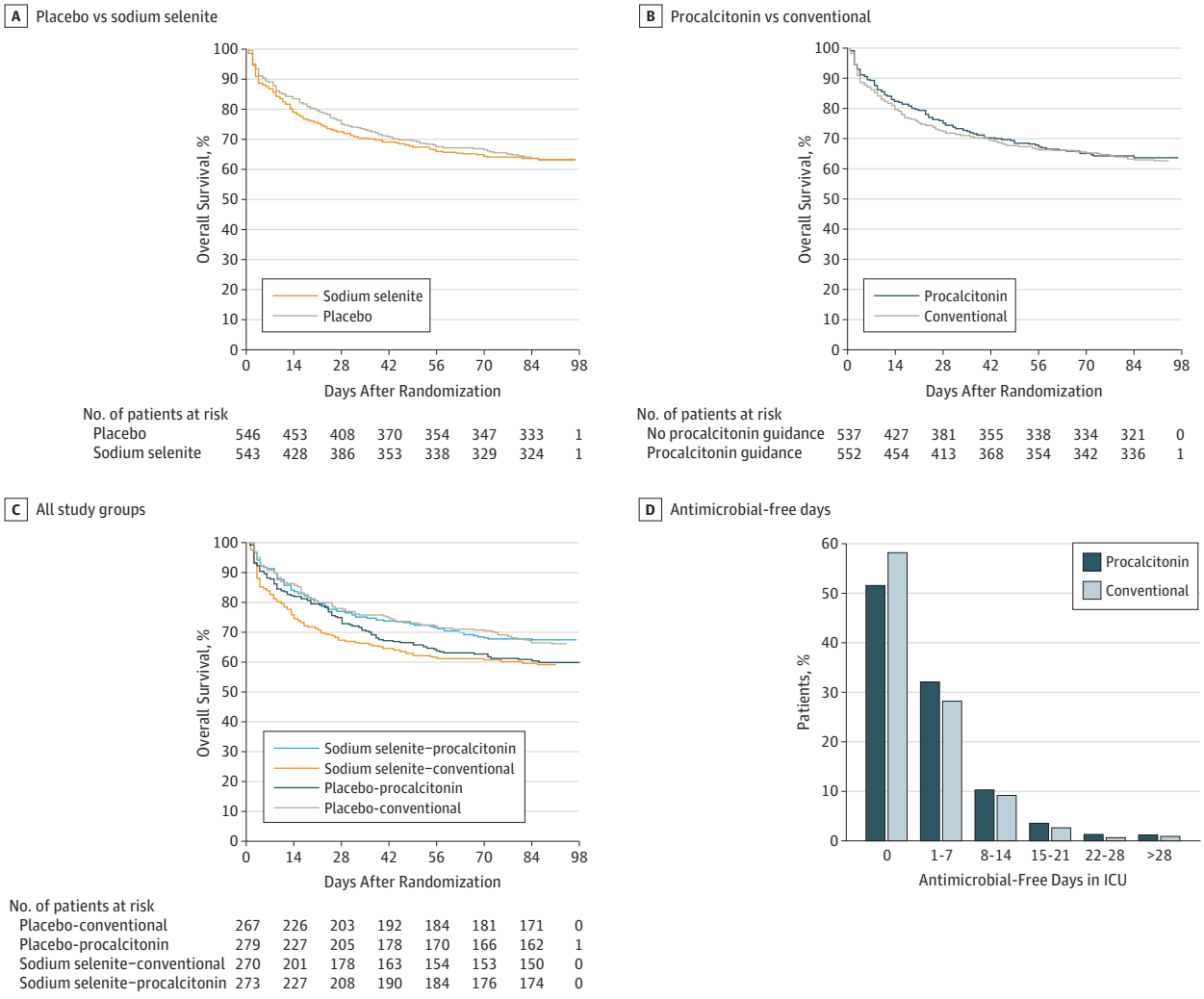
There was a significantly higher 28-day mortality in patients assigned to no procalcitonin guidance in the sodium selenite group compared with the placebo group (33.3% vs 22.9%; *P* = .008) (Table 2). Some of the baseline variables were unequally distributed, with a higher rate of renal replacement therapy at enrollment, more emergency surgery, and higher midregional proadrenomedullin concentrations in the sodium selenite group (Table 1). The difference in the primary outcome between the placebo and sodium selenite groups remained statistically significant after adjustment for these baseline differences (Table 2). There was no significant difference in the primary outcome regarding procalcitonin guidance (27.9%) vs no procalcitonin guidance (22.9%) (*P* = .18), but there were significantly fewer antimicrobial exposure days per 1000 ICU days in the procalcitonin guidance group (832 vs 878 days; *P* = .05) (eTable 11 in Supplement 2).

Discussion

To our knowledge, this is the first multicenter randomized clinical trial with an adequate sample size to evaluate the clinical efficacy of sodium selenite therapy and the efficacy of a procalcitonin-guided algorithm in patients with severe sepsis. Neither treatment with intravenous administration of high-dose sodium selenite nor the procalcitonin algorithm implemented in our study to guide diagnostic and antimicrobial measures was associated with improved 28-day mortality in patients with severe sepsis. Procalcitonin guidance did not affect resource allocation assessed by frequency of diagnostic or therapeutic procedures but did result in a reduction of antimicrobial exposure per 1000 patient-days by 4.5%. We observed a statistically significant interaction between sodium selenite and procalcitonin and, although this interaction may be spurious, if real, we found a significant increase in mortality with selenium therapy.

In previous studies, the ineffectiveness of selenium administration was believed to be attributed to underdosing,[6,21] lack of an initial loading dose, short-term treatment,[22] or inclusion of patients with normal selenium plasma concentrations at baseline.[8] Instead, we used a dosage regimen that was associated with improved survival in another randomized trial.[7] In contrast to a recent study[8] conducted in North America, baseline plasma selenium levels were subnormal in our study. Plasma selenium concentrations were within the reference range on the day of study inclusion in the sodium selenite group but remained low in the placebo group. Thus, a separation of selenium concentrations was achieved early between the 2 groups. In a recent post hoc analysis[23] of a large

Figure 2. Survival Curves



A, Placebo vs sodium selenite group (P = .81). B, Procalcitonin guided vs no procalcitonin guided (conventional) group (P = .63). C, Comparison of all 4 study groups. D, frequency of antimicrobial therapy–free days in procalcitonin algorithm group and conventional group (P = .03). ICU indicates intensive care unit.

multicenter trial, patients with renal dysfunction were reported to have a greater risk of harm when treated with antioxidants. However, we could not confirm this finding in an unplanned subgroup analysis of our study (eTable 12 in Supplement 2).

Procalcitonin guidance had no effect on the frequency of diagnostic procedures, interventions for source control, and readjustment of empirical antimicrobial therapy. This lack of effect explains why the outcomes of the study were not affected by application of this procalcitonin algorithm. Thus, our data suggest that the procalcitonin algorithm provided no added value to the clinical judgment for initiating antimicrobial measures. Our findings are in line with those of another randomized trial[15] in critically ill patients in which procalcitonin guidance of diagnostic and therapeutic measures did not improve survival but increased the duration of mechanical ventilation, prolonged antimicrobial therapy, and resulted in more microbiologic sampling. In a recent study[14] on less-sick patients, a procalcitonin algorithm designed for early discontinuation of antimicrobial therapy showed a lower mortality rate in the procalcitonin guidance group. The authors speculated that knowledge of procalcitonin concentrations would lead to earlier and more adequate diagnosis and therapy. However, we could not confirm that a procalcitonin algorithm would change antimicrobial measures.

The procalcitonin algorithm used by Jensen and coworkers[15] included additional diagnostic and therapeutic measures in all patients when procalcitonin concentrations determined on a daily basis did not drop by more than 10% or remained above 1 ng/mL. Their procalcitonin algorithm obviously resulted in increased use of broad-spectrum antibiotics and potential harm. Although the algorithm used in our study did not affect mortality, it resulted in a small reduction of antimicrobial exposure. Studies[24-26] in less-sick patient populations with mortality rates between 5% and 20% found reduced durations of antimicrobial therapy without jeopardizing sur-

Table 3. Secondary End Points

Variable	Total (N = 1089)	Sodium Selenite (n = 543)	Placebo (n = 546)	*P* Value[a]	Procalcitonin Guidance (n = 552)	No Procalcitonin Guidance (n = 537)	*P* Value[a]
90-d All-cause mortality, No.	1045	517	528		529	516	
Patients not alive at 90 d, No. (%) [95% CI]	399 (38.2) [35.2-41.2]	198 (38.3) [34.1-42.6]	201 (38.1) [33.9-42.4]	.94	200 (37.8) [33.7-42.1]	199 (38.6) [34.4-42.9]	.80
SOFA score, mean (SD)[b]	7.95 (4.07)	8.01 (4.22)	7.89 (3.92)	.62	7.78 (3.98)	8.14 (4.17)	.17
SOFA subscores, median (IQR)							
Cardiovascular	2.0 (1.2-3.2)	2.0 (1.1-3.2)	2.0 (1.2-3.1)	.83	2.0 (1.2-3.1)	2.0 (1.1-3.3)	.64
Respiratory	2.4 (2.0-2.9)	2.3 (2.0-2.9)	2.4 (1.9-2.8)	.90	2.3 (1.9-2.9)	2.4 (2.0-2.9)	.21
Coagulation	0.1 (0-1.0)	0.1 (0-1.0)	0.1 (0-0.9)	.95	0.1 (0-0.8)	0.1 (0-1.0)	.03
Renal	0.5 (0-2.0)	0.4 (0-2.0)	0.5 (0-2.0)	.63	0.5 (0-2.0)	0.5 (0-2.0)	.26
Hepatic	0 (0-0.6)	0 (0-0.6)	0 (0-0.7)	.85	0 (0-0.7)	0 (0-0.6)	.87
Central nervous system	0.6 (0-2.0)	0.7 (0-2.0)	0.5 (0-2.0)	.44	0.6 (0-2.0)	0.5 (0-1.9)	.56
Length of stay, median (IQR), d							
ICU	12 (6-23)	11 (5-22)	12 (6-24)	.08	12 (6-24)	11 (6-21)	.14
Hospital	28 (17-45)	26 (16-42)	29 (17-50)	.02	29 (18-46)	26 (16-44)	.10
Intervention-free days, median (IQR)							
Ventilator	2 (0-5)	2 (0-5)	2 (0-5)	.22	2 (0-5)	2 (0-5)	.26
RRT	7 (3-16)	7 (2-15)	8 (3-18)	.05	7 (3-17)	7 (2-16)	.34
Vasopressor	4 (1-10)	3 (1-9)	4 (1-10)	.10	4 (1-10)	4 (1-10)	.33
AT	0 (0-3)	0 (0-3)	0 (0-4)	.86	0 (0-4)	0 (0-3)	.03
Duration of AT in ICU for first septic episode, median (IQR), d	7 (3-12)	7 (3-11)	7 (4-13)	.02	7 (3-12)	7 (3-12)	.93
Cost of AT in ICU, median (IQR), $/€[c]	118 (44-512)/ 104 (39-452)	102 (43-414)/ 90 (38-366)	137 (45-684)/ 121 (40-604)	.08	118 (45-563)/ 104 (40-497)	119 (44-492)/ 105 (39-434)	.83
AT exposure days per 1000 ICU days, median (IQR)	842 (825-858)	827 (804-852)	855 (832-878)	.11	823 (800-846)	862 (838-886)	.02
Time to change of AT, median (range), d[d]	7 (3-17)	7 (3-16)	7 (3-17)	.94	7 (3-16)	7 (3-21)	.96
Secondary infections, % (95% CI)[d]							
Day 14	47.2 (43.1-51.4)	44.7 (39.0-50.9)	49.3 (43.7-55.3)	.68	47.9 (42.3-53.8)	46.4 (40.5-52.6)	.76
Day 21	59.0 (54.0-64.0)	58.8 (51.4-66.5)	59.2 (52.7-65.8)		57.9 (51.5-64.6)	60.3 (52.8-68.0)	
Patients with source control, No. (%)	447 (41.0)	208 (38.3)	239 (43.8)	.07	239 (43.3)	208 (38.7)	.13
No. of procedures per patient, median (IQR)[e]	2 (1-3)	2 (1-3)	2 (1-3)	.90	2 (1-3)	2 (1-3)	.99
Patients with procedures to diagnose infection, No. (%)	975 (89.5)	485 (89.32)	490 (89.74)	.84	496 (89.9)	479 (89.2)	.72
No. of procedures per patient[e]	9 (4-19)	8 (3-18)	9 (4-20)	.07	9 (4-19)	9 (4-18)	.52

Abbreviations: AT, antimicrobial therapy; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

[a] Values calculated by exact *t* test, χ^2 test, Wilcoxon rank sum test or log-rank test, as appropriate.

[b] Mean SOFA score is the sum of daily SOFA scores during the observation period divided by the duration of the observation period.

[c] Dollars were converted from euros using the exchange rate as of May 13, 2016 (1.1325).

[d] Analyzed by the Kaplan-Meier method.

[e] Determined if patients had undergone procedures.

vival. We did not observe such an effect in our study. A reason for the lack of effect of procalcitonin guidance on the duration of antimicrobial therapy in our study may be that treating physicians overruled the algorithm in up to 50.4% of the decision situations. Obviously, physicians refrained from discontinuing antimicrobials solely based on 1 biomarker in these high-risk patients, 87.0% of whom had septic shock. Procalcitonin-based algorithms in less-sick patients have achieved higher adherence rates of 81% and 91%.[25,26] In general, current data also support a shorter duration of antimicrobial therapy in critically ill patients.[27,28] Such trials may have generally affected prescribing behavior since the duration of antimicrobial therapy in the present study was shorter than in a former trial by our study group.[29] This change in

prescription behavior may also have contributed to the lesser effectiveness of the procalcitonin algorithm.

The procalcitonin algorithm in our study differs from previously published algorithms. Although a procalcitonin concentration of less than 0.1 ng/mL is a well-established cutoff for discontinuation of antimicrobial therapy, other studies[24-26] used an 80% to 90% decrease from baseline or from procalcitonin peak concentration as a stopping rule. The 50% rule in our study was based on the fact that such a decrease in procalcitonin concentration within 3 days is associated with improved survival.[30]

The strengths of this study include the randomized, placebo-controlled, and partially blinded design, the high rate of adherence to the study protocol regarding the sodium selenite intervention, and intention-to-treat analysis, all of which contribute to the internal validity of the trial. Use of 33 sites supports generalizability of the findings to similar health care settings. The time course of plasma selenium and procalcitonin concentrations were available in all patients and measured on a single device. Our trial has limitations. Observed 28-day mortality was lower than expected. We cannot rule out that a trial with an even larger sample size might reveal a statistically significant difference in the primary outcome. Unexpectedly, we found a statistically significant interaction between the 2 treatment factors that affects our interpretation of the primary outcome. In the procalcitonin-guided group, sodium selenite administration had no treatment effect but seemed to harm patients not receiving procalcitonin-guided therapy even after adjustment for baseline differences. We could not detect any interference between longitudinal profiles of plasma selenium and procalcitonin. Thus, there was no clinically or biochemically plausible evidence that sodium selenite administration would alter procalcitonin concentrations in a way that could affect treatment decisions in the procalcitonin-guided group. Furthermore, secondary outcomes regarding anti-infectious measures did not show relevant differences between the placebo and the sodium selenite group. This finding led us to conclude that the statistically significant interaction occurred by chance and did not reflect a true biological interaction. However, we cannot completely rule out a possible nonrandom interaction between the 2 interventions or that better adherence to the procalcitonin-guided algorithm would have improved the end points of the study. We did not assess the oxidative status of the patients. However, the effects of restoration of selenium concentrations on glutathione peroxidase activity are well described.[5]

Conclusions

In conclusion, this trial demonstrates that neither high-dose intravenous administration of sodium selenite nor procalcitonin-guided antimicrobial therapy was associated with improved 28-day mortality in patients with severe sepsis. Sodium selenite treatment remained ineffective although plasma selenium levels were normalized. Procalcitonin guidance resulted in a reduction of antibiotic exposure by 4.5% but did not influence resource utilization. These findings do not support administration of high-dose sodium selenite in critically ill patients. The application of a procalcitonin-guided algorithm needs further evaluation.

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