Effects of timing of methylprednisolone or naloxone administration on recovery of segmental and long-tract neurological function in NASCIS 2

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Previous analyses of the National Acute Spinal Cord Injury Study (NASCIS) have not distinguished recovery of segmental function at the injury level from recovery of the long spinal tracts. Recovery at the injury level could be of considerable clinical significance, but long-tract recovery is the ultimate therapeutic goal.

This analysis demonstrates that the greatest proportion of all neurological recovery and of recovery due to treatment with very high doses of methylprednisolone within 8 hours of injury occurs below the lesion. Methylprednisolone treatment administered early following injury has been found to improve recovery below the lesion in patients initially diagnosed as having complete or incomplete injuries; it also leads to greater (but still relatively small) improvement in the injury level. The analysis indicates that delayed treatment with methylprednisolone is associated with decreased neurological recovery. Naloxone administration also improved neurological function below the lesion in patients with incomplete injuries; these results support further experimental work with this drug.

This observation of differential neurological response within a narrow treatment window has important implications for both experimental studies and clinical management. Early clinical management with high-dose methylprednisolone is supported by this analysis.

KEY WORDS • acute spinal cord injury • methylprednisolone • naloxone • National Acute Spinal Cord Injury Study • neurological recovery

Many large data sets and randomized trials of therapy have measured neurological recovery after acute spinal cord injury by scoring and summing the degree of motor or sensory function at each of a number of muscle roots or spinal cord segments. The resulting neurological score can be used as a baseline against which subsequent examinations are scored; this "change score" can provide an estimate of any neurological change. These measures are very useful in the analysis of data sets containing large numbers of patients and are sensitive to relatively small changes in neurological function. It is important to document these changes because they are necessary (although not always sufficient) precursors to improved functional status of patients.

The measures of neurological change reported by large clinical trials cannot distinguish between two important components of change: 1) recovery of segmental function at the level of injury, which may reflect recovery in one or more nerve roots at the level of injury; and 2) recovery of neurological function below the level of the spinal cord lesion, which can only be due to recovery of the long spinal tracts. While either recovery at the lesion level or improvement in the severity of injury below the lesion may have important consequences for the patient's functional status, the ability to identify the source of recovery provides important insight into its nature and process. Moreover, complete recovery from spinal cord injury will only be achieved when the spinal cord itself is repaired or protected from the degenerative processes that occur in the hours following an acute spinal cord injury.

The National Acute Spinal Cord Injury Study (NASCIS), established in 1977, conducts multicenter randomized controlled trials of therapies that might improve recovery from spinal trauma. Since its inception, the NASCIS has examined drug treatments that might ameliorate the complex series of biochemical processes known to occur in the spinal cord during the hours following traumatic insult. 3,3 NASCIS 2 compared the use of large doses of methylprednisolone or naloxone to placebo and reported that patients who started treat-
ment with methylprednisolone within 8 hours post-trauma had significantly improved motor function at 6 weeks, 6 months, and 1 year after injury. Improvement in pinprick and light touch sensation followed a similar course. In this paper, a form of statistical analysis is used that has been applied to the problem of differentiating between neurological recovery due to improvements in function at the level of the lesion and amelioration due to improved neurological function below the level of the lesion. The statistical procedures were developed using data from NASCIS I and are applied here to NASCIS 2 data.

Clinical Material and Methods

Patient Population

In all, 487 patients with the NASCIS 2 were randomly assigned to one of three groups: 162 were treated with methylprednisolone, 154 with naloxone, and 171 with placebo. These three treatment groups had an even distribution of a wide range of variables including patient characteristics, study protocol violations, severity of neurological dysfunction at the emergency room admission, prognostic indicators of possible recovery, and surgical or other aspects of patient management.

All patients were given a standardized neurological examination (described below) in the emergency room, then again at 6 weeks, 6 months, and 1 year after injury; complications and mortality rates were reported at the same time. Neither mortality nor complications occurred with greater frequency in any treatment group.

Neurological Examination

Motor Function. Six categories 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 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.

Pinprick and Light Touch Sensations. Twenty-nine segments from C2 through S-5 were evaluated bilaterally and their function was assessed (and scored) as either absent (0), decreased (1), or normal (2). An expanded score for each measurement ranged from 0 (absent at all levels) to 58 (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 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; 2) analgesic and anesthetic below T-1, if sensation was absent below T-1 and in all distal segments; 3) hyperalgesic and hypesthesic at or above T-1, if sensation was decreased at T-1 or above; 4) hyperalgesic and hypesthesic below T-1, if sensation was decreased below T-1; and 5) normal, if all segments were evaluated as normal.

Neurological Recovery

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.

Figure 1 shows the conceptual approach to the present analysis. At any follow-up examination the degree of neurological function in the great majority of spinal cord-injured patients could be defined as one of three types: preserved, neurological function present after the initial injury and still present at follow-up evaluation; recovered, function initially lost but present on later examination; or lost, function lost at the time of injury and still lost.

For a small number of patients, there was no recovery of function at follow-up evaluation, but rather an increase in lost motor function; in effect, the patient's overall condition worsened. This was true for motor function in 0.7% of NASCIS 2 patients tested at 1 year. For a somewhat larger group of patients (the proportion varied depending on the parameter and examination period), there was no change in neurological function at follow-up evaluation. Degree of function can be described by the level at which it is assessed and by the severity of dysfunction at the lowest measurable level (respectively, the x and y axes on Fig. 1). Thus, improvement can be achieved by lowering the level of dysfunction, by reducing the severity of the deficit, or by a combination of both. Figure 1 shows how the same measure of neurological function could be obtained from less severe injuries relatively high in the spinal cord, as from more severe injuries occurring lower down the spinal cord (in Fig. 1, this would be represented by equivalent areas of lost function).

Table 1 presents the method for derivation of data from the patient's neurological examination form. The level and severity of each patient's lesion at a follow-up examination are compared to the same patient's level.
and severity at the time of initial emergency room admission. Each patient's change in level and severity scores are entered into analyses of variance and covariance to compare treatment groups and adjust for covariates. The procedures used for estimating each patient's neurological level and severity of injury have been described in detail elsewhere. They are briefly summarized in the Appendix to this paper.

Results

Distribution of Initial Neurological Level and Severity of Injury

Figure 2 shows the distribution of the neurological level and severity of injury as calculated in the emergency room (that is, within a few hours of injury and prior to any pharmacological treatment). The single most frequent level of injury was at Level 1 (measured by the deltoid muscle groups, C-5), found in 27.9% of all NASCIS 2 patients. The second most frequent level of injury was Level 6 (measured by the opponens pollicis muscle groups, C-8, T-1), found in 24.0% of all patients. The severity of motor function in the vast majority of patients (79.8%) was Grade 5 (no contraction), with the remaining patients spread fairly evenly across all other grades.

Because of the method of scoring sensory function (across 29 segments), there was a broader distribution of levels than with motor function (Figs. 3 and 4). For both pinprick and touch sensation, the level of injury was most frequently seen in Levels 5 (cervical, C-6) and 6 (cervical, C-7) with frequencies of 15.4% and 15.0%, respectively, for pinprick and 15.0% and 14.6% for touch sensation. The third most common level for touch sensation was in the highest level (cervical, C-2), seen in 13.6% of patients, where only 7.6% of patients reported this level for pinprick sensation. By far the most common degree of severity for pinprick (60.2%) and light touch (65.8%) was "absent sensation."

Recovery of Neurological Function

For each neurological parameter, the recovery of level and the neurological function at the lowest level (net severity, Fig. 1) were calculated for each patient as a proportion of function recovered relative to the extent of neurological loss measured pretreatment in the emergency room. The full results are shown in Tables 2 and 3 for patients whose drug therapy was initiated within

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>NASCIS neurological form for severity and level of injury, showing data for one specific patient</strong></td>
</tr>
<tr>
<td><strong>Muscle Injury Level</strong></td>
</tr>
<tr>
<td>Severity</td>
</tr>
<tr>
<td>normal function</td>
</tr>
<tr>
<td>active movement against resistance</td>
</tr>
<tr>
<td>active movement with antigravity</td>
</tr>
<tr>
<td>active movement without antigravity</td>
</tr>
<tr>
<td>flicker/trace of contraction</td>
</tr>
<tr>
<td>no contraction</td>
</tr>
</tbody>
</table>

* For this patient, circled numbers show the results of neurological examination measured in the emergency room and boxed numbers the result of the neurological examination at follow-up review. In this patient, recovery of both the level and the severity are exhibited. For ease of presentation, eight levels (external digitorum (C-7, C-8) through peroneus longus and brevis muscles (L-5, S-1) are omitted (ellipses). The level is defined as the midpoint on the curve described by the zone of injury. Severity is defined at the S-1, S-2 level.
or after 8 hours posttrauma, respectively. The data for motor function in patients treated within 8 hours are shown in Figs. 5 and 6 left.

Figure 5 shows that, for motor function, a much larger proportion of total recovery is measured at the lowest segment than at the level of injury. Placebo-treated patients at 1 year had recovered 27.2% of their initially lost function measured at the lowest segment, but had recovered only 1.3% of neurological loss that could be attributed to level of injury. At 6 weeks and 6 months there was a small improvement in the level of deficit in the placebo-treated group. For both sensory measures, the extent of recovery due to improvement in level was greater than that for motor recovery, but here, too, lessening of severity was the largest component of total recovery.

Table 4 shows recovery of neurological function below the level of the lesion for all patients according to the time of initiation of drug therapy and whether the initial injury was incomplete or complete. Figure 6 left plots the motor function data for patients treated within 8 hours posttrauma. As expected, the patients with incomplete injury experienced considerably greater overall neurological recovery than did those with complete injury. In each stratum, the patients treated with methylprednisolone within 8 hours recovered more function than did those treated with placebo. For example, at 1 year patients with complete injury treated with methylprednisolone had recovered 7.0% of lost func-

![Graph showing frequency of calculated pinprick sensation level and severity in the emergency room among all NASCIS 2 patients. For grading systems see text.](image1)

![Graph showing frequency of calculated pinprick sensation level and severity in the emergency room among all NASCIS 2 patients. For grading systems see text.](image2)

![Graphs showing frequency of calculated light touch sensation level and severity in the emergency room among all NASCIS 2 patients. For grading systems see text.](image3)

![Graphs showing frequency of calculated light touch sensation level and severity in the emergency room among all NASCIS 2 patients. For grading systems see text.](image4)

![Graph showing recovery of lost motor function at and below the level of injury for all patients treated with methylprednisolone sodium succinate (MPSS), naloxone (NAL), or placebo (PL) within 8 hours of injury. * = Significance of difference from placebo: p < 0.05.](image5)
tion below the lesion compared with recovery of 1.6% for placebo-treated patients. The recovery percentages for patients with incomplete injury are 44.1% for those treated with methylprednisolone and 20.7% for those treated with placebo.

Among patients treated after 8 hours posttrauma, patients with incomplete injury also showed considerably greater recovery of motor function than those with complete injury who, in this comparison, demonstrated virtually no recovery below the level of lesion (Fig. 6 right). Among the incomplete-injury patients, those receiving methylprednisolone after 8 hours posttrauma recovered significantly less well by 6 months and 1 year than did patients treated with placebo. Patients treated with naloxone after 8 hours showed essentially the same recovery as patients treated with placebo.

Discussion

The foregoing analysis has confirmed, expanded, and clarified the results of NASCIS 2; however, we would add a note of caution about the statistical significance tests reported in this paper. Although some p values are shown for their nominal interest, none of these analyses were planned before NASCIS 2 started, and the trial was not designed to guarantee statistical power to test drug effects on neurological level and severity of deficit. Thus, the findings here are based on a post hoc analysis (the statistical methods were developed only after NASCIS 2 was finished). These results, therefore, primarily generate hypotheses for future testing. The new information falls into four areas.

First, expanded neurological scores used in previous NASCIS analyses do not distinguish neurological recovery due to recovery of one or more nerve roots from recovery of neurological function below the level of lesion resulting from protection of the spinal cord. The present analysis demonstrates very clearly that for all three neurological parameters, the greatest proportion of total neurological recovery was due to recovery measured at the lowest segments. This appears to be particularly so for motor function. The sensory parameters indicate a somewhat greater recovery of level although this may reflect the greater technical ability of the sensory measures to evaluate sensory level over a broader range of segments than is possible for motor function measures.

Increased recovery of segmental function at the injury level due to pharmacological treatment, shown to occur in a modest way with early methylprednisolone treatment, could have considerable clinical benefit. However, recovery of neurological function below the lesion level reflects pharmacological protection of the spinal cord lesion. This provides direct evidence in support of the theor-
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...and animal studies 
...underlying human trials of pharmacological agents in the early treatment of acute spinal cord injury. If future drug therapies are to lead to major neurological recovery, they must act on the lesion in the long spinal tracts. The present analysis offers the first direct evidence that this process can occur in humans.

Second, this analysis concerns the importance of the timing of initiation of drug therapy on treatment efficacy. All previous NASCIS findings indicate that initiating treatment by methylprednisolone within 8 hours posttrauma (the mode of time from injury to treatment initiation in NASCIS 2) results in significantly better recovery than in patients treated by placebo. The present analysis confirms these results in both incomplete- and complete-injury patients whose treatment was initiated within 8 hours, and further suggests that improvement is increased by methylprednisolone when measured by recovery of motor level and by recovery of function below the level of the lesion.

Third, the present analysis indicates more strongly than was evident from prior analyses that the effects of naloxone may also be influenced by the time of treatment initiation. For incomplete-injury patients treated with naloxone within 8 hours posttrauma, recovery below the level of lesion 1 year after injury was significantly greater than in placebo-treated patients. This indicates that naloxone may still be a potentially useful candidate for therapy but that drug-dosing schedules and timing may need further refinement in new animal studies. At this point, the high cost of naloxone and the superiority of methylprednisolone in all of the early treatment comparisons precludes the adoption of naloxone for use in clinical practice.

Fourth, this new analysis provides further evidence that initiation of treatment after 8 hours posttrauma leads to a very different neurological response than early initiation of treatment. Patients who were given naloxone later than 8 hours after injury did not differ in their neurological recovery from placebo-treated patients. Patients treated with methylprednisolone later than 8 hours posttrauma, however, recovered less well than did placebo-treated patients and were significantly worse at 6 months and 1 year when recovery of function was measured below the level of lesion in incomplete-injury patients.

We have speculated previously that high doses of methylprednisolone may interfere with normal neuron protection by inhibiting immune cell activity, including antigen-processing macrophages. Hall has

FIG. 6. Graphs showing recovery of lost motor function below the level of injury for patients with incomplete versus complete injuries treated with methylprednisolone sodium succinate (MPSS), naloxone (NAL), or placebo (PL) within (left) or after (right) 8 hours posttrauma. * = Significance of difference from placebo: p < 0.05.

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TABLE 4
Comparison of motor function recovery below level of lesion in 487 NASCIS 2 patients with incomplete and complete injuries according to time of initiation of drug therapy

<table>
<thead>
<tr>
<th>Time of Drug Treatment, Degree of Injury, &amp; Treatment</th>
<th>% Recovery of Function vs. % Loss*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Wks</td>
</tr>
<tr>
<td>drug therapy &lt; 8 hours</td>
<td></td>
</tr>
<tr>
<td>incomplete injuries</td>
<td></td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>24.9</td>
</tr>
<tr>
<td>naloxone</td>
<td>20.4</td>
</tr>
<tr>
<td>placebo</td>
<td>16.1</td>
</tr>
<tr>
<td>complete injuries</td>
<td></td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>2.0</td>
</tr>
<tr>
<td>naloxone</td>
<td>0.0</td>
</tr>
<tr>
<td>placebo</td>
<td>0.0</td>
</tr>
<tr>
<td>drug therapy &gt; 8 hours</td>
<td></td>
</tr>
<tr>
<td>incomplete injuries</td>
<td></td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>27.4</td>
</tr>
<tr>
<td>naloxone</td>
<td>22.0</td>
</tr>
<tr>
<td>placebo</td>
<td>26.7</td>
</tr>
<tr>
<td>complete injuries</td>
<td></td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>0.0</td>
</tr>
<tr>
<td>naloxone</td>
<td>0.4</td>
</tr>
<tr>
<td>placebo</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Percent recovery calculated from 1 - e^-D (time in expanded neurological score), as measured in the emergency room.
proposed that glucocorticoids may exacerbate acute postschismic neuronal necrosis and inhibit axonal sprouting. Thus, the benefit conferred with the early use of methylprednisolone on mechanisms believed to inhibit lipid peroxidation is lost, and increased damage may result when treatment is delayed more than 8 hours. The present analysis, therefore, confirms the beneficial effects of early initiation of methylprednisolone treatment at the high (30-mg/kg) dose, but equally points out the need to avoid initiating methylprednisolone treatment if it cannot be started within 8 hours of injury. Fortunately, the 8-hour time window is sufficient to include the vast majority of acute spinal cord injury patients.

The third NASCIS trial will examine some questions left unanswered by NASCIS 1 and 2. Because all patients in NASCIS 3 will have drug treatment initiated within 8 hours posttrauma, treatment initiation earlier and later within the 8-hour window can be compared. This will permit a more precise estimate of when both the protective and destructive mechanisms of high-dose methylprednisolone become operational. Moreover, comparisons can be made among patients in both a 24- and 48-hour methylprednisolone treatment regimen to examine the relative importance of time to initiation and length of treatment. Finally, since one-third of patients will be treated with 48-hour tirilazad mesylate, a compound known to exhibit potent lipid peroxidation inhibition properties without any glucocorticoid activity, the role of lipid peroxidation in secondary spinal injury can be tested and the possible benefits of 48-hour treatment evaluated.

Acknowledgments

The study drugs and their respective placebos were provided without cost by the Upjohn Corporation, Kalamazoo, Michigan (methylprednisolone) and the DuPont Corporation, Wilmington, Delaware (naloxone).

APPENDIX

Summaries of the motor level and severity of injury for individual patients were derived from a model of the effect of injury on spinal cord function. The variable x represents the level of injury, where x = 1 refers to the C-2 segment, x = 2 to the C-3 segment, and so on up to x = 29 for the S-5 segment. Neurological function at level x is represented by y(x), which takes values of 0 (none) to 5 (normal for motor function) and 0 (absent) to 2 (normal for pinprick and light touch sensations). A somewhat idealized model of the effect of spinal cord injury on motor function represents the relationship between function and level by y(x) = 5 - A/F(x) where F(x) is a nondecreasing function of level that takes values of 0 at the highest level, to 1 at the point where the highest observed loss occurs. The parameter A gives the net loss in the function score observed for a patient. Figure 1 shows the possible shape of such a curve for the motor function, which starts at Level 5 and ultimately reaches the lower limit of (5 - A(1)), which measures the neurological function at the lowest segment of the spinal cord as evaluated in the emergency room. Similarly, the relationship for pinprick and light touch sensations would be given by y(x) = 2 - A·F(x).

The area above the curve shown in Fig. 1 gives the overall loss of neurological function, estimated by the difference between the highest possible and the observed expanded scores, T. This net loss of function is affected not only by the net severity but also by the level of the injury. There are several clinical measures of injury level that have been proposed, such as the first segment showing some loss of function. However, it is preferable to use a middle point on the curve to summarize the contributions of net severity and injury level to the expanded score. As one can see from Fig. 1, when there is symmetry about the point at which the curve intersects the line indicating the level of injury, B(1) for the initial measurement, then the area representing overall loss of function is given by the area of the rectangle, T(1) = A(1)·B(1), because the area outside the rectangle matches the extra piece included in the lower left corner. Obviously, this result will only be approximately true if the curve is not symmetrical; nevertheless, it should be an improvement on an estimate that uses the first segment at which some loss occurs when summarizing the components of the expanded score. A second methodological advantage to using a middle value is that it provides a sturdier estimate of level. The behavior of F(x) is much less a probability distribution function, so that it is convenient to use the mean, B(1), as the central measure of injury level.

The relationship between the expanded score and its components extends to the consideration of changes with time. If T(1) and T(2) represent the expanded neurological scores previously used in NASCIS analyses and measured at the time of injury and after a specified recovery period, then the ratio

\[ \frac{T(2)}{T(1)} = \frac{A(2)}{A(1)} \cdot \frac{B(2)}{B(1)}, \]

where A(1,2) and B(1,2) represent the corresponding measures of net severity and level of injury. Hence, if \( \Delta T = T(2)/T(1) \) represents the proportion of lost function recovered between two points in time, then

\[ 1 - \Delta T = \frac{1}{[1 - \Delta A]} \cdot \frac{1}{[1 - \Delta B]}, \]

where \( \Delta A \) and \( \Delta B \) are the corresponding proportions of level and net severity that have been recovered.

For this analysis, estimates of injury severity, \( \hat{A} \), were obtained using isotonic regression. The location of injury, \( \hat{B} \), was obtained for each subject, using the mean derived from an estimate of F(x). For pinprick and touch sensation, there is an exact relationship between the expanded score, \( \hat{T} \), and the separate component estimates of net severity, \( \hat{A} \), and injury level, \( \hat{B} \), such that \( \hat{T} = \hat{A} \times \hat{B} \). On the other hand, the relationship is only approximately true for motor function because more than one muscle can evaluate the same spinal cord segment.

Analysis of covariance was used to obtain estimates of the mean log ratio of the injury components measured after a specified period of time and also measured in the emergency room, adjusted for whether the patient showed complete neurological function in the emergency room. The proportion recovered was estimated by \( 1 - \frac{\text{adjusted mean log ratio}}{\text{frequency}} \). Factors included in the model were drug treatment, whether the patient received treatment within 8 hours posttrauma, and the corresponding interaction.

References

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