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Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data

Results of the second National Acute Spinal Cord Injury Study

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✓ The 1-year follow-up data of a multicenter randomized controlled trial of methylprednisolone (30 mg/kg bolus and 5.4 mg/kg/hr for 23 hours) or naloxone (5.4 mg/kg bolus and 4.0 mg/kg/hr for 23 hours) treatment for acute spinal cord injury are reported and compared with placebo results. In patients treated with methylprednisolone within 8 hours of injury, increased recovery of neurological function was seen at 6 weeks and at 6 months and continued to be observed 1 year after injury. For motor function, this difference was statistically significant ($p = 0.030$), and was found in patients with total sensory and motor loss in the emergency room ($p = 0.019$) and in those with some preservation of motor and sensory function ($p = 0.024$). Naloxone-treated patients did not show significantly greater recovery. Patients treated after 8 hours of injury recovered less motor function if receiving methylprednisolone ($p = 0.08$) or naloxone ($p = 0.10$) as compared with those given placebo. Complication and mortality rates were similar in either group of treated patients as compared with the placebo group. The authors conclude that treatment with the study dose of methylprednisolone is indicated for acute spinal cord trauma, but only if it can be started within 8 hours of injury.

KEY WORDS • **acute spinal cord injury** • **methylprednisolone** • **naloxone** • **randomized clinical trial**

A RANDOMIZED double-blind clinical trial of the efficacy of very high doses of methylprednisolone or naloxone, compared with placebo, in the early treatment of acute spinal cord injury was conducted. In a previous report,[8] we have shown that neurological function is significantly improved 6 weeks and 6 months after injury among patients starting methylprednisolone treatment within 8 hours of injury. In this paper, we report the 1-year follow-up results of this trial: the second National Acute Spinal Cord Injury Study (NASCIS). We provide further details about the characteristics of patients entering the study, document the full list of complications collected by the study, and report the 1-year mortality data.

Clinical Material and Methods

The study methods have been previously reported in detail[8] and are summarized here.

Organization

Ten medical centers in eight states (see Appendix) collaborated in this randomized clinical trial. A research nurse at each center coordinated daily study activities, drug administration, and all neurological examinations according to predetermined study criteria. Random assignment of patients to treatment groups was provided 24 hours a day via telephone at the coordinating center, where all aspects of the study were monitored.

Patient Recruitment and Randomization

The first patient entered the study on May 14, 1985, and the last on December 18, 1988. The last 1-year neurological follow-up examination was completed on January 22, 1990. Patients were eligible to be enrolled in the study if they were diagnosed in the emergency room as having an acute spinal cord injury according to a standardized neurological examination and they consented to participate and were randomly assigned to a treatment group within 12 hours of injury. Reasons for exclusion from the study included: 1) the patient had spinal nerve root damage or cauda equina only; 2) the injury was a gunshot wound; 3) other life-threatening morbidity was present; 4) pregnancy; 5) the patient was receiving maintenance steroids for other reasons; 5) addiction to narcotics; 6) age under 13 years; 7) the patient had received more than 100 mg of methylprednisolone (or its equivalent) or 1 mg of naloxone before admission to the center; and 8) follow-up monitoring was anticipated to be difficult.

Once eligibility was confirmed, the attending physician telephoned the pharmacist at the coordinating center. The pharmacist calculated the patient's body mass according to body surface area, for drug dosage purposes, and assigned the patient to a treatment arm using predetermined randomized lists. Every aspect of the study, including drug preparation and administration, neurological examinations, and statistical analysis, was carried out in a blinded fashion.

Drug Preparation and Administration

Methylprednisolone and its placebo were provided in 16-vial sets of 1-gm vials and were reconstituted with diluent provided with the drug to a concentration of 62.5 mg/ml. The diluent contained benzyl alcohol as a preservative. The reconstituted methylprednisolone was further diluted to a final concentration of 50 mg/ml by adding sufficient sterile water for infusion of the bolus and maintenance dose, including an additional 50 ml to prime the pumps.

Naloxone and its placebo were provided in 100-ampule sets of 2-ml parabenz-free solutions, prepared at a concentration of 25.0 mg/ml.

Each drug or its placebo required its own infusion pump, and each patient received one of three regimens: 1) one pump infused methylprednisolone and the other infused placebo for naloxone; 2) one pump infused placebo for methylprednisolone and the other infused naloxone; and 3) both pumps infused placebo. Each drug was administered as a 15-minute bolus, followed by a 45-minute pause and then a 23-hour infusion. For the methylprednisolone treatment, the bolus was 30 mg/kg and the maintenance infusion 5.4 mg/kg/hr; for the naloxone treatment, the bolus was 5.4 mg/kg and the maintenance infusion 4.0 mg/kg/hr. Drug dosage was calculated by patient body surface area so that the experimental doses derived from animal studies could be more closely approximated within a randomized controlled trial. Actual dosing schedules have been reported previously.[8]

Neurological Function Assessment

Neurological examinations were completed according to standardized protocols on admission to the center and at 6 weeks, 6 months, and 1 year after injury. The present paper is concerned with the 1-year follow-up examination, which had to be completed within a "window" of 365 to 425 days after injury. Evaluations of motor function and response to pinprick and touch sensation were recorded at each examination. On admission, complete injuries were defined as those below which the patient had no motor or sensory function, while patients with any residual distal motor or sensory function were defined as having incomplete injuries.

Motor Function

Six classifications were used to record motor function scores in 14 muscle segments: 0 = no contraction; 1 = reduced contraction; 2 = active movement without antigravity strength; 3 = active movement with antigravity strength; 4 = reduced function but active movement against resistance; and 5 = normal function. Expanded motor scores ranged from 0 (no contraction in any muscle) to 70 (all normal responses) and were obtained separately for the right and left sides.

Patients were categorized according to the degree of their paralysis as follows: 1) quadriplegic when the most cephalad muscle with no contraction was the first dorsal interosseous (C-8 to T-1) muscle or higher, and there was no contraction in any distal muscle; 2) paraplegic when the most cephalad muscle with no contraction was below the first dorsal interosseous muscle, and there was no contraction in any distal muscle; 3) quadriparetic when the most cephalad muscle with a trace of contraction or active movement without antigravity strength was the first dorsal interosseous muscle or higher; 4) paraparetic when the most cephalad muscle with a trace of contraction or active movement without antigravity strength was below the first dorsal interosseous muscle; and 5) normal when responses were normal or only minimally impaired.

Pinprick and Light Touch Sensations

Twenty-nine segments from C-2 through S-5 were evaluated bilaterally and their function was assessed (and scored) as absent (1), decreased (2), or normal (3). An expanded score for each measurement ranged from 29 (absent at all levels) to 87 (normal at all levels). In addition to being given this expanded neurological score, each patient was classified in one of five categories: 1) analgesic and anesthesic at or above T-1, if the sensations of pinprick and touch, respectively, were absent at T-1 or above and in all distal segments; 2) analgesic and anesthesic below T-1, if the sensations were absent below T-1 and in all distal segments; 3) hypalgesic and hypesthesic at or above T-1, if sensations

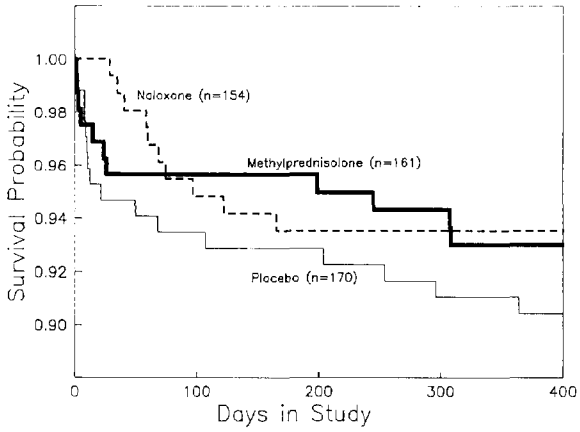

FIG. 1. Survival probability for patients in each treatment group 1 year after acute spinal cord injury. Log-rank test = 1.29, p = 0.525; n = number of cases.

were decreased at T-1 or above; 4) hypalgesic and hypesthesic below T-1, if the sensations were decreased below T-1; and 5) normal, if the sensations at segments were evaluated as normal.

Statistical Analysis

Changes in neurological function between admission to the emergency room and the 1-year examination were the primary study endpoints. Analysis of variance (two-tailed) tested preplanned hypotheses that the change in score did not differ: 1) across the three treatment groups overall; 2) according to the time the drug was first received (≤ 8 or > 8 hours from injury); and 3) according to the completeness of initial injury. Data from the right side of the body were arbitrarily chosen for the NASCIS analysis. Earlier analysis showed that using data from the left side did not materially influence the results. The analyses were also checked to see that assumptions inherent to the analysis of variance did not influence the statistical results.[8] The five injury categories were analyzed using a log-linear model[3] calculated from generalized linear interactive modeling.* The summary of 1-year survival was based on the product-limit estimator of the survival curves,[42] which were compared across study treatment using the log-rank test[41] from the PROC LIFETEST procedure in SAS.†

Results

Overall, 487 patients were randomly assigned to a treatment group and 427 (95%) of the surviving patients had a 1-year neurological examination. The mortality status was obtained at 1 year after treatment on 100% of the patients in the study. Figure 1 shows the survival curves for each treatment group during the 1st year after injury. The three curves are not significantly different (log-rank test = 1.29, p = 0.525).

TABLE 1

*Entry pattern of randomized patients correlated with treatment protocol**

Entry Pattern	Treatment Group			p Value
	Methylprednisolone	Naloxone	Placebo	
no. of cases	162	154	171	
% admitted directly to center	48.8	42.2	48.0	0.45
drugs delivered before randomization				
cases studied	149	148	169	
% no	91.3	88.5	85.8	0.31
% yes	8.7	11.5	14.2	
drugs delivered before admission				
cases studied	13	17	24	
% dexamethasone	76.9	82.4	91.7	
% methylprednisolone	0.0	5.9	4.2	0.49
% hydrocortisone	7.7	0.0	0.0	
% naloxone hydrochloride	15.4	11.8	4.2	
immobilization prior to admission to center				
cases studied	161	154	171	
% tongs	10.6	9.1	7.6	
% cervical collar	77.0	81.2	79.0	
% positioning	5.6	5.8	8.2	0.82
% sandbags	1.9	1.3	2.3	
% other	3.7	1.3	1.2	
% none	1.2	1.3	1.8	
time: accident to loading dose				
cases studied	157	154	167	
mean time (hrs)	8.9 ± 3.1	8.8 ± 3.0	8.6 ± 2.8	0.70
time: admission to loading dose				
cases studied	157	154	167	
mean time (hrs)	5.9 ± 3.6	5.3 ± 2.3	5.5 ± 2.5	0.26

* Mean values are expressed ± standard deviation.

Characteristics of the Study Population

The demographic and clinical characteristics of the study population have previously been shown to be evenly distributed across the three treatment groups (as expected from randomization) and to be typical of many series of patients with acute spinal cord injury.[8] Additional comparisons are reported here. All but two patients (one treated by methylprednisolone and one by placebo) had closed wounds. The intravenous lines for administering the study drug were placed in peripheral veins for 93% of patients; the rest received central venous placement with no significant difference between treatment groups (p = 0.72).

The entry pattern of the patients in the study is shown in Table 1. Less than half of the patients were admitted directly to the study center, and the great majority did not receive steroids or naloxone before admission. The mean times from center admission to loading dose were between 5 and 6 hours and from

* GLIM System Release 3.77 Update (0), developed by the Royal Statistical Society, Numerical Algorithms Group, London, England.

† PROC LIFETEST application developed by SAS Institute, Cary, North Carolina.

TABLE 2

Radiographic findings at admission and operative procedures during first 6 weeks after injury

Diagnostic Test	Treatment Group			p Value
	Methylpred-nisolone	Naloxone	Placebo	
plain x-ray film				
cases studied	162	154	171	
% no fracture/dislocation	16.1	12.3	12.9	
% fracture only	16.1	17.5	22.2	0.73
% dislocation only	8.6	12.3	8.8	
% fracture/dislocation	58.0	57.8	55.6	
% x-ray films not taken	0.6	0.0	0.6	
computerized tomography				
cases studied	121	120	134	
% bone fragments	45.5	40.0	49.3	0.33
% soft tissue	5.8	6.7	6.7	0.95
% hemorrhage	8.3	6.7	7.5	0.90
% other	38.8	39.2	38.8	0.99
operative treatment				
surgical cases	160	154	170	
anterior approach	10.0	14.9	10.6	0.33
% excise body	4.4	7.8	7.1	0.42
% fusion	9.4	12.3	9.4	0.61
% internal fixation	3.1	3.9	3.5	0.93
% excise disc	6.2	8.4	7.1	0.75
posterior approach	51.2	52.0	51.8	0.99
% laminectomy	15.0	17.5	15.9	0.84
% dura opened	1.2	2.6	1.2	0.54
% cord opened	0.0	0.0	0.6	0.40
% fusion	47.5	45.4	45.9	0.93
% interior fixation	43.8	41.6	42.9	0.92
% excise disc	1.9	3.2	0.0	0.07

TABLE 3

Frequency of drug and other protocol violations

Protocols & Violations	Treatment Group			p Value
	Methylpred-nisolone	Naloxone	Placebo	
drug protocol violations				
cases studied*	157	154	168	
drug administered within protocol time limit (%)†	80.3	76.6	82.7	0.39
drug administered within protocol dose (%)	89.8	92.9	93.5	0.43
other protocol violations				
cases studied	162	154	171	
no other violations (%)	90.1	96.8	93.6	0.09
ineligible for study (%)‡	6.1	1.3	2.3	
other protocol violations (%)§	3.7	2.0	4.1	

* Eight patients who were randomly assigned to a treatment group but did not receive study drug are not included in tables on drug administration.

† Violations were defined as: ± 5-minute variation of 15-minute bolus delivery; maintenance dose started ± 5 minutes from 45-minute interval after bolus; or maintenance infusion ± 20 minutes from planned 23 hours.

‡ No spinal cord injury (five cases); excess steroid or naloxone before admission (three cases); severe comorbidity (two cases); no consent (two cases); randomized > 12 hours after injury (two cases); on maintenance-dose steroid (one case); gunshot wound (one case).

§ Randomized preadmission (five cases); received different drug from that assigned (three cases); no study drug administered due to unforeseen medical problems (three cases); randomized into wrong quartile (two cases); incorrect bolus dose infused (two cases); steroids administered against medical advice (one case).

accident to loading dose were between 8 and 9 hours. The majority of patients were immobilized before admission with a cervical collar. None of the entry characteristics differed significantly by treatment group.

Table 2 shows the results of selected diagnostic tests that the patients underwent on admission to the center and the operative procedure performed. Over one-half of the patients had fractures and dislocations. Operative procedures were performed anteriorly in 11.8% of patients and posteriorly in 51.7%. The two most frequent procedures were fusion (46.3%) and internal fixation (42.8%). The operative procedures did not differ significantly by study treatment.

Strict records were kept of all violations of the study protocol. These are divided into those related to administration of the study drugs (time and dosing schedules) and other protocol violations including variations in time of conducting neurological examinations. Despite the narrow time and dose limits considered acceptable according to the study protocol, approximately 80% of drugs were administered entirely within the protocol time limits and 90% according to the prescribed dose. Over 90% of all patients were managed throughout their 1 year in the study without other study protocol violations (Table 3). None of the protocol violations differed significantly by study treatment.

Neurological Status on Admission

Neurological status on admission to the study did not differ according to treatment protocol when either categorical neurological status or the expanded scores were considered.[8] Table 4 shows that neurological status did not significantly differ on admission among those patients treated within 8 hours of injury. Considering all randomized patients at 1 year, there were no significant differences in neurological function by treatment group, although patients treated with methylprednisolone showed a slight advantage over those receiving placebo on all three neurological parameters. Patients who received their drug bolus within 8 hours of injury had significantly greater motor recovery after being treated with methylprednisolone as compared with placebo (change from admission scores of 17.2 vs. 12.0, $p = 0.030$); corresponding changes were seen for pinprick sensation (10.8 vs. 8.4, $p = 0.251$) and touch sensation (9.4 vs 6.0, $p = 0.122$). These analyses were also adjusted for initial severity of injury. Patients treated with naloxone improved neurologically at a rate between those receiving placebo and those receiving methylprednisolone; however, the differences between the neurological scores for those receiving naloxone and those receiving placebo were not statistically significant.

TABLE 4

*Neurological scores in the emergency room for patients who received the study drug within 8 hours of injury**

Neurological Score	Treatment Group			p Value
	Methylprednisolone	Naloxone	Placebo	
expanded motor				
cases studied	71	64	73	
mean score	21.1 ± 15.7	23.4 ± 17.9	23.8 ± 20.9	0.64
expanded pinprick				
cases studied	71	64	73	
mean score	51.3 ± 16.8	52.8 ± 17.6	52.6 ± 17.6	0.86
expanded touch				
cases studied	70	62	72	
mean score	53.3 ± 18.4	54.7 ± 18.1	55.0 ± 19.0	0.84

* Expanded motor score ranges from 0 (no contraction in any muscle) to 70 (all normal responses); expanded sensory scores range from 29 (absent sensation at all levels) to 87 (all levels normal). Mean values are expressed ± standard deviation.

TABLE 5

*Change in neurological function scores 1 year after injury in patients who received the study drug within 8 hours of injury**

Neurological Function	Treatment Group		
	Methylprednisolone	Naloxone	Placebo
plegic with total sensory loss			
cases studied	45	34	43
motor	11.1 (0.019)	8.1 (0.235)	4.6
pinprick	8.0 (0.268)	5.4 (0.917)	5.1
touch	8.9 (0.203)	7.4 (0.498)	5.5
plegic with partial sensory loss			
cases studied	5	11	6
motor	25.8 (0.481)	31.1 (0.971)	31.3
pinprick	13.6 (0.764)	15.0 (0.894)	15.8
touch	6.4 (0.556)	14.1 (0.610)	10.8
paretic with variable sensory loss			
cases studied	12	11	16
motor	24.2 (0.024)	14.6 (0.738)	12.9
pinprick	14.5 (0.264)	9.3 (0.996)	9.2
touch	9.2 (0.204)	5.8 (0.576)	3.0

* Values are changes in score at 1 year posttreatment. Numbers in parentheses denote p values determined from analysis of variance. Scores for motor function range from 0 (no contraction in any muscle) to 70 (all normal responses). Scores for pinprick and touch sensation range from 29 (absent sensation at all levels) to 87 (all levels normal).

When the above analyses were restricted to only those patients receiving treatment within the protocol time limits, the differences between the methylprednisolone- and placebo-treated patients increased for all three parameters: motor scores (18.1 vs. 11.5, $p = 0.014$), pinprick sensation (11.5 vs. 8.1, $p = 0.123$), and touch sensation (10.2 vs. 6.6, $p = 0.103$). The naloxone-treated patients continued to show nonstatistically significant recovery, with rates between those of patients treated with placebo and those with methylprednisolone.

Among all randomized patients more than 8 hours postinjury, those receiving either methylprednisolone ($p = 0.080$) or naloxone ($p = 0.100$) recovered less motor function than those given placebo. The neurological scores showed a similar, but less striking, improvement for pinprick and touch sensation.

Table 5 shows the change in neurological scores in patients treated within 8 hours of injury, stratified by the severity of their injury on admission to the emergency room. Among plegic patients with total sensory loss below their level of injury, those receiving methylprednisolone had significantly more improvement in motor function 1 year after injury than those given placebo (change in scores from admission of 11.1 vs. 4.6, $p = 0.019$). Among the few plegic patients with partial sensory loss, there were no significant differences. Among paretic patients with variable sensory loss, motor function also improved significantly in those receiving methylprednisolone as compared with those given placebo (change in score from admission of 24.2 vs. 12.9, $p = 0.024$). Changes in pinprick and touch sensation followed the same direction as motor function improvement, but did not reach statistical significance. The naloxone comparisons with placebo were neither as large as those between methylprednisolone and placebo nor statistically significant. The above analyses were essentially unchanged when including only patients treated according to drug protocol time limits.

Whether patients improved sufficiently at 1 year to be reassigned from one of four abnormal neurological categories (quadriplegic, paraplegic, quadriparetic, or paraparetic) to a higher functional (or sensory) level or to being normal was examined next. The likelihood of reassignment due to motor function improvement was greater in patients treated with methylprednisolone (odds ratio (OR) = 1.39, 95% confidence interval (CI) 0.64, 3.03) and naloxone (OR = 1.75, 95% CI 0.79, 3.86) as compared with placebo-treated patients. Similar results were found for methylprednisolone-treated patients on their pinprick and touch sensation examinations, but naloxone-treated patients did not improve more than placebo-treated patients on the sensory parameters. None of the changes in neurological category was statistically significant.

Complications

Complications were reported at each follow-up examination if they were new occurrences since the prior follow-up period. Most complications were reported at 6 weeks (Table 6). There were no significant differences between treatment groups for any of these complications. For all follow-up periods studied, only three complications approached statistical significance: at 48 hours, 2.6% of naloxone-treated patients had paralytic ileus compared with 8.3% for placebo ($p = 0.05$); at 6 months, arrhythmias occurred in 4.7% of naloxone-

TABLE 6
Complications at 6 weeks after injury (%) and significance

Complication	Treatment Group			p Value
	Methylpred-nisolone	Naloxone	Placebo	
no. of cases	156	154	167	
urinary tract infection	45.5	49.4	46.1	0.77
pneumonia	28.2	29.9	24.6	0.55
decubitus (breakdown)	18.6	18.2	19.2	0.39
paralytic ileus	8.3	7.8	10.8	0.61
arrhythmia	5.1	5.8	7.8	0.59
sepsis	5.8	6.5	6.6	0.95
thrombophlebitis	2.6	4.6	6.6	0.23
wound infection	7.1	3.3	3.6	0.21
gastrointestinal hemorrhage	4.5	2.0	3.0	0.44
pulmonary embolus	3.9	5.2	1.2	0.13
congestive heart failure	1.3	1.3	1.2	0.99
myocardial infarction	0	0	0	—
angina pectoris	0	0	0	—

treated patients compared with 0.6% for placebo ($p = 0.06$); and at 1 year, pneumonia occurred in 1.4% of naloxone-treated patients compared with 3.3% for placebo ($p = 0.04$). Since all three p values are of borderline significance and a large number of associations are being examined, the three complications affecting naloxone-treated patients are most likely due to chance. No statistically significant differences were seen between patients receiving methylprednisolone and those given placebo.

Discussion

Increased recovery of neurological function after acute spinal cord injury in patients treated with methylprednisolone within 8 hours of injury, as compared with those treated with placebo, was seen at 6 weeks and at 6 months after injury and continued to be observed 1 year after injury. For motor function, this difference was still statistically significant ($p = 0.030$). Naloxone-treated patients were not observed to have significantly greater improvement in their neurological parameters at earlier follow-up time periods and at 1 year. There were too few patients to evaluate the effects of methylprednisolone administration earlier in the treatment window, for example at 0 to 4.0 hours versus 4.1 to 8.0 hours.

The failure of naloxone to significantly improve neurological outcomes at the doses studied has four possible explanations. First, the study size may have been too small to detect clinical differences at a statistically significant level. A much larger trial would be necessary to disentangle real clinical effects due to the study dose of naloxone from random effects. Second, the dose of naloxone studied may have been below or above its therapeutic threshold, but there is no evidence to support this. The 5.4-mg/kg dose studied was carefully selected based on earlier animal studies[22,23,26,57] and a Phase I escalating-dose toxicity study.[25] Third, the method of administering naloxone may have been inappropriate, but this is an unlikely explanation since continuous infusion, which maximizes drug plasma levels, was used. Fourth, naloxone may not have therapeutic benefit at any dose in humans. Because of differences in drug metabolism, results in animals frequently fail to be confirmed in humans. From the results of the present trial, the failure of more recent animal studies to find any beneficial effect from naloxone administration[4–6,29,52] and the considerably greater expense of treating patients with high-dose naloxone compared with high-dose methylprednisolone, it must be concluded that naloxone has no role in the clinical management of this injury.

Methylprednisolone has a long history of being the subject of research in experimental spinal cord injury. The early studies used much lower daily doses of methylprednisolone (0.1 to 1 gm) and essentially tested hypotheses that any protective effect would be due to their glucocorticoid receptor activity. Most studies reported some benefit from steroids at these low doses[1,4,15–17,20,21,28,38,44–47,49] but others did not.[39,40,54] The first NASCIS compared daily doses of 0.1 gm and 1.0 gm of methylprednisolone over a 10-day period but did not show differential efficacy.[7,9]

The very high doses of methylprednisolone used in this trial were specifically based on a therapeutic rationale developed by Braughler and Hall,[13,35] and their earlier work suggesting that the lipid peroxidation inhibition effects of methylprednisolone were likely to have a therapeutic effect in experimental models of acute spinal cord injury.[2,10–13,33,34]

Demopoulos, *et al.*,[18,19] were among the earliest to suggest that lipid peroxidation is a major factor in postinjury degeneration after acute spinal cord injury and that corticosteroids may inhibit that process. The subsequent experimental studies of Braughler, *et al.*,[10–14,33–35] and other investigators,[50,56] all support the notion that lipid peroxidation inhibition is the major mechanism for the beneficial effects of methylprednisolone seen in the second NASCIS. Nonetheless, other effects of high doses of methylprednisolone have been studied experimentally, including an increase in blood flow through the injured cord with a concomitant increase in extracellular calcium and cell metabolism[12,13,36,37,55,56] and in electrophysiological responses in the cord.[30–32,55,56] Further experimental work with other lipid peroxidation inhibitors and their testing within rigorous randomized trials are likely to produce other therapies which may show greater efficacy than was found for methylprednisolone.

The second NASCIS has shown that the time of first administration of methylprednisolone is a critical factor in enhancing recovery. Only patients receiving methylprednisolone within 8 hours of injury benefited from treatment. The 1-year analysis follows a trend seen in the earlier follow-up periods; namely, that patients treated with methylprednisolone more than 8 hours postinjury have worse results than those given placebo.

While these differences are not statistically significant, the trend is apparent at 1 year. There is some evidence that steroids interfere with neuron regeneration,[24,51] and it has been proposed that they do so by inhibiting immune cell activity, including antigen processing macrophages.[43] It is theoretically possible that late administration of methylprednisolone confers little of the benefits of lipid peroxidation inhibition and interferes with any normal regenerative processes that may occur after this injury. The results of the present trial strongly support the clinical management of acute spinal cord-injured patients with methylprednisolone, but only if their treatment can be started within 8 hours of injury. We have estimated that 95% of patients are admitted and treated within this timeframe.

The management of patients with the NASCIS dose of methylprednisolone is further supported by the lack of significant complications or mortality associated with this treatment. Even if the small increases in wound infection and gastrointestinal bleeding found in methylprednisolone-treated patients were truly related to treatment (in this study, they cannot be distinguished from chance), they are manageable conditions and the risk associated with them would be well worth the potential therapeutic benefits of methylprednisolone administration. Although naloxone cannot be recommended for clinical use in acute spinal cord injury, the absence of complications from this high-dose protocol provides important clinical information for investigators considering its use for other conditions.

Finally, we note that methylprednisolone sodium succinate was selected for study over other steroids because the succinate radical has been demonstrated to cross cell membranes more rapidly and completely than other radicals[53] and is more effective in inhibiting neutropenia.[27,48] Consequently, administering other steroids such as dexamethasone 21-phosphate, even at doses equivalent to the methylprednisolone dose used in the present study, may not necessarily result in comparable treatment effects.

Acknowledgments

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APPENDIX

The National Acute Spinal Cord Injury Study Group

Coordination Center Personnel
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