Original Contributions

JAMA
THE JOURNAL of the
American Medical Association
Jan 6, 1984 Vol 251, No. 1

Efficacy of Methylprednisolone in Acute Spinal Cord Injury

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• **A multicenter double-blind randomized trial was conducted to examine the efficacy of a high dose of methylprednisolone (1,000-mg bolus and daily thereafter for ten days) compared with a standard dose (100-mg bolus and daily thereafter for ten days) in 330 patients with acute spinal cord injury. No difference in neurological recovery of motor function or pinprick and light touch sensation was observed between the two treatment groups six weeks and six months after injury. The lack of a treatment effect was independent of the severity of the initial lesion or the time from injury to starting treatment. Although not statistically significant, early case fatality was greater in the high-dose protocol (relative risk of 3.1 and 1.9, ≤ 14 and 15 to 28 days after injury, respectively) but not from 29 to 210 days after injury. Wound infections of both trauma and operative sites were more prevalent in the high-dose regimen (relative risk of 3.6).**

(*JAMA* 1984;251:45-52)

IT HAS been estimated that the incidence of hospitalization for acute traumatic spinal cord injury averages 40 per million population each year in the United States; particularly affected are men aged 20 through 24 years and 25 through 34 years (118 and 99 per million population, respectively). Case fatality during hospitalization averages 11.2%.[1]

Corticosteroids are widely used in the treatment of acute spinal cord injury, the rationale for which rests almost entirely on animal experiments. The majority of animal studies report improvement in functional outcome after steroid treatment,[2-14] with only three studies failing to show a beneficial effect.[15-17] Histological findings, including white-matter sparing, have been associated with steroid treatment even though functional status did not improve.[11,18] Others report no difference in central cord necrosis with demyelinization and microcysts in the white matter after steroid treatment.[19] To our knowledge, clinical trials in humans have not been conducted, and the efficacy of steroid therapy in treating patients with acute spinal cord trauma is not documented.[20,21]

For editorial comment see p 68.

This article considers the effect of high and low doses of methylprednisolone sodium succinate on neurological recovery six weeks and six months after acute spinal cord injury. Morbidity and mortality at six months are also analyzed. Methylprednisolone was chosen for the present study because it is reported to have a theoretical advantage over the more widely used dexamethasone sodium phosphate in that it (1) does not interact with anticonvulsants, phenobarbitol, and phenytoin,[22] (2) passes more rapidly through cell membranes,[23] and (3) is more effective in inhibiting the neutropenic response to activated complement components.[18,24]

METHODS

Organization

Nine hospitals in seven states participated in the study, six of which were specialized spinal cord centers. In each hospital the study was organized through the department of neurosurgery; the department chief and a senior neurosurgeon were responsible for the conduct of the study. A research assistant (typically a neurological nurse) monitored daily study activities, including administration of the research drug and scheduling follow-up examinations. The Coordinating Center was based in the Department of Epidemiology and Public Health at Yale Medical School, New Haven, Conn, for which the responsibilities included (1) the overall conduct of the trial, (2) monitoring the

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Table 1.—Distribution of Randomized Patients by Collaborating Center

Collaborating Center	No. in Steroid Protocol		Total, %
	High Dose	Low Dose	
Yale University, New Haven, Conn	23	24	14.2
New York University-Bellevue, New York	40	40	24.2
Medical University of South Carolina, Charleston	10	10	6.1
Ohio State University, Columbus	10	11	6.4
University of Texas Medical Branch, Galveston	17	18	10.6
University of Miami, Miami	37	36	22.1
University of Puerto Rico, San Juan	13	11	7.3
Riverside Methodist Hospital, Columbus, Ohio	5	5	3.0
Baylor College of Medicine, Houston	10	10	6.1
Total	**165**	**165**	**100.0**

performance of participating hospitals, and (3) data analysis and report writing. Randomization of patients was arranged through the Drug Information Center located in the Pharmacy Department of Yale-New Haven Hospital, Conn. A telephone was manned 24 hours daily by pharmaceutical technicians familiar with the study protocol. Upjohn Corporation provided the methylprednisolone in uniquely numbered, "look-a-like" packages and organized the random codes; they did not participate in any other aspect of the trial. An advisory committee was established by the National Institute of Neurological and Communicative Disorders and Stroke to monitor the conduct of the trial, particularly its clinical and ethical aspects. Data collection and analysis were conducted under masked conditions with only the two co-principal investigators, a neurosurgeon (W.F.C.) and epidemiologist (M.B.B.), being aware of the study codes during the entire course of the study. Although the neurosurgeon (W.F.C.) is also chief of neurosurgery at Yale, he did not participate in any neurosurgical evaluations and was unaware of the treatment regimen of any individual patient in the study. The entire conduct of the study was prescribed in a manual of operations developed during a two-year feasibility study before the randomization of any patients.

Patient Recruitment and Randomization

The first patient entered the study Feb 11, 1979, and the last, Nov 6, 1981. Patients were eligible for randomization if, at the participating center's emergency room, their condition was diagnosed as acute spinal cord trauma by an attending neurosurgeon. The neurological examination for which the diagnosis was made followed standardized criteria established in the study protocol. Any loss of sensation (pinprick or light touch) or motor function below the lesion was indicative of spinal cord trauma. Patients with only root involvement, and with cauda equina alone, were excluded. Additional reasons for exclusion from randomization were as follows: (1) admittance to the participating center more than 48 hours after injury, (2) the dosage of more than 100 mg of methylprednisolone (or its equivalent for other steroids) before admission, (3) severe comorbidity (such as head trauma, which might require the patients to receive a steroid regimen) and other life-threatening conditions, (4) patients younger than 13 years, (5) failure to obtain signed consent from the patient or relatives, and (6) patients whom participating physicians, at their discretion, might wish to exclude for specific reasons, including a history of diabetes, severe vascular disease, concurrent infection, gastrointestinal (GI) tract bleeding, or pregnancy. Neurological examinations following study criteria were performed on all patients with spinal cord injuries, irrespective of randomization, at admission and at six weeks to contrast the clinical status of randomized to nonrandomized patients.

After ascertaining the patient's eligibility and obtaining consent, the attending physician telephoned the 24-hour number to learn which uniquely numbered drug package (already delivered to the hospital's pharmacy) should be assigned to the patient. Within each hospital the two drug protocols were "blocked" to ensure that for every six randomized patients, three were in each study protocol. In all, 330 patients were randomized into the two steroid treatments (Table 1). We excluded 24 patients from the analysis for reasons given in Table 2. These are evenly distributed between the two steroid protocols.

Steroid Administration

Each patient's medication package consisted of 11 vials of methylprednisolone, a loading dose and daily dose for ten days. The two treatments were packaged with identical appearance and solubility characteristics and were administered in the same manner. Immediately after randomization the patient received a loading dose of methylprednisolone (100 or 1,000 mg) and a dose of either 25 or 250 mg every six hours thereafter for ten days. The loading dose was administered into the patient's

Table 2.—Distribution of All Randomized Patients

	No. in Steroid Protocol		Total, %
	High Dose	Low Dose	
Total randomized	165	165	100.0
Excluded from analysis			
No spinal cord injury	4	3	2.1
Randomized without consent	1	1	0.6
Died before loading dose	0	1	0.3
Given excess steroid before admission*	5	4	2.7
Prolonged steroid regimen before injury	1	0	0.3
Given excess steroid before loading dose	0	1	0.3
Severe head injuries	1	1	0.6
Illegal alien, not given drug	1	0	0.3
Total	**13**	**11**	**7.3**
Patients entering analysis	152	154	92.7

*Excess steroid is greater than 100 mg equivalent of methylprednisolone sodium succinate.

maintenance intravenous (IV) tube during a ten-minute period. Subsequent doses were administered using a fluid administration set, either directly or through the maintenance IV tube for one minute. In the event of breakage or lost drug, an appropriate substitution was identified from the study's reserve stock, as directed by the Drug Information Center.

Two orders of drug protocol violation were established in the study. First-order violations occurred when the patient received the correct total drug dose for 10¼ days (1,100 or 11,000 mg) but variations occurred within the regimen. For example, one or more drug administrations were not given every six (±1) hours, greater or less than 25 (or 250) mg was administered at one time, or an incomplete loading dose was given. The study protocol defined procedures for correcting these violations to prevent them from becoming second-order violations. Second-order violations were noted when the patient received less than the total drug regimen (1,100 or 11,000 mg). These violations principally occurred when patients were inadvertently not given the drug for more than 24 hours, at which point they were discontinued from the regimen, and when patients were removed from the drug regimen for reasons other than indicated in the protocol. Protocol variations occurred when patients did not complete their drug regimen

Table 3.—Frequency of Drug and Protocol Violations

	Steroid Protocol	
	High Dose	Low Dose
Drug violations, %*	(n=152)	(n=154)
None	51.3	55.2
First order	35.5	35.7
Second order	13.2	9.1
	P=.51	
Other protocol violations, %	(n=152)	(n=154)
None	86.2	83.8
Code broken†	6.6	10.4
Withdrawn from study in error	0.0	0.6
Protocol variations, %		
Withdrawn for specific medical complications	5.9	1.9
Patient requested withdrawal	0.7	1.3
Withdrawn for medical reasons excluding complications	0.7	1.9
	P=.45‡	

*First order, drug not given every six (± 1) hours; second order, total regimen not given.

†Vial labels mutilated so that drug dose could have been revealed.

‡None *v* code broken *v* remainder

for reasons considered legitimate in the study protocol. The protocol violations and variations are given in Table 3 and did not differ significantly by steroid protocol.

Neurological Examination and Clinical Data

Standards and criteria for the neurological examination were developed during a two-year feasibility study. Procedures to improve reliability in conducting the examination included using only examiners approved by the study, having examiners test the same patient, and videotaping a model examination for review. The major component of the neurological examination consisted of bilateral tests of motor function and response to pinprick, light touch, deep pain, and reflexes. The patient's baseline neurological state was assessed on admission to the participating center. Identical follow-up examinations were conducted six weeks (days 30 to 96), six months (days 170 to 240), and one year (days 365 to 425) after injury. The reports of all examinations were reviewed for completeness and internal consistency before inclusion in the master data files.

At each reporting period, a detailed report was made of all major complications experienced by the patient according to diagnostic criteria developed by the study group. Case fatality was ascertained at any time during the year after injury. At the time of admission, additional information was obtained concerning sociodemographic characteristics of the patient, hospitalizations before admittance at the study hospital, use of steroids before admittance, associated injuries, cause and type of injury, and diagnostic maneuvers. At the six-week examination, information about operative procedures and any additional steroids given after the study regimen were reported.

Development of Outcome Measures

Three neurological parameters are used in this article—motor function, response to pinprick, and light touch. Each parameter is considered in terms of the patient's score at six weeks and six months after injury compared with admission. The three neurological parameters each have two forms of measurement: (1) an expanded score and (2) a five-point scale.

Motor Function.—Fourteen muscles were assessed as to whether there was (1) normal function, (2) reduced function but active movement against resistance, (3) active movement with antigravity, (4) active movement without antigravity, (5) some trace of contraction, or (6) no contraction. These muscles were evaluated because of the spinal cord segments they represented, their functional importance, and their ease of examination. Because the score of each ranged from 1 (normal) to 6 (no contraction), an "expanded" motor score ranging from 14 (all muscles normal) to 84 (no contraction in any muscle) was derived for each patient. Scores for the right and left sides were obtained independently.

From the same source the five-point scale was derived. Patients were defined as (1) quadriplegic if the most cephalad muscle with no contraction was the first dorsal interosseus (representing spinal segments C-8, T-1) or higher and all distal muscles show no contraction, (2) paraplegic if the most cephalad muscle with no contraction was below the first dorsal interosseus and all distal muscles show no contraction, (3) quadriparetic if the most cephalad muscle with a trace of contraction or having active movement without antigravity was the first dorsal interosseus or higher, (4) paraparetic if the most cephalad muscle with a trace of contraction or having active movement without antigravity was below the first dorsal interosseus, and (5) minimal for all other patients.

Pinprick and Light Touch.—Bilaterally, for each spinal cord segment, from C-2 to S-5, the patients response to pinprick and light touch was evaluated as being (1) normal, (2) decreased, or (3) absent. The expanded score for each parameter, therefore, ranged from 29 (representing a normal response at each level) to 87 (absent response at all levels). The five-point scale was derived from the same examination. Patients were defined as (1) analgesic $\geq$T-1 and anesthesic $\geq$T-1 if pinprick and light touch sensation, respectively, were absent at T-1 or above and in all distal segments, (2) analgesic $<$T-1 and anesthesic $<$T-1 if sensation was absent below T-1 and in all distal segments, (3) hypalgesic $\geq$T-1 and hypesthesic $\geq$T-1 if sensation was decreased at T-1 or above, (4) hypalgesic $<$T-1 and hypesthesic $<$T-1 if sensation was decreased below T-1, and (5) normal for other patients.

Completeness of Neurological Deficit.—Patients were further defined as being (1) quadriplegic with total sensory loss, (2) paraplegic with total sensory loss, (3) quadriplegic with partial sensory loss, (4) paraplegic with partial sensory loss, and (5) paretic (quadriparetic, paraparetic, or minimal) with variable sensory loss. Many analyses group this scale into (1) plegics with total sensory loss, (2) plegics with partial sensory loss, and (3) paretics with variable sensory loss.

Changes in Neurological Status.—These were obtained by subtracting the expanded neurological scores at admission from the six-week and six-month scores. Therefore, a negative score represents improved neurological function and a positive score, decreased function. A zero represents no change. In the present analysis, the change score is treated as a continuous measure.

Multivariate Analysis of Six-Week Follow-up

The multivariate analysis of the six-week change scores was analyzed by regressing the change scores on the steroid protocol (high or low) and on the potentially confounding variables (Tables 4 through 7). One of the most important potential confounding variables was the study center because the types of injury, patient characteristics, and management of spinal cord injury vary among them. The second major potential confounding variable was the patient's neurological status at admission to the center.

The regression analyses were performed for all patients combined and then for each of the three categories of completeness of injury. The analysis relied on the method of "backwards elimination."[25] All potentially important independent variables were first included in the model. Because there were some missing values for pulse, systolic and diastolic BP, and time from injury to loading dose, these were checked first for nonsignificance and then deleted from further analysis to increase the usable sample size. This produced a baseline model from which all other independent variables were deleted one at a time; those with the highest *P* value were deleted first. Deletion continued until all remaining values had a *P* value of not more than .10; this was the final model. Steroid protocol and study center were deliberately retained in all models.

This process of deleting nonsignificant

Table 4.—Characteristics of Randomized Patients on Admission to Study

Characteristic	Treatment Group: High Dose (n=152)	Treatment Group: Low Dose (n=154)	P
Sex			
M	88.2	86.4	.64
F	11.8	13.6	...
Race			
Black	27.0	27.9	.40
White	55.3	48.7	...
Hispanic	17.1	22.1	...
Oriental	0.6	1.3	...
Age, yr			
13-19	19.7	20.8	.63
20-24	25.7	22.7	...
25-29	15.8	16.9	...
30-34	8.6	10.4	...
35-39	7.9	5.2	...
40-44	3.3	6.5	...
45-49	5.9	2.6	...
50-54	5.8	5.8	...
55-59	3.3	1.3	...
60+	4.0	7.8	...
Height, cm	173.7	173.7	.86
SD	11.4	10.75	...
Weight, kg	72.5	73.0	.72
SD	13.0	13.3	...
Cause of injury			
Automobile accident	32.2	27.3	.23
Fall	21.7	21.4	...
Missile	15.8	22.1	...
Water related	12.5	14.9	...
Motorcycle accident	7.2	7.8	...
Crush	5.3	0.7	...
Other	5.3	5.2	...
Unknown	0.0	0.6	...
Type of wound			
Open	17.8	22.7	.28
Closed	82.2	77.3	...
Myelogram result			
No block	24.3	13.0	.06
Partial block	13.2	13.0	...
Total block	11.8	11.0	...
Myelogram not done	50.7	63.0	...
Plain roentgenogram results			
No fracture or dislocation	19.1	16.9	.24
Fracture only	23.0	31.8	...
Dislocation only	11.8	7.1	...
Fracture and dislocation	46.1	43.5	...
Roentgenograms not taken	0.0	0.7	...
Consciousness on admission			
Normal	86.8	87.7	.83
Decreased	13.2	11.7	...
Coma	0.0	0.6	...
Systolic BP, mm Hg			
Mean	123.6	118.8	.07
SD	24.5	21.4	...
Diastolic BP, mm Hg			
Mean	76.4	75.6	.68
SD	16.2	16.9	...
Pulse rate, beats/min			
Mean	83.9	80.6	.12
SD	18.8	18.2	...
Associated injuries at admission, %			
Skin and soft tissue	50.7	55.8	.36
Musculoskeletal	17.8	17.5	.96
Pulmonary	12.5	14.9	.54
Head	11.2	14.3	.42
Gastrointestinal tract	9.2	5.2	.17
Ear, nose, and throat	3.2	3.9	.53
Genital and urinary	2.6	3.2	.75
Cardiac	1.3	1.3	.99

variables has the advantage of providing precise estimates of the effect of confounding variables and permits adjusting effects not eliminated by randomization. However, because many tests are performed, some confounding variables may be inadvertently eliminated early in the analysis. This potential problem was addressed by tracking the P value of the steroid effect as each variable was eliminated. Because the P value did not change to any great extent, no multiple comparison adjustment was considered necessary. Additionally, a simultaneous test of all variables eliminated from the final model was computed. This "lack of fit" test was nonsignificant for all final models. Finally, the partial F tests of all retained variables did not change unexpectedly as variables were deleted. This provides further reassurance as to the unimportance of the deleted variables.

Multivariate Analysis of Six-Month Follow-up

Both the baseline and final models for the six-week follow-up were fitted to the six-month change scores. Lack of fit tests indicated that none of the deleted variables was important with the exception of change in motor for all patients combined. Accordingly, this was modeled using the entire backward-elimination stepping procedure that confirmed the lack of importance of the deleted variables. Our ability to directly use the final six-week models in the six-month analysis preserved the significance levels of the six-month tests. All computations were performed with the statistical package Statistical Analysis System (SAS) 79.6.[26] The statistical tests were based on type IV sum of squares.

Study Power

The number of patients studied, when classified by completeness of lesion, are between 50 and 180 patients at six months. Substantially more patients were available for the six-week follow-up and for both follow-up periods when patients are grouped across all neurological levels of injury. Assuming an equal distribution of the steroid protocol and an 80% probability of detecting a steroid effect at $\alpha=0.05$, a sample size of 50 patients would detect a shift of 7.8 points on the 70-point expanded motor score (11.1% improvement) and 180 patients would detect a shift of 4.25 points (6.1% improvement).

RESULTS

Characteristics of Patients in the Treatment Groups

Table 4 gives the sociodemographic characteristics, cause of injury, the results of diagnostic tests, clinical status, and associated injuries on admission for patients in each steroid

Table 5.—Entry Pattern of Randomized Patients by Steroid Protocol

Entry Pattern	Steroid Protocol, % High Dose	Low Dose
Previous hospitalization	(n=152)	(n=154)
Admitted directly to study hospital	46.1	44.8
One previous hospitalization	51.3	52.6
More than one previous hospitalization	2.6	2.6
	P=.99	
Hours from accident to admission at study hospital	(n=151)	(n=152)
≤6	65.6	62.7
>6-≤12	23.2	22.0
>12	11.2	15.3
	P=.59	
Steroids administered before admission at study hospital	(n=152)	(n=154)
None	61.4	69.7
Yes	38.6	30.3
	P=.15	
If yes	(n=51)	(n=40)
Dexamethasone	92.2	95.0
Methylprednisolone sodium succinate	7.8	5.0
	P=.59	
Milligram equivalent of methylprednisolone	(n=51)	(n=40)
<50 mg	41.2	50.0
51-100 mg	58.8	50.0
	P=.40	

protocol. Differences between the two groups were extremely small and, where comparisons can be made, reflect the characteristics of patients with spinal cord injury as it occurs nationally.[1] In Table 5, referral patterns to the participating centers are given. In all, 45% of patients were admitted directly to the study hospital, 64% arrived within six hours of injury, and 87% by 12 hours. Average time to admission was 5.93 (SD=6.76) hours. About a third of patients received steroids before admission, almost always dexamethasone, and over half received 10 to 20 mg or 50 to 100 mg equivalent of methylprednisolone. The average total steroid dose, from the study and all other sources, in the first 11 days of treatment was 10,549.7 mg (SD=2,129.1) and 1,126.6 mg (SD=390.8) in the high- and low-dose steroid treatment protocols, respectively.

Neurological Status on Admission

The neurological status of patients on admission to the study hospital was not significantly different between the two treatment groups (Table 6). In this report the right side was arbitrarily selected to represent neurological status. The majority of patients were either quadriplegic (35.0%) or paraplegic (36.6%) on motor function, analgesic greater than T-1 (30.1%) or analgesic less than T-1 (31.7%) to pinprick, and similarly distributed for light touch. Spinal cord syndromes and priapism seemed to occur with equal frequency in both treatment groups. However, we are not fully satisfied with the validity and reliability of the measurement of these syndromes, and they are not considered further in the analysis.

The distribution of patients by completeness of neurological deficit did not differ between the two steroid treatment groups (Table 7). For subsequent analyses we focused on three major groups of patients—plegics with total sensory loss (51.0% of the total sample), plegics with partial sensory loss (20.6%), and paretics with variable sensory loss (28.4%).

While not given in the tables, a number of other neurological parameters were assessed on admission to the hospital, none of which differed between the two steroid protocols. These included position sense for the wrist, thumb, little finger, knee, ankle, and great toe and sensation to deep pressure in the wrist, thumb, little finger, sternum, pubis, knee, ankle, and great toe. For reflexes the following were assessed: biceps, triceps, upper abdominal, lower abdominal, knee, ankle, upper and lower extremity tone, and the plantar response.

Neurological Status at Six Weeks

Neurological status could not be evaluated for 47 patients at six weeks because 26 patients (8.5%) had died,

Table 6.—Neurological Status on Admission to Study Hospital by Steroid Protocol

Neurological Status (Right Side)	Steroid Protocol, % High Dose (n=152)	Low Dose (n=154)	P
Motor function			
Quadriplegia	30.9	39.0	.31
Paraplegia	36.2	37.0	. . .
Quadriparetic	12.5	11.0	. . .
Parapetic	8.6	3.9	. . .
Minimal	11.4	9.1	. . .
Mean expanded motor score*	53.9	57.3	.13
SD	19.8	19.3	. . .
Pinprick			
Analgesic ≥T-1	24.3	35.7	.16
Analgesic <T-1	31.6	31.8	. . .
Hypalgesic ≥T-1	17.8	11.0	. . .
Hypalgesic <T-1	16.4	13.0	. . .
Normal	9.9	8.4	. . .
Mean expanded pinprick score	56.3	59.9	.08
SD	18.2	17.9	. . .
Light touch			
Analgesic ≥T-1	23.7	33.1	.37
Analgesic <T-1	30.3	30.5	. . .
Hypalgesic ≥T-1	14.5	11.7	. . .
Hypalgesic <T-1	17.1	12.3	. . .
Normal	14.5	12.3	. . .
Mean expanded light touch score	55.0	58.6	.09
SD	18.7	18.5	. . .

*For three patients the left side was used for initial and follow-up examinations because limb trauma or body cast prevented calculation of an expanded score on the right side. Two patients could not be tested at all because of bilateral limb trauma or body cast (one patient in each steroid protocol).

18 patients (5.9%) were unavailable for follow-up or not examined on schedule, and three neurological examinations (1.0%) were incomplete because of body casts. Of the 258 patients examined at six weeks (125, high dose; 133, low dose), 55.6% showed some improvement in motor function as defined by improving at least one point on the expanded 70-point motor score, 30.5% of patients were unchanged, and 13.9% grew worse. The average improvement per patient on the expanded motor score was −6.00. Plegic patients with complete sensory loss had the least motor improvement (−1.9), while plegics

Table 7.—Completeness and Level of Lesion for Randomized Patients at Admission by Steroid Protocol*

Neurological Status (Right Side)	Steroid Protocol: High Dose (n=152)	Steroid Protocol: Low Dose (n=154)
Quadriplegic: total sensory loss††	27.0	33.1
Paraplegic: total sensory loss‡‡	24.3	27.9
Quadriplegic: partial sensory loss§§	4.0	5.8
Paraplegic: partial sensory loss‖‖	11.8	9.1
Paretics: variable sensory loss¶¶	32.9	24.0

*There is no significant difference between the two steroid groups in the distribution of patients by completeness of neurological deficit (Pearson $\chi^2_4=4.57$; $P=.33$).

†Quadriplegic and analgesic, and anesthesic.

‡Paraplegic and analgesic, and anesthesic.

§Quadriplegic and hypalgesic, or hypesthesic.

‖Paraplegic and analgesic, or hypesthesic.

¶Quadriparetic, paraparetic, and minimal motor dysfunction with variable sensory loss.

Table 8.—Summary Statistics for Steroid Effects Six Weeks* and Six Months† After Injury

Sensory Modality	Mean Change (1)‡	SD (2)	Sample Size (3)	Dose-Specific Adjusted Change: High (4)	Dose-Specific Adjusted Change: Low (5)	P Value for Dose Effect (6)	Model df (7)
Six Weeks							
Motor score, all	−6.0	11.1	258	−8.2	−8.8	.63	15
Plegic: total sensory loss	−1.9	6.0	142	−1.7	−2.8	.31	12
Plegic: partial sensory loss	−14.0	15.7	44	−25.8	−30.3	.33	9
Paretic: variable sensory loss	−9.3	11.7	72	−14.2	−10.4	.10	12
Pinprick	−4.1	10.5	258	−7.1	−6.2	.44	15
Light touch	−4.5	9.8	258	−7.4	−7.0	.68	15
Six Months							
Motor score, all	−10.0	11.2	179	−13.2	−14.1	.59	15
Plegic: total sensory loss	−6.0	10.0	102	−8.3	−7.8	.82	12
Plegic: partial sensory loss	−16.6	11.5	27	−30.5	−30.8	.95	7
Paretic: variable sensory loss	−14.4	8.7	50	−19.5	−20.2	.81	11
Pinprick	−6.4	9.7	178	−9.4	−9.9	.71	15
Light touch	−6.8	9.5	177	−10.4	−10.4	.96	15

*Thirty to 96 (for one patient, 122) days after injury; mean, 47.4 days; SD=9.1

†One hundred seventy to 237 days after injury; mean, 197.0 days; SD=14.9.

‡Numbers in parenthesis indicate column numbers.

Table 9.—Rates and Relative Risk of Complications by Steroid Protocol

Complication	Steroid Protocol, %: High Dose (n=151)	Steroid Protocol, %: Low Dose (n=153)	Relative Risk (95% CL)*
Urinary tract infection	35.4	30.1	1.18 (0.86, 1.63)
Pneumonia	17.9	19.0	0.94 (0.63, 1.42)
Decubitus	16.0	11.8	1.36 (0.77, 2.40)
Gastrointestinal tract hemorrhage	9.9	8.5	1.17 (0.58, 2.38)
Wound infection	9.3	2.6	3.55 (1.20, 10.59)
Sepsis	8.6	5.2	1.65 (0.71, 3.86)
Arrhythmia	7.3	7.8	0.93 (0.63, 1.39)
Thrombophlebitis	5.3	5.9	0.90 (0.36, 2.26)
Pulmonary embolus	4.6	2.6	1.78 (0.53, 6.03)
Paralytic ileus	4.0	3.3	1.21 (0.38, 3.86)
Congestive heart failure	2.0	2.6	0.76 (0.17, 3.31)
Myocardial infarction	0.7	2.0	0.34 (0.04, 3.07)
Angina pectoris	0.0	0.0	1.00 (not estimable)

*Ninety-five percent confidence limit (CL) calculated using the variance of the logarithm (relative risk).

with partial sensory loss showed the most motor improvement (−14.0). Paretics had average improvement (−9.3). The respective improvement in the change score for pinprick and light touch was −4.1 and −4.5, respectively, for all patients.

The upper panel of Table 8 summarizes the multivariate six-week analysis. Column 1 gives the unadjusted mean reductions in neurological dysfunction reported herein with respective SDs in column 2. Sample sizes are given in column 3. The effects of variables that may have affected the results are adjusted for in columns 4 and 5. These are the changes in dysfunction after removing differences among study centers and other variables given in Tables 4 through 7. Therefore, motor dysfunction declined 8.2 and 8.8 points in patients receiving the high and low steroid dose, respectively, after this adjustment. In comparing columns 4 and 5, the declines in dysfunction can be observed to be similar for those in the two steroid protocols. In no case are the differences statistically significant. Paretics with variable sensory loss have a somewhat greater reduction in dysfunction when given the high steroid dose ($P=.10$). The final column indicates the relative complexity of the model used in the adjustment process. Models with more degrees of freedom are more complex.

Neurological Status at Six Months

The neurological assessment at six months was performed on 179 patients (91, high dose; 88, low dose). An additional five patients had died; 95 patients were unavailable for follow-up or not examined on schedule. Among all patients, 70.6% showed some improvement in motor function (improving at least one point on the expanded motor scale), 6.1% of

Table 10.—Survival to 210 Days by Steroid Protocol

Survival	Steroid Protocol, No. (%) High Dose (n=152)	Low Dose (n=154)	Total, No. (%)
Died ≤14 days*	9(5.9)	3(1.9)	12(3.9)
Died 15-28 days†	6(3.9)	5(3.2)	11(3.6)
Died 29-210 days‡	4(2.6)	5(3.2)	9(2.9)
Survived >210 days	133(87.5)	141(91.6)	274(89.5)

*Relative risk for death less than or equal to 14 days, 3.10 (95% confidence limits of 0.85 to 11.26); χ^2=3.12, not significant.

†Relative risk for death less than or equal to 28 days, 1.92 (95% confidence limits of 0.60 to 6.19); χ^2=2.30, not significant.

‡Relative risk for death less than or equal to 210 days, 1.49 (95% confidence limits of 0.40 to 5.52); χ^2=1.34, not significant.

patients were unchanged, and 23.3% grew worse. The average improvement on the expanded motor score was −10.0 (SD=11.2). Within each category of completeness of lesion, there was a further small improvement in motor function compared with that shown at six weeks. The pinprick and light touch sensory modalities also showed further increases in sensation (Table 8, lower panel, column 1) at six months. Comparison of the steroid effects, adjusted for all other variables that might affect the results, discloses almost identical levels of dysfunction for patients in both treatment protocols (columns 4 and 5), which are confirmed by the lack of statistically significant P values (column 6).

Morbidity and Mortality

The rates and relative risks of complications associated with steroid treatment are given in Table 9 and ranked by frequency of occurrence. Only wound infection differed significantly between treatments, occurring 3.6 times more frequently in patients given the high dose (P=.01).

Table 10 reports survival at six months. Death within 14 days of injury was 3.10 times as common in patients under the high-dose protocol and 1.92 times as common within 28 days. The difference in mortality between the steroid protocols decreased after 28 days. None of the differential mortality rates was statistically significant. Of the 23 deaths occurring within 28 days, 19 were plegic patients with complete sensory loss, two in plegics with sensory sparing, and two in paretic patients. The leading cause of death in the low-dose steroid group is respiratory arrest and in the high-dose steroid group, cardiac arrest. There was no meaningful pattern to any of the causes of death when examined by steroid treatment.

The case fatality rates within 28 days were further analyzed using the Kaplan-Meier product limit survival distribution.[27] This analysis is based on the individual survival times and uses all the available follow-up information to estimate survival probabilities independent of the interval of observation. No statistically significant difference in the survival times of patients in either steroid treatment group were observed (P=.20, generalized Wilcoxon test; P=.17, generalized Savage test[28]).

COMMENT

The results of this randomized clinical trial indicate that patients with acute spinal cord injury treated with 1.0 g of methylprednisolone daily had almost identical rates of neurological recovery, six weeks and six months after injury, compared with patients treated with a 0.1-g standard dose. The study does not necessarily suggest that methylprednisolone is inefficacious in treating spinal cord injury, although that is a hypothesis that now requires testing. It is possible that the standard methylprednisolone dose improves neurological recovery and that the tenfold larger dose offers no additional improvement. Only comparison of the standard dose with a placebo can test this. The study does indicate, however, that patients with spinal cord injuries treated with 1.0 g/day of methylprednisolone for ten days are at increased risk of wound infection and, possibly, death. Differences in the case fatality rates of the two treatment groups never achieved the usual level of statistical significance. Nevertheless, patients treated with high-dose steroids experienced over three times the fatality rate of patients given the standard dose in the first 14 days after injury and while the steroid was being administered. The high-dose group's case fatality rate within 28 days was twice that of patients receiving the standard dose. None of the causes of death could be directly attributed to steroid treatment during intensive individual case review. The elevated case fatality rate in the high-dose steroid patients was of such concern, especially in the absence of any evident benefit, that patient accrual into the trial was discontinued several months before the planned termination date.

The present findings conflict with many of those of the animal studies, which show a positive effect of steroids. Physiological, biochemical, and anatomic differences, as well as possible variation in the biological response of trauma, may account for this.[29] There is also some difficulty in generalizing the weight-dropping technique, used to cause injury in experimental animals, to injuries in humans that often include a factor caused by rotation, which, in most fracture dislocations, is the principal cause of injury to the spinal cord.[17,30]

It is possible that the high dose of methylprednisolone used in this study did not reach therapeutic levels. A recent review of animal studies suggests that methylprednisolone in the range of 15 to 30 mg/kg of body weight is necessary to improve neuronal excitability and impulse conduction, increase postinjury blood flow, and preserve cord ultrastructure by reducing injury-induced, free radical-catalyzed lipid peroxidation.[31] The methylprednisolone dosages in the present study were equal to 1.43 and 14.3 mg/kg for an average (70-kg) subject.

It had been anticipated that a number of morbid conditions might be increased with the higher dose of steroids. However, only wound infection (of both the original lesion and operation site) was significantly (P=.01) increased in the high-dose steroid patients. There was also a 78% increased risk of pulmonary embolus among high-dose patients, although this occurred in a small proportion of patients and was not statistically significant. Decubitus ulcers were more prevalent in the high-

dose steroid group (P=.18), as was sepsis (P=.25). The relative risks of other complications remained close to one. It was of particular interest that the incidence of GI tract hemorrhage did not increase with the high steroid dose. Patients were treated for GI tract hemorrhage using routine procedures at each center. Of all patients, 29.6% received cimetidine hydrochloride alone, 43.1% received cimetidine and another antacid, 23.7% received an antacid without cimetidine, and 3.6% were not treated pharmacologically.

Although the six-week follow-up examination was performed on 91.8% of living patients, this dropped to 65.1% at six months. Patients not examined on schedule and those unavailable for follow-up fell equally into the two treatment groups and do not seem to have led to any bias in the study outcome.

The measures of neurological function used in this study are sensitive to small changes. Thus, improvement can, at minimum, reflect a shifting from, for example, complete absence of neurological function at any segment to a flicker or trace of contraction at the same segment or, alternatively, a lowering of the level of injury from, for example, active movement without antigravity at C-6-C-7 and below to C-7-C-8 and below. Depending on where they occur, such small neurological changes may or may not make an important difference to the patient's ability to cope with activities of daily living. Sensitive measures of neurological function were chosen as outcome measures for the trial because improvement in them is necessary, although not sufficient, if spinal cord treatments are to eventually improve the patient's ability to function.[32]

It is widely believed on theoretical grounds that steroids administered soon after injury will be more efficacious than those given later. The time from accident to administration of the first (loading) treatment dose was entered into all the analytic models but showed no significant effect. As another check on this variable, we grouped the study subjects into those starting steroid therapy within three hours of injury (n=36), 3.1 to six hours (n=62), and 6.1 or more hours (n=202); the entire analysis was repeated within each group. Although some analyses were based on small numbers, in none of the extent of injury categories or the neurosensory parameters was there any evidence for effect of steroid treatment in improving neurological outcome.

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This study was funded by the National Institute of Neurological and Communicative Disorders and Stroke grant NS 15078.

The following staff members of the National Spinal Cord Injury Study Group provided assistance: Juliette Newman; Mary McClure, PA; Terry Abel, RN; Cathy Jones, MSN; Robin Smith, PT; Ann MacDonald, PT; Ana Chinea; Jackie Parkinson, RN; Ann Wetherbee; Carol Cayard, RN; Ruth Strautz, RN; Mecca Evans; Connie Thompson; Bonnie Muntz, RN; Sandra Martinelli, RN; Jackie Mears-Mathieu, RN; Jan Rojas, RN; Susan Hodge, RN; Roxann Baumgartner, RN; John Cote, PharmD; Brian Hotchkiss; Ronald Moleski, PharmD; and Debbie Jordan.

The following persons and institutions also provided assistance:

Monitoring Committee.—Herbert Karp, MD; O. Dale Williams, PhD; Nicholas Zervas, MD; Guy Odom, MD; and Michael D. Walker, MD.

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