# Administration of Methylprednisolone for 24 or 48 Hours or Tirilazad Mesylate for 48 Hours in the Treatment of Acute Spinal Cord Injury

## Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial

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**Objective.**—To compare the efficacy of methylprednisolone administered for 24 hours with methyprednisolone administered for 48 hours or tirilazad mesylate administered for 48 hours in patients with acute spinal cord injury.

**Design.**—Double-blind, randomized clinical trial.

**Setting.**—Sixteen acute spinal cord injury centers in North America.

**Patients.**—A total of 499 patients with acute spinal cord injury diagnosed in National Acute Spinal Cord Injury Study (NASCIS) centers within 8 hours of injury.

**Intervention.**—All patients received an intravenous bolus of methylprednisolone (30 mg/kg) before randomization. Patients in the 24-hour regimen group (n=166) received a methylprednisolone infusion of 5.4 mg/kg per hour for 24 hours, those in the 48-hour regimen group (n=167) received a methylprednisolone infusion of 5.4 mg/kg per hour for 48 hours, and those in the tirilazad group (n=166) received a 2.5 mg/kg bolus infusion of tirilazad mesylate every 6 hours for 48 hours.

**Main Outcome Measures.**—Motor function change between initial presentation and at 6 weeks and 6 months after injury, and change in Functional Independence Measure (FIM) assessed at 6 weeks and 6 months.

**Results.**—Compared with patients treated with methylprednisolone for 24 hours, those treated with methylprednisolone for 48 hours showed improved motor recovery at 6 weeks ($P$=.09) and 6 months ($P$=.07) after injury. The effect of the 48-hour methylprednisolone regimen was significant at 6 weeks ($P$=.04) and 6 months ($P$=.01) among patients whose therapy was initiated 3 to 8 hours after injury. Patients who received the 48-hour regimen and who started treatment at 3 to 8 hours were more likely to improve 1 full neurologic grade ($P$=.03) at 6 months, to show more improvement in 6-month FIM ($P$=.08), and to have more severe sepsis and severe pneumonia than patients in the 24-hour methylprednisolone group and the tirilazad group, but other complications and mortality ($P$=.97) were similar. Patients treated with tirilazad for 48 hours showed motor recovery rates equivalent to patients who received methylprednisolone for 24 hours.

**Conclusions.**—Patients with acute spinal cord injury who receive methylprednisolone within 3 hours of injury should be maintained on the treatment regimen for 24 hours. When methylprednisolone is initiated 3 to 8 hours after injury, patients should be maintained on steroid therapy for 48 hours.

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ACUTE SPINAL CORD injury is a devastating, traumatic event, is experienced disproportionately by young people,[1] and has appeared refractory to treatment.[2] The National Acute Spinal Cord Injury Study (NASCIS) was established in 1975 to evaluate pharmacologic therapies in the first hours after injury.[3-5] A prior trial, NASCIS 2, demonstrated that high-dose methylprednisolone (30 mg/kg bolus followed by 5.4 mg/kg per hour for 23 hours) initiated within 8 hours of injury, resulted in greater neurologic recovery that remained evident 1 year after injury.[6,7] Neurologic recovery occurred at the injury level and in lower spinal cord segments.[8,9] NASCIS 2, replicated in Japan,[10] provided a therapy now widely used to treat acute spinal cord injury[11] and clinical evidence that destructive biologic processes within the spinal cord can be ameliorated.[12,13]

A mechanism likely to be influenced by methylprednisolone is suppression of lipid peroxidation and hydrolysis, which destroys neuronal and microvascular membranes.[13-16] These secondary

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injury processes extend beyond 24 hours.[13] The present trial was designed to evaluate whether a 48-hour maintenance dose of methylprednisolone would lead to greater recovery than the 24-hour methylprednisolone protocol. We also studied tirilazad mesylate, a potent lipid peroxidation inhibitor developed to treat central nervous system (CNS) trauma,[17-21] with potentially fewer complications than anticipated from the high-dose 48-hour methylprednisolone regimen.[22] Two preplanned subgroup analyses involved early vs late initiation of treatment within the 8-hours-of-injury window and the effect of treatment in patients with initial complete vs incomplete neurologic function.

## METHODS

### Eligibility and Randomization

The first patient was randomized December 18, 1991, and the last September 30, 1995. Eligible patients were randomized within 6 hours of injury to receive the study drug within 8 hours. Patients were diagnosed by NASCIS-approved physicians as having a spinal cord injury, consented to participate, and were at least 14 years old. We excluded pregnant women, illegal immigrants, indicted criminals, patients with serious comorbidity or specific health conditions that might affect treatment assessment, patients weighing more than 109 kg (242 lb) because of concern regarding volume overload, patients with gunshot wounds, those with previous spinal injury, or those started earlier on maintenance methylprednisolone. Approval was obtained from institutional review boards at all participating hospitals.

Once a patient was determined to be eligible, the randomizing center called the 24-hour Yale–New Haven Hospital pharmacy. The pharmacist confirmed that the caller was a NASCIS collaborator, injury was within 6 hours, and consent had been obtained. The Yale pharmacist calculated study drug dosages based on the patient's weight and provided dosing information. Within each center the 3 treatments were randomized in blocks of 9. Apart from the study protocol, all other aspects of patient management were at the discretion of each participating center.

### Preparation and Administration of the Study Drugs

Methylprednisolone or its placebo was provided in kits containing 16 2-g vials. Bacteriostatic water was used for reconstituting methylprednisolone. Tirilazad mesylate, 1.5 mg/mL, or placebo was supplied in kits containing 16 100-mL vials. All patients received a bolus of open-label methylprednisolone (20 to 40 mg/kg) at the injury site or emergency department before randomization. Patients for whom the initial bolus was less than 20 mg/kg (2.6%) were given an additional bolus on hospital admission.

Methylprednisolone and tirilazad (or placebos) were administered in separate masked infusions. Methylprednisolone was infused continuously over 48 hours at 5.4 mg/kg per hour, and 2.5 mg/kg of tirilazad mesylate was given by intravenous bolus infusion over 15 to 20 minutes every 6 hours for 48 hours. Maintenance doses were started within 3 hours of the bolus. Study personnel were blind to drug protocol. Sealed drug codes were stored in each center and returned to the coordinating center for inspection. No evidence of tampering was observed, and it was never necessary to break the code. Patients in the methylprednisolone groups were administered more than 97% of their assigned total milligram dose and the tirilazad group received 94.3%.

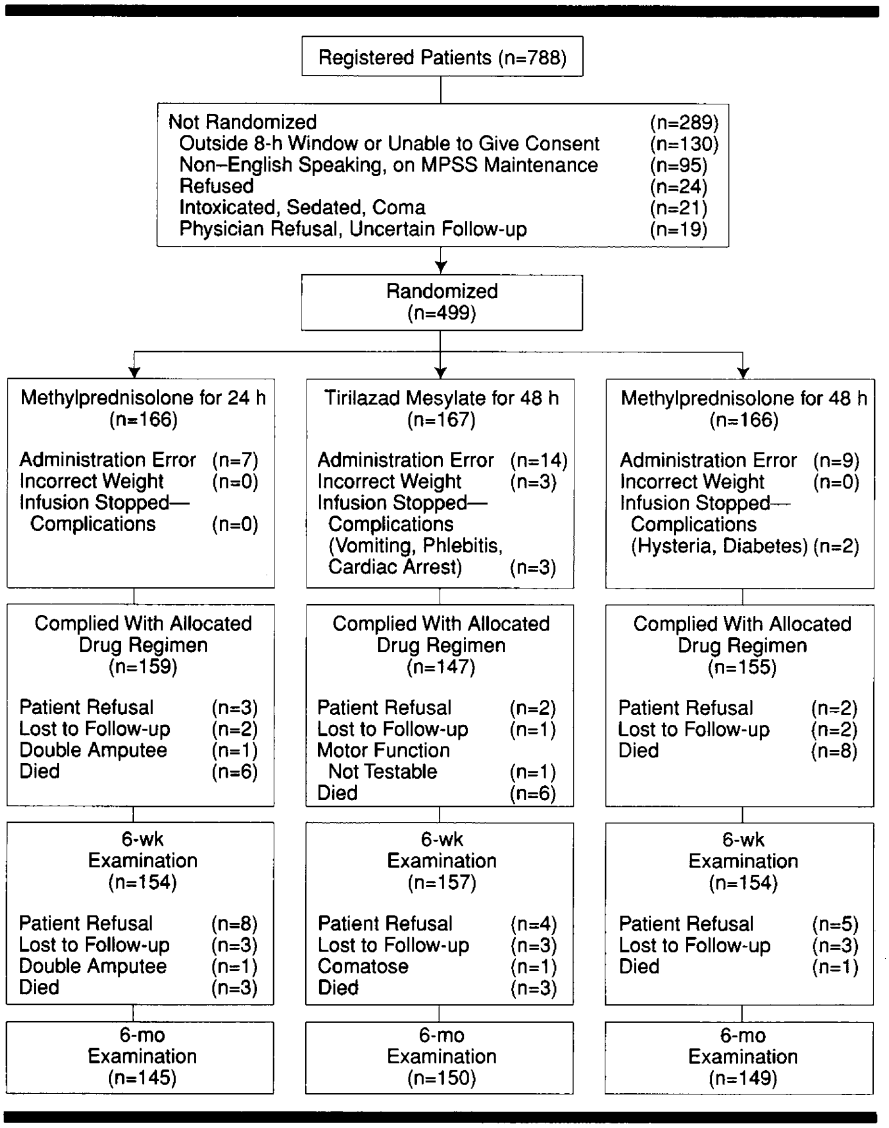


Figure 1.—Each stage of the third National Acute Spinal Cord Injury Study. Some patients were examined at 6 months who were not examined at 6 weeks. MPSS represents methylprednisolone sodium succinate.

### Assessment of Neurologic Function

Patients were examined in the emergency department immediately after injury and at 6 weeks (42-49 days) and 6 months (180-210 days) after injury by NASCIS-trained physicians and nurses, all of whom were blind to study protocol. Patients who moved away were examined at the nearest collaborating center. Ninety-eight percent of surviving patients received their 6-week and 94.7% their 6-month neurologic follow-up (Figure 1). Survival information was available for all patients.

**Motor Function.**—Motor function was tested bilaterally in 14 muscle segments. An additional segment was measured to meet American Spinal Injury

Table 1.—Demographic and Clinical Characteristics of Patients at Entry*

| Characteristics | Protocols 24MP | 48TM | 48MP | P Value |
|---|---|---|---|---|
| No. of patients | 166 | 167 | 166 | . . . |
| Sex, % | | | | |
| Male | 85.5 | 86.8 | 81.9 | .44 |
| Female | 14.5 | 13.2 | 18.1 | |
| Ethnicity, % | | | | |
| African American | 10.2 | 12.0 | 13.9 | .49 |
| Non-Hispanic white | 77.1 | 73.6 | 75.9 | |
| Hispanic | 7.2 | 9.6 | 6.0 | |
| Other | 5.4 | 5.4 | 4.2 | |
| Weight, kg | 77.3±1.1 | 75.9±1.1 | 77.7±1.1 | .40 |
| Age, % | | | | |
| 14-19 | 14.5 | 15.6 | 14.5 | .40 |
| 20-24 | 13.9 | 15.6 | 17.5 | |
| 25-29 | 13.9 | 16.2 | 13.9 | |
| 30-34 | 16.3 | 12.0 | 16.3 | |
| 35-39 | 8.4 | 10.8 | 10.2 | |
| 40-44 | 4.8 | 8.4 | 6.0 | |
| 45-49 | 6.6 | 0.6 | 5.4 | |
| 50-54 | 3.0 | 3.6 | 2.4 | |
| 55-59 | 3.6 | 7.2 | 3.0 | |
| ≥60 | 15.1 | 10.2 | 10.8 | |
| Blood pressure, mm Hg | | | | |
| Systolic | 126.1±1.8 | 121.6±1.8 | 125.7±1.8 | .15 |
| Diastolic | 76.0±1.3 | 71.6±1.3 | 76.8±1.3 | .01 |
| Pulse | 78.7±1.4 | 81.3±1.4 | 81.3±1.4 | .31 |
| Body temperature, °C | 36.1±0.10 | 36.1±0.1 | 36.1±0.1 | .88 |
| Cause of injury, % | | | | |
| Automobile crash | 37.9 | 34.7 | 36.7 | .96 |
| Motorcycle crash | 7.2 | 7.8 | 9.6 | |
| Fall | 25.3 | 27.5 | 27.7 | |
| Crush injury | 7.8 | 7.2 | 4.8 | |
| Water-related injury | 6.0 | 9.0 | 7.8 | |
| Other† | 15.7 | 13.8 | 13.2 | |
| Associated injuries | | | | |
| Skin and soft tissue | 49.4 | 54.8 | 49.7 | .54 |
| Head | 11.4 | 9.6 | 9.2 | .84 |
| Ear, nose, and throat | 3.6 | 2.4 | 2.4 | .75 |
| Cardiac | 1.8 | 2.4 | 0.0 | .16 |
| Pulmonary | 11.4 | 13.9 | 12.9 | .80 |
| Gastrointestinal | 2.4 | 1.2 | 5.5 | .06 |
| Genital or urinary | 1.8 | 1.2 | 0.0 | .25 |
| Musculoskeletal | 15.7 | 23.5 | 23.3 | .13 |
| Other | 3.6 | 3.6 | 2.4 | .79 |
| Glasgow Coma Scale score | 14.7±.09 | 14.6±.09 | 14.4±.09 | .20 |
| Extent of spinal cord injury, %‡ | | | | |
| Complete | 46.4 | 51.8 | 51.5 | .61 |
| Incomplete | 44.6 | 42.8 | 40.0 | |
| Normal | 9.0 | 5.4 | 8.5 | |
| Plain spine x-ray, % | | | | |
| Fracture only | 30.3 | 22.8 | 26.7 | .74 |
| Dislocation only | 7.9 | 9.0 | 7.5 | |
| Fracture and dislocation | 46.7 | 55.1 | 50.3 | |
| No fracture or dislocation | 15.2 | 13.2 | 15.5 | |
| Spinal cord syndrome, % | | | | |
| Anterior | 5.4 | 4.2 | 6.1 | .62 |
| Central | 17.6 | 15.6 | 21.3 | |
| Brown Séquard | 9.1 | 6.0 | 6.1 | |
| Posterior | 0.0 | 0.0 | 0.0 | |
| No syndrome | 67.9 | 74.2 | 66.5 | |
| Administered bolus before randomization, % | 73.5 | 74.2 | 68.1 | .39 |
| Time of injury to admission, mean (SD), h | 1.8 (1.4) | 1.7 (1.4) | 1.9 (1.4) | .44 |
| Time of injury to bolus dose, mean (SD), h | 3.3 (1.7) | 3.1 (1.5) | 3.4 (1.7) | .16 |
| Time center admission to start maintenance dose, mean (SD), h | 3.6 (1.6) | 3.6 (1.5) | 3.6 (1.5) | .97 |

*24 MP indicates the treatment group that received a methylprednisolone infusion for 24 hours; 48TM indicates the treatment group that received a tirilazad mesylate infusion for 48 hours; and 48MP indicates the treatment group that received a methylprednisolone infusion for 48 hours. Plus-minus values are means±SE.
†Includes sports-related injuries, n=23; pedestrian injuries, n=20; assault, n=12; and other, n=5.
‡Extent of injury was assessed by a neurologic examiner in the emergency department.

Association criteria[23] but was not used in these analyses, which replicate NASCIS 2 scoring. Possible scores were 0, no contraction; 1, a trace of contraction; 2, active movement without antigravity; 3, active movement with antigravity; 4, active movement against resistance; and 5, normal function. Expanded neurologic scores summed the neurologic score for each segment, ranging from 0 (no contraction in any muscle) to 70 (all normal responses).

Patients were classified as follows: quadriplegic, if the most cephalad muscle with no contraction was the first dorsal interosseous (C-8 to T-1) or higher with no contraction in any distal muscle; paraplegic, if the most cephalad muscle with no contraction was below the first dorsal interosseous with no contraction in any distal muscle; quadriparetic, if the most cephalad muscle with a trace of contraction or active movement without antigravity was the first dorsal interosseous or higher; paraparetic, if the most cephalad muscle with a trace of contraction or active movement without antigravity was below the first dorsal interosseous; and normal, if impairment was slight.

**Sensory Function.**—Response to pinprick and light touch was evaluated and scored bilaterally from C-2 through S-5 as 1, absent; 2, dysfunctional (including hyperesthesia); and 3, normal, for 29 spinal cord segments. Expanded scores ranged from 29 (all responses absent) to 87 (all responses normal). Patients were classified as analgesic and anesthetic at or above T-1 if response to pinprick and touch, respectively, was absent at or above T-1 and all distal segments; analgesic and anesthetic below T-1 if response to pinprick and touch was absent below T-1 and all distal segments; hypalgesic and hypoesthetic at or above T-1 if response to pinprick and touch at or above T-1 was dysfunctional, hypalgesic and hypoesthetic below T-1 if sensation was diminished below T-1; and normal if all responses were normal. Responses to deep pain and pressure were evaluated bilaterally in the wrist, thumb, little finger, knee, ankle, and great toe as 1, absent; 2, decreased; and 3, normal. Expanded scores ranged from 6 (all responses absent) to 18 (all responses normal).

Complete neurologic loss was defined as patients experiencing no motor contraction and absent sensation below the injury level, defined by highest dysfunctional level.

## Functional Independence Measure

Patients were evaluated using the Functional Independence Measure (FIM) at 6 weeks and 6 months.[24] The FIM measures self-care, sphincter control, mo-

Table 2.—Neurologic Status on Admission, According to Treatment Protocol*

| Status | Protocols 24MP | 48TM | 48MP | P Value |
|---|---|---|---|---|
| Motor function, % (n=494) | | | | |
| Quadriplegic | 31.5 | 44.0 | 30.1 | |
| Paraplegic | 29.0 | 27.1 | 36.8 | |
| Quadriparetic | 12.4 | 12.6 | 15.1 | .007 |
| Paraparetic | 2.5 | 5.4 | 4.2 | |
| Normal | 24.7 | 10.8 | 13.9 | |
| Mean expanded motor score | 33.9 | 26.5 | 30.5 | .006 |
| Response to pinprick, % (n=498) | | | | |
| Analgesic at or above T-1 | 23.6 | 32.3 | 23.5 | |
| Analgesic below T-1 | 30.9 | 27.5 | 34.3 | |
| Hypalgesia at or above T-1 | 18.3 | 18.6 | 21.1 | .46 |
| Hypalgesia below T-1 | 15.8 | 10.8 | 9.6 | |
| Normal | 10.9 | 10.8 | 11.4 | |
| Mean expanded pinprick score | 60.6 | 58.3 | 60.4 | .46 |
| Response to light touch, % (n=496) | | | | |
| Anesthetic at or above T-1 | 21.3 | 31.5 | 22.4 | |
| Anesthetic below T-1 | 31.1 | 27.3 | 32.7 | |
| Hypesthetic at or above T-1 | 18.9 | 16.4 | 20.6 | .51 |
| Hypesthetic below T-1 | 14.0 | 10.9 | 9.7 | |
| Normal | 14.6 | 13.9 | 14.6 | |
| Mean expanded touch score | 62.0 | 59.4 | 61.3 | .44 |

*No patients had normal findings on all 3 neurologic parameters. Treatment groups are defined in the first footnote to Table 1.

Table 3.—Change in Motor Function 6 Weeks and 6 Months After Injury by Time to Initiation of Treatment and Compliance With Treatment Protocol*

| Time to Initiation of Treatment | Protocols: At 6 Weeks 24MP | 48TM | 48MP | At 6 Months 24MP | 48TM | 48MP |
|---|---|---|---|---|---|---|
| <8 h | | | | | | |
| Intent to treat, No. | 151 | 156 | 154 | 142 | 149 | 149 |
| Change in score | 9.0 | 10.2 | 11.8 | 13.4 | 14.4 | 16.8 |
| *P* value | . . . | .48 | .09 | . . . | .58 | .07 |
| Compliers, No. | 144 | 139 | 145 | 136 | 131 | 141 |
| Change in score | 8.8 | 10.4 | 12.4 | 13.2 | 14.7 | 16.9 |
| *P* value | . . . | .37 | .04 | . . . | .44 | .06 |
| <3 h | | | | | | |
| Intent to treat, No. | 75 | 86 | 70 | 71 | 85 | 69 |
| Change in score | 10.5 | 10.9 | 11.1 | 15.5 | 15.5 | 15.7 |
| *P* value | . . . | .87 | .80 | . . . | .99 | .95 |
| Compliers, No. | 72 | 74 | 65 | 68 | 72 | 64 |
| Change in score | 10.6 | 11.2 | 11.3 | 15.5 | 16.0 | 15.6 |
| *P* value | . . . | .81 | .80 | . . . | .87 | .98 |
| 3-8 h | | | | | | |
| Intent to treat, No. | 76 | 70 | 84 | 71 | 64 | 80 |
| Change in score | 7.6 | 9.5 | 12.5 | 11.2 | 13.0 | 17.6 |
| *P* value | . . . | .44 | .04 | . . . | .51 | .01 |
| Compliers, No. | 72 | 65 | 80 | 68 | 59 | 77 |
| Change in score | 7.0 | 9.5 | 13.4 | 10.8 | 13.3 | 18.0 |
| *P* value | . . . | .31 | .008 | . . . | .40 | .008 |

*Treatment groups are defined in the first footnote to Table 1. The *P* values were determined from an analysis of covariance that contained parameters for the initial motor score obtained in the emergency department and a protocol by time interaction. Ellipses indicate reference value. Scores for motor function range from 0 to 70. Motor scores were not obtained during some examinations because of casts, braces, and other immobilization requirements.

bility, locomotion, communication, and social cognition, and provides an overall score of function ranging from 18, indicating the need for assistance in all areas, to 126, indicating complete independence. Patients are grouped into 4 categories depending on whether they need assistance: complete dependence (help is needed but patient may assist 25% of the time), modified dependence (patient can function between 50% and 75% of the time or needs supervision), modified independence (patient does not need help but uses devices), and complete independence. All study nurses were credentialed to perform FIM examinations.[25]

### Compliance

Protocol violations occurred when a patient was not given the designated study drug dose. Noncompliance was analyzed only if it involved active drug administration. In addition to the intent-to-treat analysis, analyses of compliers were performed to examine treatment effects among optimally dosed patients.

### Statistical Analysis

All analyses were preplanned by protocol. The primary end point was change in neurologic function between baseline and follow-up examination. The trial was designed to detect motor change score differences of 5+ with $\alpha = .05$ and $\beta = .20$, which required 150 patients in each group. Analysis of variance tested the hypothesis that the change score was not different across treatment groups. Calculations used the GLM procedure in SAS statistical software,[26] and overall significance was tested using type III sums of squares. We summarized results according to time the bolus was received ($\leq 3$ or $>3$ hours, the modal value from injury) and degree of neurologic loss (complete or incomplete). Analysis of neurologic scores used data from the right side of the body. In the few instances for which these data were unavailable, the left side was used. (The number of these instances varied by examination time and modality tested, but it was never more than 2.5% of the examinations.) Two-tailed significance tests were used with a nominal *P* value of .05.

To adjust for the effect of baseline measures on neurologic change, analysis of covariance used the initial measure of function as a covariate. Adjusted means were used as the summary. If there was significant lack of parallelism, such as the interaction between baseline neurologic function and degree of neurologic loss (complete or incomplete), adjusted means resulting from an analysis including the interaction are appropriate for drug protocol comparisons within the complete and incomplete groups.

A summary of patient survival used the product-limit estimator of the survival curve, truncating follow-up at 213 days. The curves of the 3 treatment groups were compared using the log-rank test, calculated using LIFETEST in SAS software.[26]

## RESULTS

A total of 499 patients were randomized (485 planned) and were evenly distributed by protocol at each collaborat-

ing center. Study patients were predominantly male, white, and aged 14 to 34 years (Table 1). Cause of injury was most likely a motor vehicle crash or a fall. The majority of patients were without major comorbidity (by design) and were conscious at admission. Approximately half the patients (49.7%) had complete spinal cord injuries, and 77.2% had spinal fractures, including 50.7% with fracture dislocations. Patients treated with tirilazad had lower blood pressure at entry to the study (about 5 mm Hg), significantly so for diastolic pressure compared with both methylprednisolone groups. Overall, 69.8% of patients were admitted directly to a study center, and 71.9% received a methylprednisolone bolus before entering the study center. Average times from injury to admission and infusion of bolus and from center admission to starting maintenance infusion were equivalent in all 3 protocols.

Patients randomized to receive tirilazad had significantly worse motor function than patients randomized to either methylprednisolone group (Table 2). However, the difference in motor function between the 2 methylprednisolone groups was not significant ($P=.10$). Smaller differences were seen for the pinprick and light touch measures.

Motor function change scores are shown for 6 weeks and 6 months (Table 3). Compared with patients receiving 24-hour methylprednisolone, those given a 48-hour treatment of the same drug showed more motor function recovery at 6 weeks and 6 months in the intent-to-treat analysis (change scores, 9.0 vs 11.8 [$P=.09$] and 13.4 vs 16.8 [$P=.07$], respectively). When the 38 noncompliers were excluded, these differences increased ($P=.04$ and $P=.06$, respectively). Stratification by time to beginning of treatment showed essentially identical rates of motor recovery among patients treated less than 3 hours after injury, irrespective of treatment protocol. Among patients who started treatment between 3 and 8 hours of injury, the 48-hour methylprednisolone group recovered significantly more motor function at 6 weeks and 6 months than those given 24-hour methylprednisolone (7.6 vs 12.5 [$P=.04$] and 11.2 vs 17.6 [$P=.01$], respectively). These differences also were greater in the compliers' analysis ($P=.01$ for both time periods). In all motor function comparisons, patients who received 48 hours of tirilazad recovered at rates equal to or slightly higher than patients in the 24-hour methylprednisolone group, but no difference approached nominal statistical significance.

As expected, overall neurologic recovery was considerably greater in patients with incomplete vs complete injuries. The 24- and 48-hour methylprednisolone group motor change scores for patients with complete injuries at 6 weeks were 1.7 and 4.6 ($P=.08$), and at 6 months 1.9 and 6.1 ($P=.05$), respectively (intent-to-treat analysis). The corresponding scores for patients with incomplete lesions were 19.8 and 22.0 ($P=.16$) at 6 weeks and 25.3 and 28.1 ($P=.18$) at 6 months. These differences were all enhanced among protocol compliers: 1.6 and 4.8 ($P=.05$) at 6 weeks and 1.7 and 6.5 ($P=.03$) at 6 months for patients with complete injuries; and 20.1 and 24.2 ($P=.02$) at 6 weeks and 25.4 and 28.9 ($P=.12$) at 6 months for those with incomplete injuries. Patients receiving tirilazad recovered at rates between the 2 methylprednisolone groups and no comparisons reached nominal statistical significance.

All analyses were repeated for sensory function using deep pain, pinprick, and light touch sensation. Patterns of recovery were essentially the same as those for motor function, although treatment differences tended to be smaller and less likely to achieve statistical significance. For example, among patients starting treatment 3 to 8 hours after injury, the 24-hour methylprednisolone, tirilazad, and 48-hour methylprednisolone pain recovery scores at 6 months were 1.9, 2.3 ($P=.41$), and 3.0 ($P=.13$), respectively (using intent-to-treat adjusted for baseline). At 6 months, the respective pinprick sensation recovery scores were 8.0, 8.1 ($P=.98$), and 9.7 ($P=.39$); and light touch recovery scores were 9.0, 8.4 ($P=.80$), and 9.0 ($P=.99$).

Improvement on the FIM was greater 6 months after injury in all patients given 48-hour vs 24-hour methylprednisolone as assessed by total FIM score ($P=.08$), self-care ($P=.03$), and sphincter control ($P=.01$) (Table 4). Mobility scores showed more modest improvement ($P=.12$), and locomotion, communication, and social cognition were not influenced by treatment. Among compliers, respective dif-

Table 4.—Change in Functional Independence (FIM) 6 Weeks and 6 Months After Injury by Compliance and Treatment Protocol*

| | Protocols | | | | | |
|---|---|---|---|---|---|---|
| | At 6 Weeks | | | At 6 Months | | |
| Compliance | 24MP | 48TM | 48MP | 24MP | 48TM | 48MP |
| Intent-to-treat | n=151 | n=156 | n=154 | n=142 | n=149 | n=149 |
| Total FIM | 84.5 | 85.4 | 85.0 | 99.1 | 100.5 | 103.3 |
| *P* value | ... | .72 | .86 | ... | .57 | .08 |
| Self-care | 24.4 | 25.2 | 25.8 | 30.9 | 32.0 | 33.3 |
| *P* value | ... | .44 | .17 | ... | .34 | .03 |
| Sphincter control | 7.5 | 7.7 | 7.9 | 9.4 | 9.9 | 10.5 |
| *P* value | ... | .57 | .36 | ... | .27 | .01 |
| Mobility | 11.3 | 11.2 | 11.5 | 14.7 | 15.1 | 15.8 |
| *P* value | ... | .85 | .72 | ... | .58 | .12 |
| Locomotion | 7.6 | 7.6 | 7.4 | 9.4 | 9.4 | 9.5 |
| *P* value | ... | .99 | .68 | ... | .99 | .77 |
| Communication | 13.6 | 13.4 | 13.3 | 13.9 | 13.7 | 13.9 |
| *P* value | ... | .29 | .08 | ... | .08 | .75 |
| Social cognition | 20.1 | 19.9 | 19.4 | 20.7 | 20.4 | 20.5 |
| *P* value | ... | .38 | .03 | ... | .09 | .23 |
| Compliers | n=144 | n=139 | n=145 | n=136 | n=131 | n=141 |
| Total FIM | 84.0 | 85.2 | 86.6 | 98.9 | 101.0 | 103.8 |
| *P* value | ... | .64 | .29 | ... | .40 | .05 |
| Self-care | 24.3 | 25.3 | 26.2 | 30.8 | 32.2 | 33.5 |
| *P* value | ... | .32 | .06 | ... | .23 | .02 |
| Sphincter control | 7.4 | 7.8 | 7.9 | 9.3 | 10.0 | 10.5 |
| *P* value | ... | .34 | .24 | ... | .13 | .01 |
| Mobility | 11.2 | 11.2 | 11.7 | 14.7 | 15.2 | 15.9 |
| *P* value | ... | >.99 | .46 | ... | .51 | .08 |
| Locomotion | 7.5 | 7.5 | 7.6 | 9.4 | 9.4 | 9.6 |
| *P* value | ... | .83 | .73 | ... | .92 | .67 |
| Communication | 13.6 | 13.4 | 13.5 | 13.9 | 13.7 | 13.9 |
| *P* | ... | .14 | .46 | ... | .11 | .56 |
| Social cognition | 20.1 | 19.8 | 19.7 | 20.7 | 20.4 | 20.5 |
| *P* value | ... | .27 | .20 | ... | .15 | .37 |

*Treatment groups are defined in the first footnote to Table 1. From an analysis of covariance adjusted for initial motor scores obtained in emergency department. *P* values denote change in FIM score. Ellipses indicate reference value.

Table 5.—Six-Week Complications by Degree of Severity and Treatment Protocol*

| Complications | Severity | Protocols | | | P Value |
|---|---|---|---|---|---|
| | | 24MP | 48TM | 48MP | |
| Evaluable respondents, No. | ... | 154 | 157 | 154 | ... |
| Urinary tract infection | Mild-moderate | 34.4 | 36.3 | 38.3 | .78 |
| Decubiti | Mild-moderate | 12.3 | 18.5 | 13.6 | .28 |
| | Severe | 0.6 | 0.6 | 0.6 | >.99 |
| Other infection | Mild-moderate | 3.9 | 4.4 | 7.8 | .26 |
| Phlebitis | Mild-moderate | 2.6 | 1.9 | 1.3 | .71 |
| | Severe | 0 | 0.6 | 0 | .37 |
| Incision, pin, halo infection | Mild-moderate | 1.9 | 3.2 | 2.6 | .79 |
| | Severe | 0.6 | 0 | 1.9 | .17 |
| Sepsis | Mild-moderate | 3.9 | 3.2 | 4.5 | .82 |
| | Severe | 0.6 | 0 | 2.6 | .07 |
| Adult RDS | Mild-moderate | 1.9 | 2.5 | 1.9 | .44 |
| | Severe | 1.3 | 1.9 | 1.9 | .37 |
| Atelectasis | Mild-moderate | 5.2 | 9.5 | 7.1 | .33 |
| | Severe | 0 | 0.6 | 0 | .37 |
| Other respiratory failure | Mild-moderate | 7.8 | 9.1 | 9.1 | .91 |
| | Severe | 1.9 | 1.3 | 3.2 | .48 |
| Pneumonia | Mild-moderate | 12.3 | 13.4 | 11.0 | .82 |
| | Severe | 2.6 | 0.6 | 5.8 | .02 |
| GI hemorrhage | Mild-moderate | 0 | 1.3 | 1.3 | .37 |
| | Severe | 0 | 0 | 0.6 | .36 |
| Bradycardia | Mild-moderate | 2.6 | 0 | 0.6 | .07 |
| | Severe | 1.3 | 2.5 | 0 | .14 |
| Tachycardia | Mild-moderate | 0.6 | 0.6 | 2.6 | .21 |
| Other arrhythmia | Mild-moderate | 0.6 | 1.3 | 1.9 | .60 |
| Thrombophlebitis | Mild-moderate | 2.6 | 5.1 | 4.5 | .51 |
| | Severe | 0.6 | 1.3 | 0 | .37 |
| Pulmonary embolus | Mild-moderate | 0 | 0.6 | 0.6 | .37 |
| | Severe | 1.3 | 1.9 | 0.6 | .37 |
| Paralytic ileus | Mild-moderate | 1.3 | 2.5 | 3.2 | .53 |
| | Severe | 0 | 0 | 0.6 | .36 |
| Other complications | Mild-moderate | 11.7 | 15.3 | 18.2 | .28 |
| | Severe | 4.5 | 5.7 | 5.8 | .85 |

*Treatment groups are defined in the first footnote to Table 1. Values are %. RDS indicates respiratory distress syndrome; and GI, gastrointestinal.

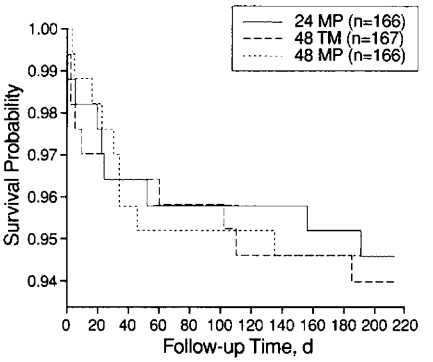


Figure 2.—Survival probability for patients in each treatment group 6 months after acute spinal cord injury. Log rank test=0.07, 2 df, $P$=.97. Treatment groups are defined in the first footnote to Table 1.

ferences were total FIM ($P$=.05), self-care ($P$=.02), sphincter control ($P$=.01), and mobility ($P$=.08). Patients treated with tirilazad generally improved on the FIM at rates between the 2 methylprednisolone groups. When time to treatment and completeness of initial injury were considered, the patterns of FIM recovery were similar to those observed for motor function.

We examined whether improved neurologic recovery was sufficient to reassign patients from 1 of the 4 dysfunctional categories (Table 2) to a higher functional group. Using intent-to-treat analysis at 6 months, 56.2% of patients treated with the 48-hour methylprednisolone regimen improved at least 1 full category compared with 44.0% of patients in the 24-hour methylprednisolone group (relative risk, 1.28; 95% confidence interval, 0.98-1.68; $P$=.06). Respective improvement rates for patients starting treatment 3 to 8 hours after injury were 59.2% and 39.3% (relative risk, 1.51; 95% confidence interval, 1.03-2.20; $P$=.03). Corresponding improvement for patients receiving tirilazad was not statistically significant.

The differences in complications among the 3 treatment groups at 6 weeks were small (Table 5). The notable exceptions were severe sepsis (reported in 2.6% of patients in the 48-hour methylprednisolone group compared with 0% in the 48-hour tirilazad group and 0.6% in the 24-hour methylprednisolone group [$P$=.07]) and severe pneumonia (with rates of 5.8%, 0.6%, and 2.6% [$P$=.02], respectively). Survival was similar in all 3 groups (Figure 2).

## COMMENT

We observed significantly improved motor function at 6 weeks and 6 months after injury in patients treated with high doses of methylprednisolone for 48 hours compared with 24-hour methylprednisolone treatment. The difference in recovery occurred only among patients starting treatment 3 to 8 hours after injury. Patients starting treatment before 3 hours from injury showed essentially the same recovery pattern in all treatment regimens. Extending methylprednisolone maintenance in patients treated after 3 hours is likely to be beneficial because interrupting posttraumatic spinal cord pathophysiology is more difficult the longer initial treatment is delayed. Single-bolus dosing does not attenuate posttraumatic spinal ischemia,[25,27,28] and experimental models that have successfully used 48-hour dosing[29] did not directly compare 24-hour and 48-hour regimens. Hall[13] has suggested that lipid peroxidation reactions are fueled by hemoglobin,[30] which may not peak in spinal tissue for hours or days, as is found after subarachnoid hemorrhage for delayed hemoglobin oxidation in the subarachnoid clot.[31]

We observed functional recovery that correlated with neurologic recovery. Although statistically significant, differences in FIM recovery were relatively small and appear to benefit upper body function, as represented by self-care and mobility, more than actual locomotion. Nonetheless, even small improvements in functional activity can influence quality of life in patients recovering from acute spinal cord injury.

We have previously described a method for distinguishing separate components of neurologic recovery that includes recovery of segmental function, which could represent recovery of nerve roots at the injury level, and recovery of neurologic function below the injury level, which must be due to improved function of long spinal tracts.[8] As in NASCIS 2,[9] most recovery in this study occurred below the lesion level. For example, this accounted for 85.6%, 85.5%, and 89.9% of all motor function recovery at 6 months in the 24-hour methylprednisolone, 48-hour tirilazad, and 48-hour methylprednisolone groups, respectively.

These results provide a rationale to prolong maintenance infusion of high-dose methylprednisolone to 48 hours in patients who begin treatment more than 3 hours after injury. If patients in this trial are comparable to all patients, almost all spinal cord–injured patients could start treatment within 8 hours but only half of these within 3 hours. Thus, approximately half of patients who fulfill the eligibility criteria for our study could benefit from extending the length of their methylprednisolone therapy.

The 48-hour treatment with tirilazad (2.5 mg/kg every 6 hours) provided equivalent recovery to 24-hour administration of methylprednisolone. However, tirilazad was given after a methylprednisolone bolus of 30 mg/kg, and the study design does not permit us to distinguish the effect of bolus from maintenance dose. Our study indicates that for many patients, 48-hour methylprednisolone is more effective than 24-hour dosing. It seems logical, therefore, that either 24-hour methylprednisolone dosing or a methylprednisolone bolus with a 48-hour dosing of tirilazad, which show equivalent efficacy, would be superior to a single methylprednisolone bolus. Although the benefits of a single high-dose bolus of methylprednisolone have not been clinically studied, it has been shown in spinal-injured animals[25,27] that single-dose administration does not adequately interrupt posttraumatic pathophysiology.

As we hypothesized, 48-hour tirilazad showed some advantage over 48-hour methylprednisolone in producing fewer complications since tirilazad is devoid of glucocorticoid adverse effect potential.[15] However, these differences were small, and complications with the largest increase using 48-hour methylprednisolone (ie, severe sepsis and severe pneumonia) were rare, are usually amenable to treatment, and did not increase mortality. A recent trial that examined the efficacy of tirilazad for subarachnoid hemorrhage suggested that women may metabolize the drug more rapidly than men, which may result in lower blood levels and reduced neuroprotective activity.[32] When only male patients were analyzed, there was no meaningful difference in the treatment effects seen for the entire sample.

Tirilazad is a powerful lipid peroxidation inhibitor,[22] and its use in our trial, to some extent, tested the lipid peroxidation hypothesis.[33,34] Insofar as equivalence with 24-hour methylprednisolone is suggested, the study supports a major role for lipid peroxidation and hydrolytic destruction of neuronal and microvascular membranes in the secondary injury processes following acute spinal cord injury.

Failure of 48-hour tirilazad to improve neurologic recovery as much as 48-hour methylprednisolone has several possible explanations. First, the benefits of high-dose methylprednisolone may be due to additional mechanisms beyond lipid peroxidation inhibition, particularly the well-known anti-inflammatory action of methylprednisolone.[12,13] However, in animal studies, doses of methylprednisolone that effectively inhibit lipid peroxidation failed to exert a readily apparent anti-inflammatory action. Posttraumatic administration of high-dose methylprednisolone does not significantly reduce posttraumatic elevation in spinal cord levels of potentially deleterious prostaglandins or thromboxane[35] or delayed posttraumatic influx of polymorphonuclear leukocytes.[36] Second, the reduced effect of 48-hour tirilazad may be due to a less-than-optimal dose or regimen. Third, patients randomized to receive tirilazad had significantly worse motor scores prior to treatment in comparison with both methylprednisolone groups, a difference that statistical correction by baseline scores may not fully alleviate.

Although the present study does not provide a rationale for the clinical use of tirilazad to treat spinal injury, the apparent efficacy of the compound suggests that further study with alternative dosing regimens is worthwhile. Indication of fewer adverse effects in comparison with 48-hour methylprednisolone implies that tirilazad dosing could be studied beyond 48 hours to inhibit posttraumatic lipid peroxidative pathophysiology more effectively.

In summary, NASCIS 3 demonstrates that patients initiating methylprednisolone treatment within 3 hours of injury should be maintained on the treatment regimen for 24 hours. Patients initiating treatment 3 to 8 hours after injury should have their maintenance dose extended for 48 hours.

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