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A CONTROLLED CLINICAL TRIAL OF HIGH-DOSE METHYLPREDNISOLONE IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

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Abstract The use of high-dose corticosteroids in the treatment of severe sepsis and septic shock remains controversial. Our study was designed as a prospective, randomized, double-blind, placebo-controlled trial of high-dose methylprednisolone sodium succinate for severe sepsis and septic shock. Diagnosis was based on the clinical suspicion of infection plus the presence of fever or hypothermia (rectal temperature $>38.3^{\circ}\text{C}$ [101°F] or $<35.6^{\circ}\text{C}$ [96°F]), tachypnea (>20 breaths per minute), tachycardia (>90 beats per minute), and the presence of one of the following indications of organ dysfunction: a change in mental status, hypoxemia, elevated lactate levels, or oliguria. Three hundred eighty-two patients were enrolled. Treatment — either methylprednisolone sodium succinate (30 mg per kilogram of body weight) or placebo

— was given in four infusions, starting within two hours of diagnosis.

No significant differences were found in the prevention of shock, the reversal of shock, or overall mortality. In the subgroup of patients with elevated serum creatinine levels (>2 mg per deciliter) at enrollment, mortality at 14 days was significantly increased among those receiving methylprednisolone (46 of 78 [59 percent] vs. 17 of 58 [29 percent] among those receiving placebo; $P<0.01$). Among patients treated with methylprednisolone, significantly more deaths were related to secondary infection.

We conclude that the use of high-dose corticosteroids provides no benefit in the treatment of severe sepsis and septic shock. (N Engl J Med 1987; 317:653-8.)

SEPSIS can be defined as the systemic response to infection and has been estimated to occur in 70,000 to 300,000 patients in the United States each year.^{1,2} Hypotension is present in approximately 40 percent of these patients and has been shown to affect survival adversely.³⁻⁸ Septic shock has been associated with mortality rates ranging from 40 to 90 percent.^{1,2,4-6,8-10}

There is still considerable controversy concerning the use of high doses of corticosteroids in the treatment of severe sepsis or septic shock.¹¹⁻¹⁶ Studies using infusions of endotoxin or live bacteria to produce

an injury resembling septic shock in animals have had mixed results.¹⁷⁻²³ Beneficial effects have been shown in animals when corticosteroids have been administered before or as early as possible after the insult.¹⁷ These effects were manifested by improved survival rather than improved hemodynamic function.^{11,12}

Clinical trials of corticosteroids in patients with septic shock have been criticized for a lack of randomization, double-blind placebo-controlled design, or standardization of regimens.^{11,12} Schumer studied patients with a history of sepsis, positive blood cultures, and a falling blood pressure.²⁴ Saline placebo

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was compared with either methylprednisolone sodium succinate (30 mg per kilogram of body weight) or dexamethasone (3 mg per kilogram). Both steroid regimens were found to reduce mortality significantly (methylprednisolone, 11.6 percent; dexamethasone, 9.3 percent) as compared with placebo treatment (38.4 percent). Concerns about this study have been reviewed,^{11,12} and a need for confirmatory clinical trials has been expressed.²⁵ However, the study stood alone for nearly 10 years, until the study of Sprung and coworkers appeared.²⁶ These authors compared the effect of a two-dose regimen of corticosteroid (30 mg of methylprednisolone per kilogram, or 6 mg of dexamethasone per kilogram) with that of placebo in 59 patients with established septic shock, but found no difference in mortality in the three treatment groups. However, when corticosteroid therapy was administered within four hours of the onset of shock, there was a trend toward a higher incidence of reversal of shock. A major criticism of this study was the long delay between the onset of shock and the initiation of investigational therapy.

Recognizing that early initiation of corticosteroid therapy might be an essential component of a beneficial response, Hinshaw et al. conducted a study in baboons that was designed to determine the effect of delayed treatment on survival after administration of a lethal (LD_{100}) dose of *Escherichia coli* endotoxin.²⁰ The results of this study indicated that if corticosteroid therapy was initiated within four hours of the insult, a survival rate of 65 to 85 percent was achieved. On the basis of this study and previous clinical trials, we defined criteria for the presumptive diagnosis of severe sepsis and septic shock and established a two-hour limit for initiation of investigational therapy.

METHODS

This study was conducted at 19 centers throughout the United States. The project began on November 1, 1982, with the goal of enrolling 400 patients. The study was concluded on December 31, 1985, with an actual enrollment of 382 patients.

Study Design

Patients with a clinical diagnosis of sepsis were enrolled in the study according to the criteria listed in Table 1.

The presence of sepsis was considered to be confirmed if one positive culture from blood or an intraperitoneal source was obtained within 48 hours of study entry. Two positive cultures were required if a patient had bacteroides or *Staphylococcus epidermidis* infections.

Septic shock was defined as the presence of the sepsis syndrome according to the criteria for inclusion in the study, accompanied by a sustained decrease in systolic blood pressure to less than 90 mm Hg, or a drop of 40 mm Hg from base line, for at least one hour. The presence of shock for more than two hours precluded enrollment. Septic shock was diagnosed only if the preceding criteria were met when volume replacement was adequate and the patient was taking no antihypertensive medication. Shock was considered to have been reversed if none of the preceding criteria were met.

Treatment Protocol

Patients enrolled in the study first received all standard therapies except corticosteroids or other experimental treatments. As soon as possible after entry, initial laboratory specimens were obtained and

Table 1. Criteria for Inclusion or Exclusion of Subjects.

Inclusion (all of the following)

1. Clinical evidence of infection
2. Fever ($>38.3^{\circ}\text{C}$, rectal) or hypothermia ($<35.6^{\circ}\text{C}$, rectal)
3. Tachycardia (>90 beats/min)
4. Tachypnea (>20 breaths/min while breathing spontaneously)
5. At least one of the following manifestations of inadequate organ perfusion or organ dysfunction
 - a. Altered mentation (in relation to patient's base line)
 - b. Hypoxemia (arterial oxygen tension <75 mm Hg while breathing room air, without overt pulmonary disease as a cause)
 - c. Elevated lactate ($>$ the upper limit of normal at the participating institution)
 - d. Oliguria (output <30 ml or 0.5 ml/kg for at least 1 hr)

Exclusion (any of the following)

1. Age <18 or >75 yr
2. Failure to obtain written informed consent from the patient, next of kin, or legal representative
3. History of hypersensitivity to corticosteroids, or treatment with corticosteroids within the last 48 hr
4. Uncontrolled diabetes mellitus
5. Vaccination with a live virus within the preceding 28 days
6. Burns
7. Pregnancy
8. Documented active peptic ulcer within the preceding 6 mo
9. History of active tuberculosis or fungal infection
10. Any condition for which corticosteroids are specifically indicated (e.g., adrenal insufficiency or asthma)
11. Administration of any experimental antibiotic regimen
12. Previous inclusion in this study
13. Administration of naloxone within 4 hr of the onset of severe sepsis or during the course of the study
14. Imprisonment

the patient was assigned in a blinded randomized fashion to treatment with methylprednisolone or placebo. The treatment groups were determined by computer. Treatment had to be initiated two hours from the time when a patient was considered to have met the entry criteria. One treatment group received a 20-minute intravenous infusion (30 mg per kilogram) of methylprednisolone sodium succinate (Solu-Medrol sterile powder, Upjohn [Kalamazoo, Mich.]) every six hours, for a total of four doses. The second group received a placebo infusion in an identical manner.

Clinical Evaluation

History taking and physical examination were performed upon study admission. The patients were evaluated and placed in one of three categories on the basis of the perceived severity of their primary disease. The group with rapidly fatal disease comprised patients expected to die during the current hospital admission. The group with ultimately fatal disease comprised patients expected to survive the current hospital admission but to die of their primary disease within five years. Mortality was not an expected result of the primary disease process in the group with nonfatal diseases.

The patients were monitored continuously for complications of investigational therapy or for other untoward medical events. Data relative to secondary infection were recorded, and the relation between these characteristics and eventual mortality was analyzed retrospectively but before unblinding.

Hemodynamic and Laboratory Data

Patients were studied at enrollment and at 12 hours, 24 hours, 3 days, 7 days, and 14 days or at discharge or death (if either event occurred before 14 days). The following data were recorded: body weight, temperature, respiratory rate, heart rate, blood pressure, use of vasopressors, complete blood count, platelet count, prothrombin time, partial thromboplastin time, urine output, results of

urinalysis with microscopical examination, serum glucose, creatinine, blood urea nitrogen, protein, albumin, total bilirubin, serum aspartate aminotransferase, alkaline phosphatase, lactate, bicarbonate, potassium, sodium, chloride, arterial pH, partial pressure of oxygen in arterial blood, partial pressure of carbon dioxide in arterial blood, use of a mechanical ventilator, use of positive end-expiratory pressure, and fraction of inspired oxygen. Hemodynamic data obtained by means of indwelling arterial and pulmonary-artery catheters were recorded when available.

Consent and Study Approval

The study protocol was submitted to the Food and Drug Administration and approved by each study center's institutional review board for human experimentation. Written informed consent was obtained from the patient, next of kin, or legally authorized guardian.

Primary Study End Points

The three primary end points were the development of septic shock within 14 days of study admission in patients not in shock at entry; the reversal of septic shock within 14 days of study admission; and death within 14 days of study admission.

Statistical Analysis

An intention-to-treat format was followed in analyzing the study data. Every patient who received investigational therapy was included in the data analysis.

Continuous and ordered categorical variables were evaluated with analysis-of-variance techniques. Discrete data were analyzed with the chi-square test (and Fisher's exact test when appropriate). A difference was considered statistically significant if $P < 0.05$. If $0.05 \leq P \leq 0.10$, differences were referred to as trends approaching significance. All tests were two-tailed.

In addition to the clinical investigators, the entire monitoring staff remained blinded throughout the trial. To assist in the early detection of clinically important differences between the two treatment groups, a blinded interim data summary was performed as each 100 patients were enrolled. This summary examined the two treatment groups with regard to the three main study end points (development of septic shock, reversal of septic shock, and death) and subgrouped patients according to whether they had gram-negative or gram-positive bacteremia. The interim summary was reviewed by the study consultant. If clinically relevant trends developed, the consultant was to be unblinded and was to determine whether ethical considerations might preclude continuation of the study. At no time during the course of the study did a need for unblinding arise.

RESULTS

Three hundred eighty-two patients with sepsis syndrome or septic shock were enrolled in the study. There were 147 female and 235 male patients. Their mean age (\pm SD) was 53.6 ± 16 years (methylprednisolone group, 53.0 ± 16 ; placebo group, 53.7 ± 16). Blood cultures were positive in 47 percent of the patients; 115 cultures were positive for gram-negative organisms, 59 for gram-positive bacteria, and 5 for fungi. The two study groups were similar in terms of primary disease states (Table 2). The distribution of disease severity according to category was 44 percent non-fatal, 40 percent ultimately fatal, and 15 percent rapidly fatal. There were no significant differences between treatments in any of the three categories. The methylprednisolone group tended to have more patients with genitourinary infections (methylprednisolone group, 40 of 188 [21 percent] vs. placebo group,

Table 2. Distribution of Primary Disease States According to Treatment Group.

TYPE OF DISEASE	METHYLPREDNISOLONE	PLACEBO
	(N = 191)	(N = 191)
	number of subjects (percent)	
Cardiovascular	12 (6)	7 (4)
Endocrine or metabolic	7 (4)	3 (2)
Gastrointestinal	19 (10)	19 (10)
Infectious	60 (31)	62 (32)
Hematologic	0	1 (0.5)
Renal	6 (3)	6 (3)
Neurologic	10 (5)	12 (6)
Musculoskeletal	1 (0.5)	0
Pulmonary	9 (5)	8 (4)
Malignant neoplastic	37 (19)	34 (18)
Trauma	22 (12)	22 (12)
Other	6 (3)	12 (6)
Unknown	1 (0.5)	3 (2)
None	1 (0.5)	2 (1)

26 of 190 [14 percent]; $P = 0.06$), and the placebo group had significantly more patients with multiple sites of infection (methylprednisolone, 27 of 188 [14 percent] vs. placebo, 43 of 190 [23 percent]; $P < 0.05$). The two groups were similar in the number of criteria met that indicated inadequate perfusion (altered mentation, hypoxemia, elevated lactate, and oliguria). Significantly more patients in the methylprednisolone group had elevated serum creatinine levels at entry (>2 mg per deciliter [180 μ mol per liter]) (methylprednisolone, 78 of 187 [42 percent] vs. placebo, 58 of 186 [31 percent]; $P < 0.05$). This imbalance in the distribution of serum creatinine values occurred because more patients assigned to methylprednisolone had values in the range of 2.1 to 2.5 mg per deciliter (190 to 220 μ mol per liter) at the time of randomization (methylprednisolone, 30 of 187 [16 percent] vs. placebo, 9 of 186 [5 percent]; $P < 0.05$). The distribution of patients with serum creatinine levels above 2.5 mg per deciliter did not differ in the two treatment groups. No differences in the number, type, location, or timing of surgical procedures (defined as those requiring general anesthesia) were found between the two groups.

The first main study end point was the ability of methylprednisolone to prevent shock. Among the patients not in shock at entry, shock developed in 51 of 112 (46 percent) in the methylprednisolone group, as compared with 45 of 122 (37 percent) in the placebo group. Among the patients in whom shock developed, it occurred in 72 percent within 24 hours of enrollment. The development of shock was not dependent on the presence or absence of a positive blood culture.

The second main end point was the ability of methylprednisolone to reverse shock. A total of 244 of the 382 patients were in shock at admission (148 of 382 [39 percent]) or during the course of the study (96 of 234 [41 percent]). Overall, there were no treatment-related differences in the reversal of shock (methylprednisolone, 85 of 130 [65 percent] vs. placebo, 83 of 114 [73 percent]). No significant differences were

found in shock reversal in relation to the severity of the primary disease or to the presence or absence of positive blood cultures. No effect of treatment on shock reversal was observed regardless of whether shock was present at study entry or developed during the course of the study. Most patients who recovered from shock did so within 72 hours.

The final study end point was the effect of methylprednisolone on mortality. The total mortality in this study was 30 percent. Mortality tended to be increased at 14 days among the methylprednisolone-treated patients (methylprednisolone, 65 of 191 [34 percent] vs. placebo, 48 of 190 [25 percent]; $P = 0.06$). Overall, there were no significant differences in mortality in relation to the presence or absence of confirmed bacteremia (bacteremic infection, 56 of 179 [31 percent] vs. no bacteremia, 57 of 201 [28 percent]). The mortality rate among patients with documented gram-negative bacteremia was 33 percent (20 of 60) in the methylprednisolone group and 29 percent (16 of 55) in the placebo group (difference not significant). The rate among patients with gram-positive infections was 33 percent (10 of 30) in the methylprednisolone group and 24 percent (7 of 29) in the placebo group (difference not significant). The mortality rate was not affected by treatment in the patients in whom shock was present at study entry (methylprednisolone, 31 of 79 [39 percent] vs. placebo, 19 of 69 [28 percent]) or developed during the study (23 of 51 [45 percent] vs. 19 of 44 [43 percent]).

A treatment-dependent association between the serum creatinine level at admission and the patient's outcome became apparent from the data. The creatinine level was categorized as normal (≤ 2.0 mg per deciliter [$180 \mu\text{mol}$ per liter]) or as elevated (> 2.0 mg per deciliter). Of the patients with elevated serum creatinine levels at entry, significantly more in the methylprednisolone group were in shock at the time of randomization (methylprednisolone, 43 of 78 [55 percent] vs. placebo, 23 of 58 [40 percent]; $P < 0.05$). Figures 1 and 2 show the development of shock, the reversal of shock, and mortality according to the creatinine level at admission. Comparing the primary study end points between the subgroups revealed that among the patients receiving methylprednisolone, the outcomes of those with elevated creatinine concentrations were significantly worse than those of patients with "normal" concentrations ($P < 0.001$ for all comparisons). In the placebo subgroups, this was true only for the development of shock ($P < 0.05$). Within the subgroup with elevated creatinine concentrations, patients receiving methylprednisolone had a higher incidence of shock development and mortality and a trend toward a decreased rate of shock reversal, as compared with patients receiving placebo ($P = 0.06$). When all patients were subgrouped according to main end point, severity of the primary disease, and creatinine level at admission, only one significant difference was found. Patients in the methylprednisolone group who had nonfatal disease and elevated creatinine concentra-

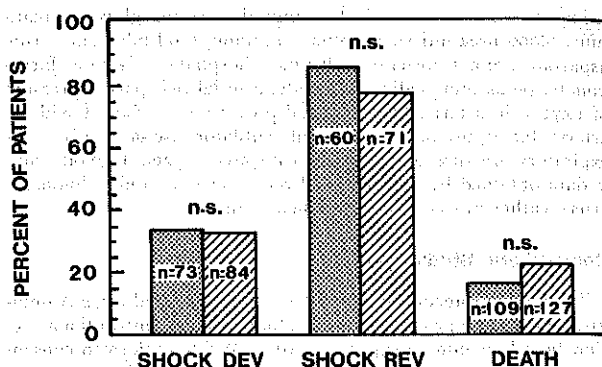


Figure 1. Distribution of Principal Study End Points among Patients with Initial Serum Creatinine Concentrations Less than or Equal to 2.0 mg per Deciliter ($180 \mu\text{mol}$ per liter).

The methylprednisolone group is represented by the stippled bars, and the placebo group by the hatched bars. DEV denotes development, REV reversal, and n.s. not significant.

tions had a significantly higher mortality than their counterparts in the placebo group (methylprednisolone, 13 of 25 [52 percent] vs. placebo, 4 of 24 [17 percent]; $P < 0.05$).

Information on secondary infections was available for 299 patients. The incidence of secondary infection in the two treatment groups did not differ (methylprednisolone, 29 of 152 [19 percent] vs. placebo, 30 of 147 [20 percent]). However, mortality directly attributed to the secondary infection was significantly increased in the methylprednisolone group (methylprednisolone, 10 of 29 [34 percent] vs. placebo, 2 of 30 [7 percent]; $P < 0.015$). There were no imbalances in underlying risk factors, severity of illness, or primary disease that could account for this difference.

DISCUSSION

In designing this clinical trial, the study participants made a concerted effort to address common areas of criticism from previous clinical trials while incorporating favorable design factors (e.g., early treatment) from animal studies of septic shock.²⁰⁻²⁵ Serious consideration was given to two issues concerning administration of investigational therapy — the amount of drug to be administered and the duration of drug administration. Animals in which septic shock was induced had generally received bolus doses of 15 to 30 mg per kilogram. The clinical trials of Schümer,²⁴ Sprung,²⁶ and Thompson²⁷ and their colleagues used two (Schümer and Sprung) to four (Thompson) bolus doses of 30 mg of methylprednisolone per kilogram in patients with established septic shock. Although the results of these studies differed with regard to efficacy, they did not demonstrate that any significant adverse effect followed the administration of up to four bolus doses of the drug. The second issue concerned the duration of treatment. In this regard, animal studies were of little assistance since they defined treatment relative to an insult of known onset

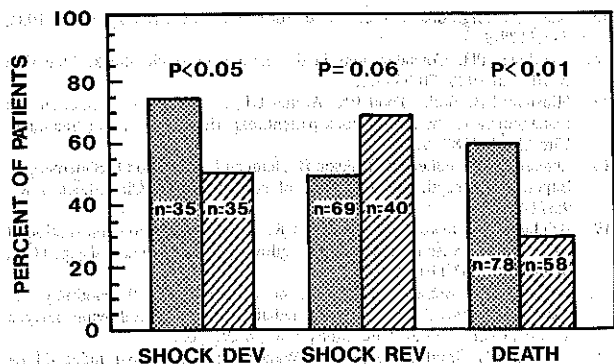


Figure 2. End Points among Patients with Initial Creatinine Concentrations above 2.0 mg per Deciliter.

For explanation of symbols and abbreviations, see legend to Figure 1.

and duration. Since clinical studies of the prophylaxis of septic shock had not previously been attempted, the latency period for the development of shock was unknown. Given the absence of any previous animal-model or clinical evidence of toxicity in studies of septic shock treated with steroid regimens for less than 24 hours, and our desire to provide therapeutic coverage over the period of risk for the development of shock, we chose to administer four doses of drug as investigational therapy. In 46 percent of our patients in whom shock developed, it occurred 8 to 72 hours after study entry, suggesting a need for prolonged therapy for any agent given as prophylaxis for shock.

Our study addressed the issue of prophylaxis by treating patients with the sepsis syndrome. By intervening at this point, we attempted to maximize the effect of corticosteroids on the physiologic evolution from sepsis syndrome to septic shock. The data from this study failed to demonstrate that corticosteroids had any prophylactic value. The data did show that shock develops as frequently in the absence of documented bacteremia as in its presence, regardless of whether the causative organism is gram-positive or gram-negative.

In the subgroup of patients with shock at admission, we began therapy within two hours of the onset, allowing us to attempt to confirm the results of the Sprung study, in which patients treated with methylprednisolone who were in shock for four hours had a trend toward shock reversal. In our study, there was no indication that the drug had an effect on increasing the rate of shock reversal overall, in either the subgroup in which shock was present at admission or the subgroup in which it developed after study entry.

In the Schumer study,¹⁴ patients treated with corticosteroids within four hours of the onset of shock had significantly reduced mortality. Treatment before or within two hours of onset in our study was not efficacious and in fact produced a trend toward higher mortality in the methylprednisolone group. Since many of the studies in animals showing benefit with corticosteroid treatment involved gram-negative bacteremia,

we examined patients with documented bacteremia according to Gram's stain. We found no treatment-related differences in mortality in these subgroups. Early identification and aggressive treatment of the patients did result in a survival rate (74 percent) in the placebo group that was comparable to the rate that Hinshaw et al. obtained with early administration of methylprednisolone in baboons.²⁰

The increasing awareness of the effect of multiple organ failure on outcome in sepsis-related syndromes^{28,29} led us to analyze outcome on the basis of serum values on admission, in particular values for creatinine and bilirubin. The influence of serum bilirubin was not significant relative to the primary study end points. However, the association between an elevated admission creatinine level and outcome in the patients receiving methylprednisolone was striking and unexpected. Shock development and mortality were significantly increased, and shock reversal tended to be strongly decreased. The exact mechanism for this effect will be difficult to determine because of the design of this clinical trial. Examination of creatinine levels over the 14-day study period did not reveal any progressive renal failure in the methylprednisolone group.

Corticosteroid use carries the risk of complications, including psychosis, immune suppression,³⁰ gastrointestinal bleeding, and secondary infection. Although the treatment groups did not differ with regard to the type or number of secondary infections, the steroid group had a significantly increased incidence of mortality directly attributed to secondary infections. Previous trials with steroids have shown an increased incidence of infectious complications.^{26,31} Weigelt et al. found almost twice the incidence of secondary infectious complications in patients with respiratory failure treated with high-dose methylprednisolone (eight doses), as compared with controls given placebo.³¹ Sprung et al. noted that the incidence of infectious complications among patients with septic shock was 35 percent in those treated with dexamethasone, 16 percent in those treated with methylprednisolone, and 6 percent in those not treated with a corticosteroid.²⁶ When coupled with a lack of documented efficacy, the potential for an increased incidence of death due to secondary infections strongly argues against the prophylactic use of corticosteroids in sepsis.

In summary, our prospective, randomized, placebo-controlled, double-blind multicenter trial in patients with severe sepsis and septic shock has shown no benefits from the use of high doses of corticosteroids, in contrast to previous reports showing substantial benefits from their early administration. Our patients with sepsis or septic shock were identified early and were treated within two hours of diagnosis. No improvement was found in shock prevention, shock reversal, or mortality at 14 days. In addition, patients who had renal insufficiency at entry and received methylprednisolone had a decreased rate of shock reversal and a significantly increased mortality. Although the inci-

dence of secondary infection did not differ between the two treatment groups, the mortality attributed to secondary infections was significantly increased in the steroid group. These results strongly argue against the use of high-dose corticosteroids as an adjunct in severe sepsis and septic shock.

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To obtain information on continuing medical education courses in the New England area, write or call, indicating field(s) or specialty in which information is desired, the Committee on Medical Education, 1440 Main St., Waltham, MA 02254; telephone (617) 893-4610 (Metropolitan Boston) or WATS 1-800-322-2303 (Massachusetts).

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