Effect of Prolonged Methylprednisolone Therapy in Unresolving Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

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Context.—No pharmacological therapeutic protocol has been found effective in modifying the clinical course of acute respiratory distress syndrome (ARDS) and mortality remains greater than 50%.

Objective.—To determine the effects of prolonged methylprednisolone therapy on lung function and mortality in patients with unresolving ARDS.

Design.—Randomized, double-blind, placebo-controlled trial.

Setting.—Medical intensive care units of 4 medical centers.

Participants.—Twenty-four patients with severe ARDS who had failed to improve lung injury score (LIS) by the seventh day of respiratory failure.

Interventions.—Sixteen patients received methylprednisolone and 8 received placebo. Methylprednisolone dose was initially 2 mg/kg per day and the duration of treatment was 32 days. Four patients whose LIS failed to improve by at least 1 point after 10 days of treatment were blindly crossed over to the alternative treatment.

Main Outcome Measures.—Primary outcome measures were improvement in lung function and mortality. Secondary outcome measures were improvement in multiple organ dysfunction syndrome (MODS) and development of nosocomial infections.

Results.—Physiological characteristics at the onset of ARDS were similar in both groups. At study entry (day 9 [SD, 3] of ARDS), the 2 groups had similar LIS, ratios of Pao_2 to fraction of inspired oxygen (FIO_2), and MODS scores. Changes observed by study day 10 for methylprednisolone vs placebo were as follows: reduced LIS (mean [SEM], 1.7 [0.1] vs 3.0 [0.2]; $P<.001$); improved ratio of Pao_2 to FIO_2 (mean [SEM], 262 [19] vs 148 [35]; $P<.001$); decreased MODS score (mean [SEM], 0.7 [0.2] vs 1.8 [0.3]; $P<.001$); and successful extubation (7 vs 0; $P=.05$). For the treatment group vs the placebo group, mortality associated with the intensive care unit was 0 (0%) of 16 vs 5 (62%) of 8 ($P=.002$) and hospital-associated mortality was 2 (12%) of 16 vs 5 (62%) of 8 ($P=.03$). The rate of infections per day of treatment was similar in both groups, and pneumonia was frequently detected in the absence of fever.

Conclusions.—In this study, prolonged administration of methylprednisolone in patients with unresolving ARDS was associated with improvement in lung injury and MODS scores and reduced mortality.

JAMA. 1998;280:159-165

ACUTE RESPIRATORY distress syndrome (ARDS) is a frequent cause of hypoxemic respiratory failure caused by the sudden development of diffuse injury to the terminal respiratory units with exudative pulmonary edema.[1] Although most patients (85%-95%) survive the initial insult that precipitates ARDS,[1] no pharmacological therapeutic protocol is effective in modifying the course of this condition,[2] and mortality remains greater than 50%.[3] During the first week of ARDS, nonsurvivors compared with survivors have laboratory and histological evidence of a more intense inflammatory and fibrotic activity with maladaptive lung repair.[1] Mortality for patients failing to improve gas exchange by day 7 of ARDS is reported to exceed 80%.[4-6]

For editorial comment see pp 181 and 182.

Two recently conducted meta-analyses[7,8] of randomized trials investigating a *short course* (≤48 hours) of high-dose methylprednisolone in early sepsis and ARDS found no evidence of a beneficial effect. In contrast, we and others have reported significant improvement in lung function during *prolonged* methylprednisolone administration in medical[9-13] and surgical[14,15] patients with unresolving ARDS and have found that survival correlated with improvement in lung function. In phase 2 trials involving 34 patients, we reported mortalities of 17% in

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Caring for the Critically Ill Patient section editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*. Advisory Board: David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD.

29 patients who improved lung function (responders) and 100% in 5 nonresponders.[11,12] Based on open lung biopsy specimens obtained prior to methylprednisolone treatment, lung histology showed myxoid cellular fibrosis and preserved alveolar architecture in responders but dense acellular fibrosis in nonresponders.[11] These findings suggested that the efficacy of prolonged methylprednisolone therapy may be lost once end-stage fibrosis had begun. Responders invariably had greater than a 1-point reduction in lung injury score (LIS) by day 10 of treatment. From these findings, we concluded that, if administered before end-stage fibrosis develops, prolonged methylprednisolone therapy could be effective in improving lung function and outcome in patients with unresolving ARDS.

In this study, we evaluated the efficacy and safety of prolonged methylprednisolone therapy in a prospective, randomized, double-blind, placebo-controlled trial of patients with unresolving ARDS. The primary objective was to test the hypothesis that methylprednisolone treatment combined with sepsis surveillance would improve lung function and decrease mortality in patients with unresolving ARDS. The study design also permitted us to prospectively evaluate the effects of methylprednisolone therapy on multiple organ dysfunction syndrome (MODS) and on the development of nosocomial infections.

METHODS

Patient Selection, Management, and Randomization

This investigation was conducted between October 1994 and November 1996 in the medical intensive care units (ICUs) of Baptist Memorial Medical Center and East Hospitals, the Regional Medical Center, University of Tennessee Bowld Medical Center, and the Veterans Affairs Medical Center, all in Memphis. The study protocol was approved by each institutional review board, and informed consent was obtained from patients or from patients' next of kin prior to enrollment.

Patients older than 18 years were eligible if they met all of the following criteria: (1) diagnosis of ARDS by consensus criteria,[17] (2) 7 days of mechanical ventilation with an LIS of 2.5 or greater and less than a 1-point reduction from day 1 of ARDS, and (3) no evidence of untreated infection. Exclusion criteria were enrollment in any other investigation, ARDS for 3 or more weeks, extensive burns, life expectancy of less than 3 months because of terminal illness, pregnancy, major gastrointestinal bleeding within the last 3 months, or presence of a disease requiring more than 1 mg/kg per day of methylprednisolone equivalent (eg, asthma).

Ventilator management was designed to limit plateau pressure at 35 cm or less of water.[18] Unless contraindicated,[19] diagnostic fiberoptic bronchoscopy with bilateral bronchoalveolar lavage (BAL) was performed on day 5 of mechanical ventilation to exclude occult ventilator-associated pneumonia (VAP).[6,20] Method of BAL, laboratory processing, and diagnostic criteria followed consensus guidelines.[19] Febrile patients received a previously described diagnostic evaluation.[21] Patients with documented infections required appropriate antibiotic therapy for 3 or more days prior to study entry.

After verification of eligibility, patients were randomized to either methylprednisolone or placebo in blocks of 3 according to a random-number generator. Randomization was stratified by site. The randomization schedule was 2 (methylprednisolone) to 1 (placebo) and remained double-blind through the course of therapy.

Treatment Protocol

Methylprednisolone or placebo was given daily as intravenous push every 6 hours (one fourth of the daily dose) and changed to a single oral dose when oral intake was restored. A loading dose of 2 mg/kg was followed by 2 mg/kg per day from day 1 to day 14, 1 mg/kg per day from day 15 to day 21, 0.5 mg/kg per day from day 22 to day 28, 0.25 mg/kg per day on days 29 and 30, and 0.125 mg/kg per day on days 31 and 32. If the patient was extubated prior to day 14, treatment was advanced to day 15 of drug therapy and tapered according to schedule. The approximate half-life of methylprednisolone is 180 minutes,[22] and we administered the drug at 6-hour intervals. Patients randomized to the control arm received sterile normal saline in a volume equal to the study drug or placebo tablets, which were similar in shape, size, and color to methylprednisolone tablets.

The protocol contained a crossover provision for patients who did not respond to the other treatment intervention. Study patients whose LIS failed to improve by at least 1 point after 10 days of treatment were blindly crossed over to the alternative treatment to avoid unnecessary exposure to ineffective therapy; this alternative treatment regimen was continued for 32 days. Patients exited the study if they developed gastrointestinal bleeding requiring transfusion, had *Candida* species recovered from multiple sites, or developed a new life-threatening condition that might be improved by methylprednisolone treatment. Rapid tapering of the original treatment was instituted if a patient crossed over into the alternate treatment arm or exited the study.

Surveillance bronchoscopy was performed on study day 5 and weekly while patients were intubated. Patients were monitored daily for the development of infections or other complications. If a patient developed fever or had more than 0.10 immature neutrophils on peripheral white blood cell count or an unexplained increase in minute ventilation of more than 30%, a search for infection was initiated.[21] We implemented a previously described systematic protocol with careful search for VAP, sinusitis, catheter-related infection, urinary tract infection, and abdominal pathology.[21] The diagnosis of infection(s) was established by strict criteria.[21]

Data Collection and Outcome Definitions

The precipitating cause of ARDS was classified as either direct or indirect lung injury. Direct lung injury was defined as a direct insult to the lung such as that occurring with pneumonia or aspiration of gastric content. Indirect lung injury was defined as an extrapulmonary insult such as that occurring with an extrapulmonary source of infection, inflammation, or shock.

During the course of ARDS, the following data were obtained on days 1, 2, 3, 5, and 7 of ARDS and on days 1, 3, 5, 7, 10, 14, and 21 of treatment: components of the LIS (while intubated),[23] MODS score,[24] systemic inflammatory response syndrome (SIRS) score,[25] ventilatory requirements, and hemodynamic variables if a pulmonary artery catheter was in place.

Improvement in lung function was defined as a reduction in LIS of more than 1 point.[11] Resolution of individual organ dysfunction followed expert panel recommendations.[23] Death was defined as associated with unresolving ARDS if respiratory failure did not resolve and the patient required more than 0.8 fraction of inspired oxygen (FIO_2) to maintain a PaO_2 of more than 60 mm Hg. The adjudication of death with refractory hypoxemia associated with unresolving ARDS was made by 2 blinded investigators who independently reviewed the collected data.

Statistical Analysis

This study was designed as a sequential clinical trial with nonconstant inspection intervals based on the number of deaths observed (ie, after 3 and 5 deaths in the ICU). The primary variables of interest were ICU survival and improvement in LIS (>1 point) after 10 days of treatment. We made the explicit assumption that improvement in LIS

and ICU survival were highly correlated. The question this trial sought to answer was whether adding methylprednisolone to standard care for patients with unresolving ARDS provided a clinically meaningful benefit compared with standard care alone. In a sequential clinical trial, the goal is to stop the trial as early as possible, thereby avoiding unnecessary morbidity and potential mortality. In a 1-sided scenario, the trial could be stopped if the methylprednisolone treatment was either superior to or no different from placebo. Determining whether the methylprednisolone treatment was inferior to placebo would require more patients than determining whether it was not different from the placebo. Therefore, the alternative hypotheses concerning the primary variables of interest were 1-sided; the null hypotheses was that with the addition of methylprednisolone, ICU survival was the same or worse than standard care (placebo) and that LIS remained the same or worsened in both groups. All other hypotheses were tested against 2-sided alternatives.

By design, based on both significance level and power, the decision to end admission to the trial was determined by sequential analyses of results as data were accumulated.[16] In this sequential clinical trial, the sample size was not a fixed number. The actual number of subjects was determined by the differences between the groups receiving and not receiving methylprednisolone. The sequential triangular test of Whitehead[16] was used for testing differences between the 2 groups. The working levels of α and β were .05. Thus, the working level of power was 0.95. During the design of this trial, we postulated that the proportion of patients with improvement as determined by LIS and the proportion surviving in the methylprednisolone group would both be 0.80 and that those proportions in the placebo group would both be 0.50. A fixed sample size of 99 patients was required to detect a difference of 0.30 between the proportion of survivors among patients who were treated with methylprednisolone and the proportion of survivors among those treated with standard care (ie, placebo). Sequential triangular test or stopping boundaries were constructed to satisfy the working levels of α and β. The decision to end the trial was made when the test statistic exceeded the upper boundary, thereby signifying that the null hypothesis should be rejected. The actual number of patients enrolled was 24. Because no deaths had occurred in the methylprednisolone group, the natural logarithm of the realized odds ratio, needed for the Whitehead sequential triangular test, was undefined. Therefore, a formal method of repeated significance testing was adopted instead of the Whitehead triangular test. Two sequential inspections of the data were conducted with Fisher exact tests. Total sample sizes, 1-tailed P values, and unconditioned power (ignoring accumulated data) for the first inspection were 14, .03, and 0.63, respectively, and for the second inspection were 24, .002, and 0.79, respectively. After the second inspection, a confirmatory test was made using the Whitehead sequential triangular test under the presumption of 1 hypothetical death in the methylprednisolone group (data not presented). Because the test statistic exceeded the upper stopping boundary for the Whitehead sequential triangular test, the decision to reject the null hypothesis had been made at a significance level of less than .05 and a power level of greater than 0.95. Subsequently, despite a total sample size of only 24 patients, enrollment was stopped. There were no protocol violations; all data were analyzed according to the randomization scheme.

For 2-by-2 tables, the Fisher exact 1-tailed or 2-tailed tests were used, or ϕ coefficients and asymptotic SEs were estimated. For infection rates assessed over time, the Cochran-Mantel-Haenszel test was used; infection rate ratios and 95% confidence intervals were estimated. Survival estimates were obtained using the Kaplan-Meier method, and distributions were compared using the log-rank test. For survival curves, censored times were obtained from survivors in both the methylprednisolone and placebo groups. For continuous variables, the treatments were compared by the Student t test and the Mann-Whitney U test. For continuous variables assessed over time, least-squares means for the 2 groups at each time were compared with preplanned contrasts in the context of repeated-measures analysis of variance (split plot).[26] Because enrollment was stopped early, to control for potential confounding variables (ie, all 30 variables used to calculate the Acute Physiology and Chronic Health Evaluation [APACHE] III, MODS, and SIRS scores), post hoc analyses (against 2-sided alternative hypotheses) using Cochran-Mantel-Haenszel tests were performed with strata defined by severity of the confounding variables.

RESULTS

During a 25-month period, 33 patients with ARDS who met entrance criteria were screened, and 24 entered the study (Figure 1). Sixteen patients received methylprednisolone and 8 received placebo. Data were reported as mean (SE). Both groups had similar clinical and physiological[23-25,27] characteristics at onset of ARDS and at study entry (Table 1). We

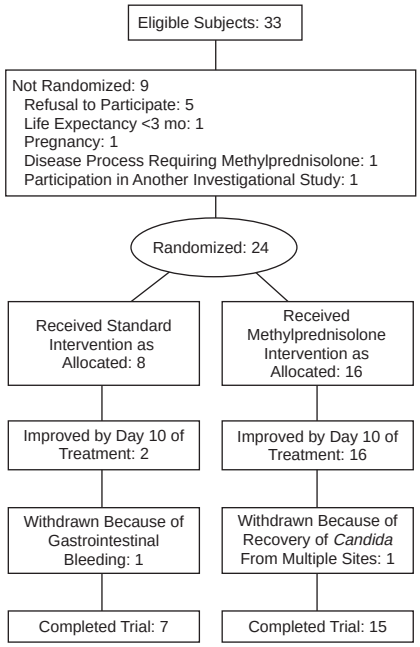

Figure 1.—Flow diagram showing the progression of patients through the study.

analyzed each clinical variable used to calculate the LIS,[23] MODS scores,[24] and SIRS[25] scores at study entry and found a nonsignificant difference only for a lower platelet count in the placebo group (150 [30] vs 290 [49]; $P = .09$). In the methylprednisolone and placebo groups, 6 patients (38%) and 4 patients (50%), respectively, had an LIS of greater than 3 ($P = .19$). In the methylprednisolone group, 9 patients (56%) had MODS scores of 2 or more compared with 5 (63%) in the placebo group ($P = .13$). Twelve patients had undergone recent surgery (4 [3] days to ARDS), and 2 had immediate postoperative ARDS caused by intra-abdominal sepsis (methylprednisolone group) and aspiration (placebo group). Ten infections were identified within 5 days of study entry (Table 1), and all patients received antibiotic treatment for at least 3 days prior to treatment randomization.

Physiological response during the first 10 days of the study is shown in Figure 2 and Table 2. In the methylprednisolone group, improvement was observed in the ratio of Pa_{O_2} to F_{IO_2} by day 5 (161 [13] to 217 [16]; $P = .01$), static lung compliance by day 7 (25 [1] to 32 [2]; $P = .002$), LIS by day 5 (3.0 [.01] to 2.2 [.01]; $P < .001$), mean pulmonary artery pressure by day 5 (30 [1] to 22 [3]; $P = .04$), and MODS score[24] by day 7 (1.7 [.01] to 1.2 [.01]; $P < .001$). None of these variables improved in the placebo group. During the first 10 days of treatment, the percentage of circulating immature neutrophils and the minute ventilation did not change in either group. In the

Table 1.—Clinical and Physiological Characteristics at Onset of ARDS*

Characteristics	Methylprednisolone	Placebo	*P* Value
At Onset of ARDS			
No. of patients	16	8	NA
No. of male patients	5	4	.42
Age, mean (SEM), y	47 (3.9)	51 (6.6)	.58
APACHE III score, mean (SEM)†	58 (14)	55 (16)	.61
Direct cause of ARDS, No. (%)‡	9 (56)	6 (75)	.66
Presence of sepsis, No. (%)	12 (75)	5 (63)	.65
Presence of septic shock, No. (%)	10 (63)	3 (38)	.39
Ratio of PaO_2 to FIO_2, mean (SEM)	110 (11)	123 (11)	.30
Lung injury score, mean (SEM)	2.9 (0.1)	2.9 (0.1)	.77
MODS score, mean (SEM)	2.4 (0.3)	2.0 (0.3)	.37
At Study Entry			
No. of patients	16	8	NA
Duration of ARDS, mean (SEM), y	9.4 (0.9)	8.8 (1.2)	.70
Recent nosocomial infections, No. (%)§	8 (50)	2 (25)	.39
Temperature, mean (SEM), °C	37.3 (0.3)	37.8 (0.4)	.29
Pulmonary artery pressure, mean (SEM)	31 (4.1)	33 (3.2)	.53
Ratio of PaO_2 to FIO_2, mean (SEM)	161 (14)	141 (19)	.39
PEEP, mean (SEM), cm H_2O	12 (1.2)	14 (1.7)	.26
Lung injury score, median (IQR)	3.0 (2.5-3.4)	3.3 (3.0-3.6)	.16
MODS score, median (IQR)	1.5 (1.0-2.0)	2.5 (1.0-3.0)	.22
Presence of pneumothorax, No. (%)	5 (31)	2 (25)	.99

*ARDS indicates acute respiratory distress syndrome; NA, not applicable; APACHE, Acute Physiology and Chronic Health Evaluation; FIO_2, fraction of inspired oxygen; MODS, multiple organ dysfunction syndrome; PEEP, positive end-expiratory pressure; and IQR, interquartile range.

†Indicates APACHE III score on admission to intensive care unit.[27]

‡Causes of direct injury to the lung include 11 bacterial pneumonias (8 community acquired, 4 in each group), 3 chemical aspirations (2 in patients randomized to placebo), and 1 pulmonary blastomycosis (patient randomized to placebo). Causes of indirect injury to the lung include 5 extrapulmonary sepsis, 2 postoperative ARDS, and 2 drug reactions (1 tricyclic antidepressant overdose and 1 anaphylactic reaction to urokinase [patient randomized to placebo]).

§Nosocomial infections diagnosed by strict criteria within 5 days of randomization in the methylprednisolone group include bacteremia, fungemia, sinusitis, wound infection, 2 urinary tract infections, and 2 ventilator-associated pneumonias; the placebo group had 2 catheter-related infections.

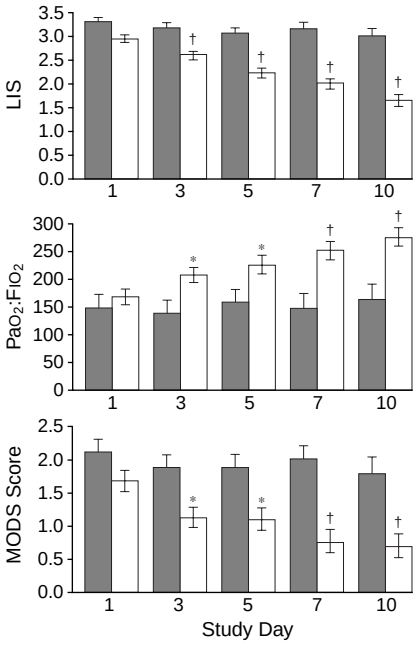

Figure 2.—Mean (SE) changes in lung injury score (LIS), the ratio of PaO_2 to fraction of inspired oxygen (FIO_2), and multiple organ dysfunction syndrome (MODS) score during the first 10 days of treatment in the methylprednisolone group and placebo group. Error bars indicate SEs. There was no statistical difference between the methylprednisolone and placebo groups at the time of entry into the study. The values on day 1 were obtained prior to initiating treatment. In the methylprednisolone group, a statistically significant improvement was achieved for the ratio of PaO_2 to FIO_2 on day 5 ($P<.01$), LIS on day 5 ($P<.001$), and MODS score on day 7 ($P<.001$). In the placebo group, no statistically significant improvement was achieved during the first 10 days of treatment. The number of patients in the methylprednisolone groups on study days 7 and 10 were 14 and 9, and in the placebo group, 6 and 6, respectively. The asterisk indicates $P<.01$; dagger, $P<.001$.

methylprednisolone group, a persistent reduction in body temperature was observed by day 3 ($P = .004$) and an increase in total leukocyte count by day 7 ($P = .04$).

In the methylprednisolone group during the first 10 days, all patients improved as measured by LIS and none were crossed over to the placebo (as dictated by protocol). In the placebo group during the first 10 days, 2 patients improved (survivors), 2 died, and 4 who failed to improve were blindly crossed over to methylprednisolone (as dictated by the protocol). Among the patients who were crossed over, 2 failed to improve and died after 11 and 69 days, respectively, 1 improved and survived, and 1 improved but exited the study, then experienced a deterioration of health and died. Thus, improvement in LIS was observed in all patients initially randomized to methylprednisolone and in 2 of 4 of those crossed over to methylprednisolone after 10 days of placebo ($P = .04$). Mortality was significantly higher in those crossed over compared with those randomized to methylprednisolone.

Median duration of mechanical ventilation is shown in Table 3. For survivors of the placebo group, median duration of mechanical ventilation was 14 days. Extubated patients were discharged from the ICU without assisted breathing, all but 1 within 4 days of removal of mechanical ventilation. One patient in the methylprednisolone group was discharged directly to a rehabilitation unit and was successfully weaned from mechanical ventilation. Improvement in LIS after 10 days of treatment and hospital survival were correlated ($r = 0.688$ [0.165]).

Mortality data are shown in Figure 3 and Table 3. After controlling for potential confounding variables, differences in ICU mortality between the 2 groups remained significant (all P values $<.008$). No differences in mortality rates were observed among hospitals. In the placebo group, death was always associated with unresolving ARDS; 4 of 5 patients had hypercarbia. The 2 deaths in the methylprednisolone group occurred after ICU discharge and were not related to ARDS (cardiac arrhythmia in a patient with known coronary artery disease and prior cardiac arrest and recurrent aspiration in a patient with neurological dysfunction).

Complications observed during treatment are shown in Table 4. The infection rate was constant over time and was similar between both groups. The infection rate ratio per day of mechanical ventilation for methylprednisolone compared with placebo was 1.80 (95% confidence interval, 0.86-3.76). Because this trial ended early, a sufficient number of patients could not be enrolled to assess this hypothesis. In the methylprednisolone group, 27 bronchoscopies were performed to rule out pneumonia; 4 of 16 surveillance bronchoscopies in patients without fever identified a significant growth of pathogens. Most pneumonias were diagnosed during the first week of investigative treatment. No idiosyncratic reactions developed during methylprednisolone therapy and no patient developed upper gastrointestinal tract bleeding that required transfusion.

Two patients exited the study (Figure 1). One patient, randomized to methylprednisolone, exited on study day 20 because of candidemia with positive findings in urine and central line catheter cultures; this patient responded to amphotericin treatment and was extubated. The other was a placebo patient who was crossed over to methylprednisolone and who developed thrombocytopenia and a

Table 2.—Outcome Measures on Study Day 10*

Outcome Measures	Methylprednisolone	Placebo	*P* Value
No. of patients	16	8	NA
Ratio of Pao_2 to FIO_2	262 (19)	148 (35)	<.001
Lung injury score	1.7 (0.1)	3.0 (0.2)	<.001
Patients with >1-point reduction in LIS, No. (%)	16 (100)	2 (25)	<.001
Crossed over because of failure to improve LIS†	0	4	.007
Pulmonary artery pressure‡	22.5 (3.2)	30 (2.7)	.01
Successful extubation, No. (%)	7 (44)	0 (0)	.05
MODS score	0.7 (0.2)§	1.8 (0.3)	<.001
Infections per 100 patient-days of treatment‖	8	7	.99
New ventilator-associated pneumonia	6	1	.70
Survivors, No. (%)	16 (100)	6 (75)	.10

*Data are reported as absolute or mean (SEM). NA indicates not applicable; FIO_2, fraction of inspired oxygen; and MODS, multiple organ dysfunction syndrome.
†Four patients randomized to placebo failed to reduce lung injury score of 1 point or more from study entry and were blindly crossed over to methylprednisolone. Two patients randomized to placebo died before study day 10.
‡Pulmonary artery pressure values are reported for study day 7.
§Improvement was significant for platelet count by day 5 ($P = .004$), serum creatinine by day 7 ($P = .04$), and serum total bilirubin by day 5 ($P = .02$).
‖Number of infections divided by number of treatment days received and multiplied by 100.

Table 3.—Outcome Measures*

Outcome Measures	Methylprednisolone	Placebo	*P* Value
Survivors of ICU admission, No. (%)	16 (100)	3 (37)	.002
Survivors of hospital admission, No. (%)	14 (87)	3 (37)	.03
Death associated with unresolving ARDS, No.†	0 of 2	5 of 5	NA
MODS-free days by study day 28, mean (SEM)‡	16 (2)	6 (2)	.005
Duration of mechanical ventilation, median, d	11.5	23	.001

*ICU indicates intensive care unit; ARDS, acute respiratory distress syndrome; NA, not applicable; and MODS, multiple organ dysfunction syndrome.
†ARDS failed to resolve and the patient required more than 0.8 fraction of inspired oxygen (FIO_2) to maintain a Pao_2 of more than 60 mm Hg at the time of death.
‡Resolution of individual organ dysfunction followed expert panel recommendations[23] and included cardiovascular system, a systolic blood pressure greater than 90 mm Hg; respiratory system, a ratio of Pao_2 to FIO_2 greater than 400; nervous system, a Glasgow coma score of 15 or greater; coagulation, a platelet count greater than 120×10^9/L (120 000 µL); renal system, a serum creatinine level less than 133 µmol/L (1.5 mg/dL); and hepatic system, a bilirubin level less than 21 µmol/L (1.2 mg/dL).[24]

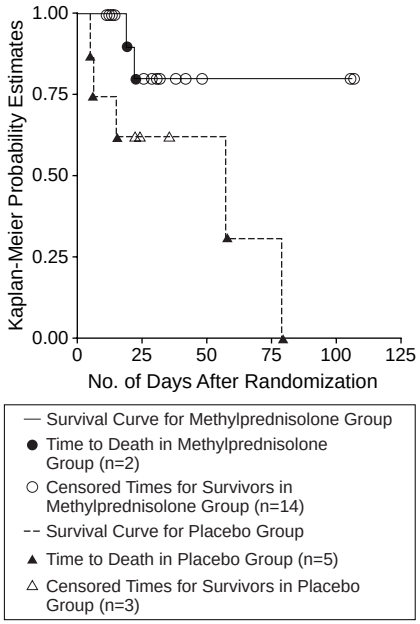

Figure 3.—Survival curves of patients receiving methylprednisolone and placebo. In the methylprednisolone and placebo groups, survival times for 14 and 3 patients, respectively, were classified as censored.

large bleeding rectal ulcer requiring major transfusion; she exited the study on day 31, after 22 days of methylprednisolone therapy, with an LIS of 1. Her LIS and MODS score later deteriorated and she died on study day 57.

COMMENT

We evaluated the efficacy and safety of prolonged methylprednisolone therapy in a prospective, randomized, double-blind, placebo-controlled study of patients with unresolving ARDS. The protocol contained a provision for blindly crossing over patients who did not respond initially to the alternate treatment and procedures for infection surveillance, including bronchoscopy with bilateral BAL. Using a sequential clinical trial, we have demonstrated that prolonged methylprednisolone treatment of patients with unresolving ARDS is associated with improvement in LIS and MODS score and with a significant reduction in mortality. Timing of methylprednisolone administration influenced response to treatment, and clinically important complications of therapy were few.

A protracted and exaggerated release of host defense mediators is accountable for the pulmonary and systemic manifestations of unresolving ARDS.[1,28,29] Improvement in both LIS and MODS during methylprednisolone therapy supports a common pathogenetic mechanism for pulmonary and extrapulmonary organ dysfunction in ARDS.[1] In unresolving ARDS, disruption of the alveolocapillary membrane[30] favors the passage of cytokines produced in the lung into the systemic circulation and contributes to the development or maintenance of MODS.[1]

In our study, improvement in LIS and survival were correlated. The degree of improvement in LIS was similar to the response that we had observed previously in 20 (rapid responders) of 34 patients with ARDS receiving methylprednisolone rescue treatment.[11,12] In rapid responders, this treatment was associated with a decrease in plasma and BAL tumor necrosis factor α, interleukin (IL) 1ß, IL-6, and IL-8 levels that paralleled reductions in LIS and BAL albumin; normalization of gallium citrate Ga 67 pulmonary uptake; restoration of normal alveolar architecture (follow-up histology); and a lower mortality rate.[11,12]

In the current study, delayed administration of methylprednisolone in patients who did not improve with placebo was associated with a 50% failure rate; a significant association was found between this late initiation of treatment and failure to improve ($P = .04$). In agreement with experimental work,[31] we previously provided data to support a causal relationship between intensity and duration of the host defense response in ARDS, progression of pulmonary fibroproliferation, and response to methylprednisolone treatment.[12] This line of evidence indicates that methylprednisolone therapy should be started before fibroproliferation advances to end-stage acellular fibrosis in which type I collagen, which is more resistant to digestion, predominates.[11]

The current study is in agreement with our prior observation that methylprednisolone therapy should be prolonged to effect a containment of the host defense response, which is crucial to the reversal of ARDS and MODS.[11,12] This finding is supported by previous animal[32-34] and clinical[9,13,14,35,36] studies. In experimental acute lung injury, glucocorticoid administration has been effective in decreasing lung collagen and edema formation as long as treatment was prolonged, whereas drug withdrawal rapidly negated this positive influence.[33,34,37] Furthermore, a short course of glucocorticoid therapy may compromise ARDS recovery; limiting treatment to the first 6 days of experimental acute lung injury enhanced accumulation of collagen after discontinuing therapy.[34] Additionally, cytokine response to lipopolysaccharide challenge in humans is significantly enhanced by a prior short course

Table 4.—Complications Observed During Therapy*

Complications	Methylprednisolone*	Placebo
No. of patients	16	8
Patients with a new infection	12 (75)	6 (75)
New infections†	24	10
Pneumonia‡	9 (38)	1 (10)
Sinusitis§	2 (8)	0 (0)
Catheter-related infection	3 (12)	3 (30)
Urinary tract infection	4 (17)	0 (0)
Bacteremia	2 (8)	4 (40)
Candidemia	2 (8)	0 (0)
Others‖	2 (8)	2 (20)
New pneumothorax	2 (12)	4 (50)
Reduction in hemoglobin >0.20	1 (6)	4 (50)
New hyperglycemia (glucose >13.9 mmol/L [250 mg/dL])	5 (31)	4 (50)

*Data are expressed as No. (%). There was no statistically significant difference in any variable among the 2 groups except for reduction in hemoglobin of more than 0.20 g/L vs study admission ($P = .03$).

†In the methylprednisolone group, 4 of these infections were identified after intensive care unit discharge. In the placebo group, 4 of these infections (2 *Staphylococcus epidermidis* bacteremias, 1 *Klebsiella* empyema, and 1 *Clostridium difficile* colitis) developed after crossover to methylprednisolone.

‡Etiology of ventilator-associated pneumonias in the methylprednisolone group included 3 *Staphylococcus aureus*, 2 *Pseudomonas aeruginosa*, 1 *Acinetobacter*, 1 *Klebsiella pneumoniae*, 1 *Escherichia coli*, and 1 *Enterobacter*, and in the placebo group, 1 *Pseudomonas aeruginosa*.

§Etiology of sinusitis included 1 *Staphylococcus aureus* and 1 *Staphylococcus aureus* and *Proteus mirabilis*.

‖Other infections in the methylprednisolone group included 1 lung abscess and 1 infected intra-abdominal hematoma (both requiring surgical drainage); the placebo group included 1 empyema and 1 *Clostridium difficile* colitis.

of glucocorticoids,[38] and this response may explain the difference in infection-related mortality between studies using short-course, 24-hour treatment[39] and the findings of our investigation.

We have previously shown that during methylprednisolone treatment VAP frequently develops in the absence of fever, and infection surveillance, including weekly surveillance bilateral BAL, is required for early detection of pneumonia and other serious infections.[11] In the current study, the infection rate was not significantly affected by methylprednisolone treatment or by the duration of mechanical ventilation. None of the nosocomial infections with potentially lethal pathogens developing during methylprednisolone therapy affected resolution of ARDS or clinical outcome. This evidence reinforces the findings of Headley et al[6] that appropriately treated nosocomial infections, albeit a frequent complication of ARDS, do not themselves cause death.

Glucocorticoids inhibit the host defense response network at virtually all levels and exert most of their effects through specific, ubiquitously distributed intracellular glucocorticoid receptors.[40] After steroid binding, activated glucocorticoid receptors inhibit the transcriptional activation of several cytokines and cell adhesion genes by binding to transcription factors (type 2 mechanism) or blocking their activation.[40,41] Glucocorticoids also suppress the synthesis of phospholipase A_2, cyclooxygenase 2, and nitric oxide synthetase 1 genes, decreasing the production of prostanoids, platelet-activating factor, and nitric oxide (3 key substances in the inflammatory pathway)[42] and have an inhibitory effect on fibrogenesis.[10]

Although the pharmacokinetics of methylprednisolone are influenced by age, sex, and race,[22,43] no experimental data exist to guide ARDS treatment dosing. Dosage, administration interval, and duration of treatment in this study were dictated by our prior experience and modeled on standard practice for the treatment of interstitial inflammatory lung diseases.[11] To evaluate the effectiveness of methylprednisolone treatment on fibrogenesis, we obtained serial measurements of plasma and BAL type I and III procollagen aminoterminal propeptide levels, before and after randomization.[44] Patients randomized to methylprednisolone had a rapid, significant, and sustained reduction in plasma and BAL levels of both markers, whereas no reduction was observed in patients randomized to placebo.[44]

Terminating this sequential trial early produced 3 major consequences. The first was unavoidable because stopping any trial early biases the estimate of the treatment effect. In this trial estimates of the positive effects of methylprednisolone on survival of ICU patients and improvement in LIS compared with the placebo were probably greater than those estimates would have been if the trial had not been terminated. The second consequence, distrust of how the protocol was executed, was addressed by verifying that all investigators and ancillary personnel strictly adhered to the protocol. The third consequence involved potential lack of comparability between the 2 groups of patients to the extent that the treatment effect might merely have reflected some confounding variable, such as severity of illness. When the total sample size is relatively small, the process of randomization may not prevent some important variable from being confounded with both treatment group and outcome. Based on the APACHE III score at entry, the most severely ill patient was randomized to the placebo group and did die. On the day of randomization, other nonsurvivors in the placebo group had APACHE III scores that were less than those of several survivors in the methylprednisolone group. Therefore, although estimates of the positive effects of methylprednisolone may have been biased, we believe it is unlikely that any confounding variable could have explained the differences in outcome between the 2 groups.

This randomized, placebo-controlled trial confirms and expands the observations in 7 prior observational studies[9-15] involving 76 patients with unresolving ARDS. Our findings suggest that, in previous large, randomized, multicenter studies evaluating high doses of methylprednisolone in sepsis and early ARDS, the relatively short duration of treatment may be related to failure to detect a beneficial effect. Timing and duration of corticosteroid therapy appear to be critical variables in therapeutic outcome. This investigation and recent appreciation of the complex relationship among the hypothalamic-pituitary-adrenal axis, glucocorticoid receptor function, and cytokine modulation of the host defense response in critical illness suggest the need for reappraisal of methylprednisolone for treatment of ARDS.[1]

We are indebted to Harold Dickson, PhD, and Sandra Tsiu, PharmD, of the Baptist Health Care Foundation, Memphis, Tenn, for their invaluable help in initiating this study; to the following physicians for allowing us to study their patients: Johnny Belenchia, MD, Albert Chinn, MD, Lisa Kennedy, MD, Roy Fox, MD, Kenneth V. Leeper, MD, Muhammad Zaman, MD, and Glen Williams, MD; to the Fellows of the Pulmonary and Critical Care Division, Department of Medicine, University of Tennessee, Memphis, for their generous help; to Julia Campbell for assistance in data management; to the APACHE Medical System Inc, McLean, Va, for assistance in the calculation of the APACHE III score; and to John Griffin, MD, Dennis Schaberg, MD, and David Armbruster, PhD, for helpful critique of this article. Special thanks go to our patients Janet Machala and Sharon Johnson for their support.

This study was supported by the Baptist Memorial Health Care Foundation, Memphis, and by the University of Tennessee, Clinical Research Center, Memphis.

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