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A RANDOMIZED, CONTROLLED TRIAL OF METHYLPREDNISOLONE OR NALOXONE IN THE TREATMENT OF ACUTE SPINAL-CORD INJURY

Results of the Second National Acute Spinal Cord Injury Study

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Abstract Studies in animals indicate that methylprednisolone and naloxone are both potentially beneficial in acute spinal-cord injury, but whether any treatment is clinically effective remains uncertain.

We evaluated the efficacy and safety of methylprednisolone and naloxone in a multicenter randomized, double-blind, placebo-controlled trial in patients with acute spinal-cord injury, 95 percent of whom were treated within 14 hours of injury. Methylprednisolone was given to 162 patients as a bolus of 30 mg per kilogram of body weight, followed by infusion at 5.4 mg per kilogram per hour for 23 hours. Naloxone was given to 154 patients as a bolus of 5.4 mg per kilogram, followed by infusion at 4.0 mg per kilogram per hour for 23 hours. Placebos were given to 171 patients by bolus and infusion. Motor and sensory functions were assessed by systematic neurologic examination on admission and six weeks and six months after injury.

After six months the patients who were treated with methylprednisolone within eight hours of their injury had significant improvement as compared with those given placebo in motor function (neurologic change scores of 16.0 and 11.2, respectively; $P = 0.03$) and sensation to pinprick (change scores of 11.4 and 6.6; $P = 0.02$) and touch (change scores, 8.9 and 4.3; $P = 0.03$). Benefit from methylprednisolone was seen in patients whose injuries were initially evaluated as neurologically complete, as well as in those believed to have incomplete lesions. The patients treated with naloxone, or with methylprednisolone more than eight hours after their injury, did not differ in their neurologic outcomes from those given placebo. Mortality and major morbidity were similar in all three groups.

We conclude that in patients with acute spinal-cord injury, treatment with methylprednisolone in the dose used in this study improves neurologic recovery when the medication is given in the first eight hours. We also conclude that treatment with naloxone in the dose used in this study does not improve neurologic recovery after acute spinal-cord injury. (N Engl J Med 1990; 322:1405-11.)

ACUTE spinal-cord injury has been extraordinarily resistant to effective treatment. The improved longevity of patients with spinal-cord injuries is almost certainly due to general advances in nursing and acute medical and rehabilitational care.[1] There have not been accompanying improvements in neurologic outcome.

Interest in the pharmacologic treatment of acute spinal-cord injury dates back at least 20 years.[2] In an earlier trial (the National Acute Spinal Cord Injury Study, or NASCIS 1) we compared a 1000-mg infusion of methylprednisolone sodium succinate with a 100-mg dose of methylprednisolone given as a bolus and daily thereafter for 10 days. No significant difference in motor or sensory outcomes was observed between the treatments.[3,4]

Near the conclusion of that study, new data from studies in animals suggested that the dose of methylprednisolone in NASCIS 1 was below the theoretical therapeutic threshold, believed to be about 30 mg per kilogram of body weight.[5,6] The present trial, NASCIS 2, was undertaken to study this higher dose of methylprednisolone. A placebo arm was added to NASCIS 2, and a second therapeutic candidate, the opiate-receptor blocker naloxone hydrochloride, was added as a third treatment arm. In several animal studies naloxone had improved neurologic recovery.[7-9] A Phase I

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human study conducted at three NASCIS centers indicated that toxicity and safety were not problems at the planned naloxone trial dose of 5.4 mg per kilogram.[10]

METHODS

Eligibility and Randomization

Eligible patients were those who had a spinal-cord injury diagnosed by a physician associated with the study, who consented to participate, and who were randomized within 12 hours of their injury. Ineligible patients were those with involvement of the nerve root or cauda equina only, gunshot wounds, or life-threatening morbidity; those who were pregnant, addicted to narcotics, receiving maintenance steroids for other reasons, or under 13 years of age; those who had received more than 100 mg of methylprednisolone or its equivalent, or 1 mg of naloxone before admission to the center; and those in whom follow-up would be difficult.

After determining a patient's eligibility, the attending physician telephoned the pharmacist at the Yale–New Haven Hospital, who obtained the patient's height and weight, calculated the body mass (on the basis of body-surface area), and assigned the patient to one of three schedules of administration (Table 1). Within each center the three treatments were randomized in blocks of nine.

Preparation and Administration of the Drugs

Methylprednisolone and its placebo were provided in 16-vial sets of 1-g vials and prepared with diluent (bacteriostatic water) at a concentration of 62.5 mg per milliliter. Naloxone and its placebo were provided in 100-ampule sets of 2-ml parabens-free ampules and prepared at a concentration of 25.0 mg per milliliter.

Because of differences in the appearance, solubility, and concentration of the two active drugs, each required its own placebo and infusion pump. For each patient, one pump infused methylprednisolone or its placebo and a second pump administered naloxone or its placebo. Thus, each patient received one of three regimens: active methylprednisolone and naloxone placebo, methylprednisolone placebo and active naloxone, or methylprednisolone placebo and naloxone placebo. No patient received both methylprednisolone and naloxone. Separate intravenous sites were required for each pump.

Both drugs were administered in a bolus dose over a 15-minute period, followed by a 45-minute pause and then a 23-hour maintenance infusion. Methylprednisolone was given in a bolus dose of 30 mg per kilogram and a maintenance dose of 5.4 mg per kilogram per hour, and naloxone in a bolus dose of 5.4 mg per kilogram and a maintenance dose of 4.0 mg per kilogram per hour. For each drug the bolus and maintenance doses varied according to body-surface area (Table 1).

All phases of the study (preparation and administration of the drugs, neurologic examinations, and statistical analyses) were carried out in a blinded fashion. The progress of the study was monitored by a National Institutes of Health committee, but the need for it to know the drug codes never arose. Institutional review boards at each center approved the study protocol.

Assessment of Neurologic Function

Neurologic function was assessed on admission to each center and after six weeks and six months. Measurements of motor function and the sensations of pinprick and light touch were recorded at each examination.[11] On admission, the patients' injuries were categorized as complete or incomplete. Complete injuries were those below which the patient had no motor or sensory function. Incomplete injuries were those below which some sensory or motor function remained.

Pinprick and Light Touch

Twenty-nine segments from C-2 through S-5 were evaluated bilaterally and their function 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 neurologic score, each patient was classified in one of five categories: analgesic and anesthetic 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; analgesic and anesthetic below T-1, if sensation was absent below T-1 and in all distal segments; hypalgesic and hypesthesic at or above T-1, if sensation was decreased at T-1 or above; hypalgesic and hypesthesic below T-1, if sensation was decreased below T-1; and normal, if all segments were evaluated as normal.

Table 1. Schedule of Drug Administration According to Body-Surface Area.

DRUG	BOLUS		MAINTENANCE	
	DOSE	FLOW RATE	DOSE	FLOW RATE
	ml	*ml/hr*	*ml*	*ml/hr*
Methylprednisolone				
1.16–1.70 m^2	31	124	138	6
1.71–2.35 m^2	44	176	184	8
2.36–3.00 m^2	59	236	253	11
Naloxone				
1.16–1.70 m^2	11	44	184	8
1.71–2.35 m^2	16	64	276	12
2.36–3.00 m^2	22	88	368	16

Motor Function

Six classifications were used to record motor function in 14 muscle segments. A score of 0 indicated no contraction; 1, reduced contraction; 2, active movement without antigravity (side to side but not upward); 3, active movement with antigravity; 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 as quadriplegic if the most cephalad muscle with no contraction was the first dorsal interosseous muscle (C-8 to T-1) or higher and there was no contraction in any distal muscle, paraplegic if the most cephalad muscle with no contraction was below the first dorsal interosseous muscle and there was 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 muscle or higher, paraparetic if the most cephalad muscle with a trace of contraction or active movement without antigravity was below the first dorsal interosseous muscle, and normal if responses were normal or only minimally impaired.

Neurologic examinations were performed only by approved personnel. If patients moved from the area of initial treatment, follow-up examinations were conducted at the closest center. The follow-up examinations were performed within prescribed time limits — the six-week examination between 42 and 49 days after the injury, and the six-month examination between 180 and 210 days after.

Compliance

The administration of the study drug was monitored for each patient. Deviations in the timing of administration were considered first-order violations, and they occurred when infusion of the maintenance dose began more or less than 45 minutes after the end of the bolus dose, or when the maintenance infusion lasted an hour more or less than 23 hours. Second-order violations occurred when patients did not receive the assigned amount of study drug. Other violations generally reflected deviations from the protocol in eligibility.

Statistical Analysis

The primary end point was a change in neurologic function between base line and the follow-up examination. Analysis of variance was used to test the hypothesis that the change in score was not different across the three treatment groups. We summarized the

results using an analysis of variance for the effects of the protocol, the time the dose was received (≤8 or >8 hours from injury), and the degree of neurologic loss (complete or incomplete).

The analyses of neurologic scores used data from the examination of the right side of the body. Each analysis was repeated with scores from the left side, with essentially identical results. To simplify the presentation of the results, only data from the right side are presented here. As a check to ensure that the conclusions were not influenced by the assumptions of the analysis of variance, the standard error from the analysis of variance was compared with the standard error calculated with the use of 50 bootstrap samples.[12,13] The agreement was excellent and did not result in any differences in the overall conclusions.

In addition to the expanded neurologic score, the five categories of injury were analyzed according to whether the patient's condition improved, remained the same, or regressed. This analysis used a log-linear model[14] to determine the effects of treatment, time before the administration of the dose, and severity on improvement in the patient's condition. Calculations were done with use of generalized linear interactive modeling.[15]

A summary of survival in the patients made use of the product-limit estimator of the survival curve.[16] The curves of the three treatment groups were compared by the log-rank test,[17] with use of the PROC LIFETEST procedure in SAS.[18]

Results

The distribution of the patients randomized at each collaborating center is shown in Table 2. A total of 487 patients were randomized, and their characteristics are shown in Table 3. As in most series of patients with spinal-cord injuries, our patients were typically male, white, and 13 to 34 years old. The single most common cause of injury was automobile accidents, followed by falls and water-related injuries. The large majority of patients were conscious on admission and had no specific cord syndromes (for example, Brown–Sequard syndrome or central cord syndrome). Only two patients had open wounds. About 60 percent of the patients had complete injuries on admission. Peripheral drug-infusion lines were placed in 92 percent of the patients. There were no meaningful differences in the distribution of patients' characteristics among the three treatment groups.

Fewer than half the patients were admitted directly to the study center; most were first admitted to another hospital. A majority received neither steroids nor naloxone before entering the study center and were immobilized by cervical collars. The average (±SD) time from accident to admission was 3.1±2.6 hours, from admission to infusion of the bolus dose 5.6±2.7 hours, and from accident to bolus dose 8.7±3.0 hours.

Over half the study population had spinal fractures and dislocations. Bone fragments were seen in over 40 percent. Table 4 shows the neurologic status of the patients who were randomized. There was no difference among the randomized groups; a majority had quadriplegia or paraplegia, with corresponding levels of analgesia and anesthesia. Overall, 80 percent of the patients received their study drug within the protocol's time limits, and 92.1 percent received the drug according to the protocol's dose schedule.

Since two a priori hypotheses were that any effects of treatment would be influenced by how quickly the drug was given and by the severity of injury, the analysis was also stratified on the basis of time to loading dose (≤8 vs. >8 hours from injury) and adjusted for the severity of injury (complete vs. incomplete). Considering all the patients six weeks after injury, we found that the scores of those treated with methylprednisolone improved more than the scores of those given placebo for the sensations of pinprick (change from admission score, 6.7 vs. 4.8; P = 0.079) and touch (6.1 vs. 3.9; P = 0.066). No comparable improvements in motor function were observed. Among the patients treated within eight hours, however, those given methylprednisolone had significantly more improvement than those given placebo in their motor-function (10.6 vs. 7.2; P = 0.048) and touch (6.3 vs. 2.5; P = 0.034) scores. Improvements in pinprick scores were also greater (7.8 vs. 4.8; P = 0.061). Patients treated with naloxone did not show significantly more change in neurologic function than those given placebo. Patients treated with either drug more than eight hours after injury also had changes in neurologic scores that were not significantly different.

After six months the patients treated with methylprednisolone had greater sensory improvement than those receiving placebo (pinprick, 10.0 vs. 6.6; P = 0.012; and touch, 8.7 vs. 5.9; P = 0.042). Among the patients treated within eight hours of their injury, those receiving methylprednisolone recovered more motor function than those given placebo (16.0 vs. 11.2; P = 0.033), and they also had greater sensory function (pinprick, 11.4 vs. 6.6; P = 0.016; and touch, 8.9 vs. 4.3; P = 0.030). None of the differences in patients taking naloxone or in patients first treated more than eight hours after injury were statistically significant.

Table 5 shows the change in scores in the patients treated within eight hours of their injury, grouped

Table 2. Distribution of Randomized Patients According to Collaborating Center.*

Center	Group			Percentage of Study Patients
	Methylprednisolone	Naloxone	Placebo	
Allegheny General Hospital, Pittsburgh	32	34	37	21.1
Barrow Neurological Institute, Phoenix	27	25	29	16.6
University of California, San Diego	21	21	22	13.1
University of California, Davis	18	14	21	10.9
University of Washington — Harborview Medical Center, Seattle	16	14	16	9.4
New York University–Bellevue Medical Center, New York	13	13	12	7.8
Medical University of South Carolina, Charleston	12	13	12	7.6
University of Texas Medical Branch, Galveston	11	10	10	6.4
Yale University, New Haven, Conn.	9	7	7	4.7
Baylor College of Medicine, Houston	3	3	5	2.3
Total	162	154	171	100.0

*The study's blocked design was disturbed at three centers because one patient in each block was given an incorrectly assigned drug.

Table 3. Demographic and Clinical Characteristics of the Patients at Entry.*

Characteristic	Group			P Value
	Methyl-prednisolone	Naloxone	Placebo	
No. of patients	162	154	171	
Sex (%)				
Male	86.4	80.5	84.8	0.34
Female	13.6	19.5	15.2	
Race or ethnic group (%)				
Black	14.2	8.4	14.0	0.35
Non-Hispanic white	73.5	81.8	71.9	
Hispanic	8.0	4.6	9.4	
Other	4.3	5.2	4.7	
Height (cm)	175.0±9.8	176.5±9.8	174.7±9.9	0.23
Weight (kg)	75.0±13.0	75.4±15.5	76.0±16.7	0.81
Age (%)				
13–19	15.4	14.9	15.2	0.37
20–24	29.0	33.8	22.8	
25–29	11.1	14.9	14.6	
30–34	14.8	7.1	14.6	
35–39	9.3	5.8	8.2	
40–44	3.1	5.8	5.9	
45–49	1.9	2.0	3.5	
50–54	4.3	4.6	1.8	
55–59	2.5	1.3	4.7	
≥60	8.6	9.7	8.8	
Blood pressure (mm Hg)				
Systolic	118.6±21.3	118.6±22.4	114.6±21.1	0.14
Diastolic	75.2±16.4	72.5±17.1	70.7±16.8	0.07
Pulse	80.5±19.8	80.6±19.9	79.7±18.9	0.13
Body mass (%)				
1.16–1.70 m^2	11.7	18.2	14.6	0.18
1.71–2.35 m^2	87.0	77.9	80.7	
2.36–3.00 m^2	1.2	3.9	4.7	
Cause of injury (%)				
Automobile accident	37.7	46.1	43.3	0.41
Motorcycle accident	9.3	3.2	8.8	
Fall	17.9	20.8	19.9	
Crush	4.9	4.6	5.3	
Water related	16.7	13.0	15.2	
Other	13.6	12.3	7.6	
Associated injuries (%)				
Skin and soft tissue	56.2	57.8	51.5	0.49
Head	17.3	18.8	15.8	0.77
Ear, nose, and throat	4.3	5.2	5.8	0.82
Cardiac	1.9	1.3	1.2	0.86
Pulmonary	8.0	11.0	9.4	0.66
Gastrointestinal	1.9	1.3	2.9	0.57
Genital or urinary	2.5	3.2	4.1	0.70
Musculoskeletal	18.5	18.8	19.9	0.95
Glasgow coma scale (%)				
<15	13.6	11.0	12.3	0.79
15	86.4	89.0	87.7	
Extent of injury (%)†				
Complete	64.6	53.9	58.8	0.15
Incomplete	35.4	46.1	41.2	
Cord syndrome (%)‡				
Anterior	7.5	7.8	7.6	0.53
Central	15.6	14.3	11.2	
Posterior	0.0	0.0	1.2	
None	76.9	77.9	80.0	

*Plus–minus values are means ±SD.

†Extent of injury was assessed by a neurologic examiner in the emergency room. Measured in 161 patients in the methylprednisolone group, 154 in the naloxone group, and 170 in the placebo group.

‡Measured in 160 patients in the methylprednisolone group, 154 in the naloxone group, and 170 in the placebo group.

according to the neurologic characteristics of the injury. Among plegic patients with total sensory loss below the level of their injury, those treated with methylprednisolone had significantly more improvement in motor function after six weeks than those given placebo (change, 6.2 vs. 1.3, from admission scores of 16.9 and 15.6, respectively; P = 0.021). Improvements in the sensations of pinprick and touch approached significance. In the few plegic patients with partial sensory loss, no differences were observed between those taking methylprednisolone and those taking placebo. Among the patients with paresis, motor function also improved more in those treated with methylprednisolone than in those given placebo (change, 18.3 vs. 10.8, from admission scores of 37.5 and 48.2, respectively; P = 0.054). Among the plegic patients with partial sensory loss, there was significantly more improvement in those treated with naloxone than in those given placebo only in pinprick sensation.

After six months, the plegic patients with total sensory loss who were treated with methylprednisolone had significantly more improvement than those given placebo in all three neurologic measurements (Table 5). Similarly, in the patients with paresis and variable sensory loss, those given methylprednisolone within eight hours of injury improved in all three measures, and significantly in motor function. No statistically significant differences were observed in the patients treated with naloxone or with either drug more than eight hours after their injury.

Patients first treated more than eight hours after their injury did not differ in the changes in their neurologic scores according to study treatment. When plegic patients with total sensory loss who had been treated within eight hours of injury were classified as quadriplegics and paraplegics, essentially the same treatment effects as those shown in Table 5 were seen in each subgroup.

The foregoing analyses included the data from all randomized patients, irrespective of whether they received their study drug according to the protocol. The analyses were then repeated for the patients who received the drug within the protocol's time limits. The six-week differences in neurologic outcome between the patients given methylprednisolone within eight hours of injury and the patients given placebo were larger in the group that had complied with the protocol. The respective changes in scores for the patients given methylprednisolone and those given placebo were as follows: motor function, 12.1 and 6.8 (P = 0.008); pinprick, 8.9 and 4.0 (P = 0.003); and touch, 7.1 and 2.9 (P = 0.034). After six months, the changes for the two groups were as follows: motor function, 17.2 and 10.7 (P = 0.011); pinprick, 12.9 and 5.9 (P = 0.001); and touch, 9.8 and 4.6 (P = 0.020). No significant differences were seen at any time in the patients first treated more than eight hours after injury or those treated with naloxone.

We next examined whether the treatments under study led to improvement sufficient to reassign patients from one of the four abnormal neurologic categories shown in Table 4 to a higher functional (or sensory) group. Among the patients treated within eight hours of injury, the odds of improving by a full category after six weeks were always higher in the methylprednisolone group than in the placebo group. For motor function, the odds ratio, as adjusted for initial level of injury, was 2.04 (95 percent confidence interval, 0.81 to 5.12); for the sensation

of pinprick, the odds ratio was 2.93 (1.26 to 6.79); and for the sensation of touch, it was 1.69 (0.72 to 3.94). For example, in 33 percent of the patients given methylprednisolone, pinprick sensation improved by at least one category after six weeks, as compared with 17 percent of the placebo group. The differences between treatments were all reduced after six months and were not observed in the naloxone group or in any group of patients who first received their study drug more than eight hours after injury.

Wound infections occurred in 7.1, 3.3, and 3.6 percent of the patients given methylprednisolone, naloxone, and placebo, respectively (P = 0.21). For gastrointestinal bleeding the rates were 4.5, 2.0, and 3.0 percent (P = 0.44). The rates of other complications were also essentially the same in the three groups six weeks after injury.

Discussion

In this randomized, controlled trial of methylprednisolone, naloxone, or placebo in the treatment of acute spinal-cord injury, we observed a significant improvement in motor function and the sensations of pinprick and touch six weeks and six months after injury in the patients treated with methylprednisolone. The beneficial effect of methylprednisolone was limited to the patients treated within eight hours of their injury, supporting the hypothesis that early treatment is more effective. The importance of early treatment was further supported by the enhanced effect of treatment in the patients who were given the drug according to the study protocol. The vast majority of the patients (92.1 percent) completed the entire study regimen. The mean bolus and maintenance doses that were achieved were within 5 percent of the planned dose according to the weight of the patients.

We had also hypothesized that patients with complete injuries would be unlikely to benefit from drug therapy. Although the completeness of injury was strongly related to the degree of neurologic recovery, both patients with complete injuries and those with incomplete injuries improved more after treatment with methylprednisolone than after placebo. Clearly, any notion that patients seen in the emergency room with complete spinal-cord injuries will be unresponsive to therapy must be reconsidered.

In NASCIS 1,[3,4] in which a lower dose of methylprednisolone was given for 10 days, we observed a significantly increased risk of infection of both the trauma site and surgical wounds. In the present study, more patients treated with methylprednisolone had wound infections, but the difference was not statistically or clinically meaningful. Similarly, despite previous concern that large doses of methylprednisolone could cause increased gastrointestinal bleeding, no meaningful differences were observed between patients given methylprednisolone and those given placebo. Mortality in the first six months after injury did not differ among the three treatment groups. Moreover, the overall mortality rate of 6 percent in this study is about half that reported in many series of patients with acute spinal-cord injury.[19]

The neurologic improvement seen after six weeks in the patients treated with methylprednisolone was fur-

Table 4. Neurologic Status on Admission, According to Protocol.*

Status	Group			P Value
	Methylprednisolone	Naloxone	Placebo	
Motor function (%)†				
Quadriplegic	46.0	48.4	47.1	0.78
Paraplegic	35.4	32.7	30.6	
Quadriparetic	11.8	7.8	10.6	
Paraparetic	1.9	2.6	2.9	
Normal	5.0	8.5	8.8	
Mean expanded motor score	23.7±17.4	24.9±18.2	24.0±19.6	0.85
Response to pinprick (%)‡				
Analgesic at or above T-1	41.6	34.4	36.7	0.53
Analgesic below T-1	32.9	31.8	30.2	
Hypalgesic at or above T-1	12.4	18.2	14.8	
Hypalgesic below T-1	5.6	10.4	11.2	
Normal	7.5	5.2	7.1	
Mean expanded pinprick score	53.0±17.1	54.5±16.9	54.4±17.5	0.71
Response to light touch (%)§				
Anesthetic at or above T-1	40.6	32.2	37.5	0.43
Anesthetic below T-1	31.3	29.6	25.6	
Hypesthetic at or below T-1	10.0	17.8	14.9	
Hypesthetic below T-1	8.1	7.2	10.7	
Normal	10.0	13.2	11.3	
Mean expanded touch score	54.3±17.9	56.5±18.5	55.7±18.3	0.53

*Plus–minus values are means ±SD. Neurologic examinations were not performed in three patients after randomization (one in each group).

†Measured in 161 patients in the methylprednisolone group, 153 in the naloxone group, and 170 in the placebo group.

‡Measured in 161 patients in the methylprednisolone group, 154 in the naloxone group, and 169 in the placebo group.

§Measured in 160 patients in the methylprednisolone group, 152 in the naloxone group, and 168 in the placebo group.

Table 5. Change in Neurologic Measures Six Weeks and Six Months after Injury in Patients Who Received the Study Drug within Eight Hours of Injury.*

Category of Injury and Measure†	Six Weeks			Six Months		
	Methylprednisolone	Naloxone	Placebo	Methylprednisolone	Naloxone	Placebo
	change in score (P value)					
Plegic with total sensory loss						
No. of patients	*47*	*37*	*46*	*45*	*34*	*44*
Motor	6.2 (0.021)	3.2 (0.394)	1.3 (R)	10.5 (0.019)	7.5 (0.254)	4.2 (R)
Pinprick	5.9 (0.062)	3.0 (0.690)	2.2 (R)	9.4 (0.028)	4.2 (0.947)	4.0 (R)
Touch	6.8 (0.051)	3.7 (0.622)	2.6 (R)	9.7 (0.050)	7.1 (0.374)	4.7 (R)
Plegic with partial sensory loss						
No. of patients	*5*	*12*	*6*	*5*	*11*	*6*
Motor	14.4 (0.564)	14.1 (0.447)	18.0 (R)	23.0 (0.652)	28.9 (0.711)	26.5 (R)
Pinprick	11.8 (0.168)	13.9 (0.037)	4.0 (R)	11.6 (0.803)	18.4 (0.152)	9.8 (R)
Touch	4.4 (0.515)	7.1 (0.204)	0.3 (R)	0.0 (0.479)	13.5 (0.181)	5.2 (R)
Paretic with variable sensory loss						
No. of patients	*14*	*12*	*17*	*12*	*11*	*17*
Motor	18.3 (0.054)	12.7 (0.635)	10.8 (R)	24.3 (0.018)	14.5 (0.738)	12.9 (R)
Pinprick	10.7 (0.368)	8.2 (0.844)	7.5 (R)	14.3 (0.133)	9.6 (0.633)	7.5 (R)
Touch	3.8 (0.518)	6.1 (0.237)	1.2 (R)	7.6 (0.174)	6.2 (0.285)	1.0 (R)

*R denotes reference value. The P values were determined from analysis of variance.

†Scores for motor function range from 0 to 70. Scores for sensations of pinprick and touch each range from 29 to 87.

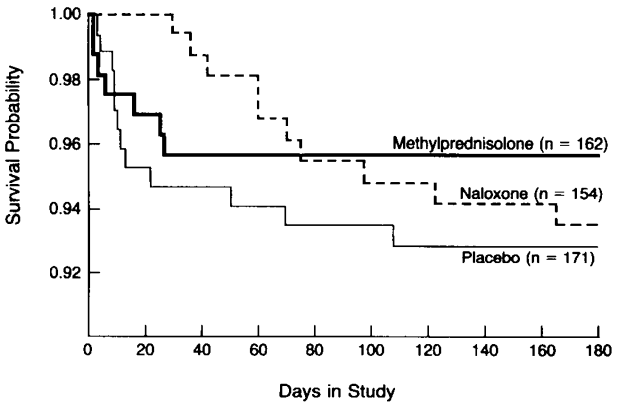

Figure 1. Survival Probability for Patients in Each Treatment Group Six Months after Acute Spinal-Cord Injury.
Log-rank test = 1.53; P = 0.465.

ther enhanced after six months. This observation is unlikely to have been biased, since the study achieved almost complete follow-up. Of the surviving patients, 97.9 percent underwent a neurologic examination after six weeks, and 96.5 percent after six months. We obtained mortality data on all patients. In view of the results of this study, naloxone cannot be recommended for general use in acute spinal injury. No consistent evidence of efficacy was seen, as some recent studies in animals have also shown.[20-23] We did not contemplate treating patients with a combination of high-dose methylprednisolone and naloxone, since there is no clear pharmacologic rationale for greater efficacy and there is evidence of increased mortality in cats treated with both drugs.[24]

There is some evidence from studies in animals that a dose of 60 mg of methylprednisolone per kilogram does not provide benefit.[25,26] Nonetheless, future clinical studies might usefully examine the effect of the earlier and longer administration of methylprednisolone. In a recent study,[26] cats received an intravenous bolus of methylprednisolone (30 mg per kilogram) 30 minutes after injury, followed by intravenous boluses of 15 mg per kilogram 2 and 6 hours after injury and then by a continuous 48-hour infusion of 2.5 mg per kilogram per hour. Neurologic recovery was significantly greater in the cats treated with methylprednisolone than in those given placebo. No adverse effects of treatment were noted. The animal study of Braughler et al.[26] (total dose, 165 mg per kilogram given over a 48-hour period) can be compared with NASCIS 2 (154.2 mg per kilogram over a 24-hour period). Additional therapeutic benefit might be achieved by extending the duration of administration in NASCIS 2 to 48 hours, but because there is residual uncertainty about the safety of extended high-dose therapy, this must be done as part of a randomized, controlled study.

The present study focused on neurologic changes after injury. The improvements in neurologic function presumably reflect biologic changes in the spinal cord and should provide the basis for the patient's subsequent rehabilitation. Previous work using measures of neurologic status almost identical to those of the present study showed that motor and sensory function have independent and additive effects on locomotor recovery and self-care after injury.[27] For example, in the present study a quadriplegic patient with very little motor function after injury (motor score, 12) who recovered 10 points regained normal upper-body strength with gross movement of some fingers. Such patients may be able to feed themselves with the aid of an adapter or brace and to assist in moving themselves. Another patient with paraplegia, who had no function from the quadriceps down after injury (motor score, 37), gained 10 points. Such patients may be able to stand with braces, bend their knees, and pivot, permitting movement without assistance. Nonetheless, the improvements in neurologic function attributable to methylprednisolone seen in the present study cannot readily be translated into specific improvements in functional status. Improvement sufficient to advance by one of the five neurologic categories (e.g., analgesic at or above T-1) clearly denotes better functional status. However, many patients improved neurologically in several spinal-cord segments but remained in their original category.

Since mobility requires neurologic function at the first lumbar level and below, we examined patients treated within eight hours of injury, irrespective of injury level. Among those who received methylprednisolone as compared with placebo, a larger proportion had improved (as opposed to stable or worsening) motor function (difference, 11.8 percent; 95 percent confidence interval, −2.9 to 25.5), pinprick sensation (16.2 percent; 1.9 to 30.5), and sensation of touch (17.9 percent; 3.6 to 32.2). The differences were all sustained six months later. No naloxone comparisons were statistically significant.

The dose of methylprednisolone used in the current study far exceeds the dose necessary to activate corticosteroid receptors. This suggests that methylprednisolone may act through mechanisms unrelated to corticosteroid receptors. Means et al. showed that very high doses of methylprednisolone are required to improve the histologic outcome[28] and perfusion in the microvasculature,[29] as well as to reduce lipid peroxidation,[30] in compressed feline spinal cords. Braughler et al. studied the dose–response relation between methylprednisolone treatment and the reduction of lipid peroxidation,[26] protein degradation, and metabolic dysfunction[31,32] in injured feline spinal cords. They found a narrow bell-shaped curve in which the beneficial effects peaked at about 30 mg per kilogram. The beneficial effects were barely detectable at 15 mg per kilogram, and the effects became deleterious at 60 mg per kilogram. Methylprednisolone may act through other mechanisms. High doses of methylprednisolone markedly enhance the flow of blood in injured spinal cords, preventing the typical decline in white-matter blood flow, extracellular calcium levels, and evoked potentials[33] that occurs after spinal-cord injury. The transmission of monosynaptic and polysynaptic reflexes in the lumbosacral spinal

cord is also facilitated by methylprednisolone, although the effect is transient and occurs only during treatment.[5]

The most likely explanation for the observed effects of treatment is that methylprednisolone suppresses the breakdown of membrane by inhibiting lipid peroxidation and hydrolysis at the site of injury. The doses required for a treatment effect are similar to those shown to be most effective in inhibiting lipid peroxidation and the breakdown of neurofilament in injured spinal cords.[26] These events in the breakdown of membrane begin and peak within eight hours of injury.[31,32] A secondary effect of the inhibition of lipid peroxidation is that vasoreactive byproducts of arachidonic acid metabolism are reduced, which improves the flow of blood at the injury site.[34] Thus, a number of studies in animals support methylprednisolone's beneficial effect on injured spinal cords. These studies, together with the present results, provide a reason to investigate further the mechanisms and efficacy of methylprednisolone and other inhibitors of lipid peroxidation.

Appendix

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