Complications associated with the prophylactic use of methylprednisolone during surgical stabilization after spinal cord injury

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Object. The authors attempted to determine if there is a significant relationship between the incidence of medical complications and the prophylactic use of methylprednisolone (MP) during spine surgery in patients with acute spinal cord injury (SCI) who had already received MP on hospital admission (typically in the setting of an Emergency Room/ Trauma Center).

Methods. The authors studied 73 patients with acute SCI who were admitted to the hospital for at least 7 days postinjury. All patients 1) received a 24-hour regimen of MP in the acute period of hospitalization; and 2) underwent surgery to stabilize the spine and/or decompress the spinal cord. Patients were separated into two groups on the basis of whether they received additional MP therapy during spine surgery. A chart review was conducted retrospectively to determine the incidence of complications up to 6 weeks postinjury. Muscle strength and American Spinal Injury Association grades were determined prospectively throughout the follow-up period.

In patients who received two courses of MP following acute SCI (one at initial hospitalization and one during surgery), a significantly increased probability of complications was demonstrated compared with those who received no MP therapy during surgery. This was particularly evident when the incidences of serious complications were compared.

Conclusions. Prophylactic use of MP as a neuroprotective agent during spine surgery in patients with acute SCI should be avoided in those in whom MP was administered on admission to the hospital.

KEY WORDS • spinal cord injury • methylprednisolone • steroids • complications

Since findings of the second NASCIS were published more than a decade ago,8 use of MP for the treatment of acute SCI has been considered a standard of care in the United States (and some other countries),4,14,19,27,30,33,41 despite the fact that the Food and Drug Administration has not granted an “indication of use” to this drug for treating SCI.18 In a number of recent reports and letters authors have questioned the safety and efficacy of MP in the treatment of acute SCI.17,19,23,36,38

Methylprednisolone and related glucocorticoid agents have a host of physiological actions, but many believe that, with respect to acute neurotrauma, they are most valuable as antiinflammatory agents.1,13,21,43 This property of glucocorticoids has long been recognized by neurosurgeons. Steroids were widely used for treating injury to the spinal cord prior to publication of the NASCIS II findings.19,37,40 There is also an extensive body of literature in which authors have reported on the successful use of steroids for minimizing postsurgical pain following lumbar discectomy.15,16,20,24,28,42 although positive effects have not been shown in all such studies.26,29,32 Patients who awaken after spine surgery with evident deterioration of central nervous system function are also often treated with high-dose steroids.25,39

In our medical center, steroids are often administered in a prophylactic manner prior to or during spine surgical procedures that place the spinal cord at risk. This includes patients with recent spine fractures who are undergoing surgery to correct alignment and achieve spinal stabilization. Glucocorticoids are known to cause a variety of adverse side effects, as noted in both NASCIS II and NASCIS III trials themselves. These side effects include increased risk for infection, delayed wound healing, and GI bleeding. In the present study, we sought to examine whether patients with acute SCI who received MP in the emergency room as well as during surgery (that is, two courses of MP therapy) were at greater risk for steroid-related side effects than patients who received steroids in...
the acute phase and who underwent surgery during which steroids were not administered.

Clinical Material and Methods

Patients with acute SCI admitted to JMH were recruited for neurophysiological study after providing informed consent to participate in a research protocol approved by the University of Miami’s Institutional Review Board. The mean patient age was 38.8 ± 16.5 years. Voluntary contraction in as many as 24 upper- and lower-limb muscles was assessed using surface EMG electrodes. All muscle responses were studied bilaterally. In patients with cervical injury, we assessed biceps brachii, triceps brachii, wrist extensors, wrist flexors, thenar group, hypothenar group, psoas, quadriceps, hamstring, tibialis anterior, soleus, and abductor hallucis muscles. Only lower-limb muscles were studied in patients who sustained thoracic or thoracolumbar injury. Determination of ASIA grade31 was also made at this evaluation. This initial assessment was typically performed within the first 5 days following injury. Assessments were not conducted within 24 hours following a surgical procedure because of the uncertainty of patient-related compliance associated with pain medications. Additional details regarding neurophysiological assessment have been reported elsewhere.10

Medical records were studied retrospectively to obtain other data. All patients included in this study were hospitalized for a minimum of 7 days following admission. Chart reviews extended to a period of no more than 6 weeks postinjury, despite the fact that the majority of individuals were admitted for periods extending beyond this point. This cutoff was made to minimize the probability of including complications associated more with prolonged immobility than with MP administration early after a patient's injury. Details of MP administration (including dosing protocol) at the acute stage were extracted from the medical records. All individuals underwent surgery for spinal stabilization. Records pertaining to surgery and anesthesiology were examined to determine MP administration (including dosing protocol). Details of the surgical procedures, although available, are not included in the present study.

All patients were treated in the same facility and housed on the same two hospital floors postoperatively. These sites included the neurosurgical intensive care unit, the step-down unit, and the neurosurgery and orthopedics wards. Some individuals were discharged or transferred to the rehabilitation unit (also in the same facility) prior to the 6-week cutoff for study results. Patients who were transferred to JMH after undergoing medical stabilization elsewhere and for whom there was uncertainty about MP administration were excluded from this study.

The following complications were tallied: urinary tract infection (based on laboratory findings and a urologist’s diagnosis), pneumonia (based on symptoms, radiological findings, and a critical care specialist’s diagnosis), decubitus ulcer (pressure sore, based on physical examination and orders for altered patient positioning), GI bleeding (confirmed by endoscopic examination), DVT (based on ultrasonographic findings), pulmonary embolus (based on computerized tomography angiography and ventilation-perfusion scanning), and sepsis (based on laboratory findings and a critical care specialist’s diagnosis). Instances of death were also tallied in this analysis. Any one patient could sustain multiple complications, which were tallied independently.

Muscle contraction attempts were recorded on magnetic tape for off-line analysis. An investigator blinded to the clinical status of each patient assigned numerical values of 0 (no EMG recruitment) through 5 (normal interference pattern) to each contraction attempt; these values correspond with those of the widely used “manual muscle test.”11 Upper-limb muscle scores were summed and divided by the number of muscles examined to produce a mean score for each limb. This averaging approach was used to accommodate those cases in which EMG responses from one or more muscles could not be recorded for injury- or treatment-related reasons (including the presence of casts, wound dressings, or intravenous/arterial lines). With this numerical system, normal muscle strength across all muscles in each limb would be scored 5 (that is, \[5 + 5 + 5 + 5 + 5 + 5\]/6). Any value less than 5 indicated diminished EMG recruitment within one or more of the muscles examined in that limb.

For categorical variables, a chi-square test was used to determine significant differences. To analyze days to surgery, incidence of complications, and incidence of severe complications, a two-sample t-test was used. For ASIA grade distributions, the Fisher exact test was used. Results were considered significant if the probability value was less than 0.01.

Results

Results were studied over a 3.5-year period in 73 patients with acute SCI recruited who 1) were admitted to JMH for a minimum of 7 days; 2) had complete medical records available for review; 3) received MP within 8 hours of injury, according to their medical record; 4)

| Table 1 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Group           | No. of Patients | No. of Males    | No. of Females  | Age (yrs)       |
| MPw            | 18              | 16              | 2               | 37 ± 14         |
| MPw ++         | 55              | 39              | 16              | 40 ± 17         |
|                |                 |                 |                 | Min 17          |
|                |                 |                 |                 | Max 66          |
|                |                 |                 |                 | Cervical Injury (%) 50 |

* Max = maximum; Min = minimum; SD = standard deviation.
underwent spinal surgery for decompression and/or stabilization of the spine; and 5) consented (and assented, for children) to participate. Table 1 provides a summary of demographic data as well as the percentage in each group with cervical spine injuries. The mean patient age was 38.8 ± 16.5 years, a somewhat higher value than was reported in any of the three NASCIS trials.7–9 Table 2 provides a summary of the primary injury mechanism. Not surprisingly, motor vehicle accidents were the most common cause of injury. In Table 3 ASIA grades determined at the time of initial evaluation are listed.

In all patients MP was administered within 8 hours of injury, according to NASCIS II recommendations (loading [bolus] dose of 30 mg/kg, supplemented over 23 hours at 5.4 mg/kg/hr). Surgery was performed in all cases to decompress the spinal cord and/or stabilize the spine. Patients were grouped according to whether they received a course of MP during surgery. In one group of patients MP was delivered acutely but not during surgery (MPa; 18 patients). In the second group patients received MP acutely and during surgery (MPa+s; 55 patients). The average time to surgery was 4.8 ± 6.3 days and 5.2 ± 6.7 days for the MPa and MPa+s groups, respectively. This difference was not statistically significant (p = 0.80). Delivery of MP intraoperatively followed the NASCIS II protocol, but maintenance doses were sometimes discontinued once the patient had left the surgical suite. That is, all patients in this group received a second loading dose with maintenance while they were in the surgical suite, but additional doses were sometimes discontinued after they were moved to the recovery room and then to the unit.

The graphs in Fig. 1 show the incidence of MP-associated complications in the two groups as a percentage of each group’s total population. Those in the MPa+s group experienced a total of 110 complications during their acute hospitalization (a mean of 2 complications per case), whereas those in the MPa group sustained just less than 0.9 complications per case, on average. This intergroup difference with regard to incidence of complications was statistically significant (p < 0.01). Moreover, the graphs in Fig. 1 also show that the nature of the side effects was much more likely to be serious (GI bleeding, DVT, pulmonary embolus, or sepsis) in patients in the MPa+s group (29 serious complications of 110 total) compared with those in the MPa group (one serious complication of 16 total). This difference in incidence of MP-associated serious side effects was also significant (p < 0.01). Finally, three patients in this study died within 42 days of SCI; all received MP both acutely and intraoperatively (each was in the MPa+s group). These cases were not tallied in the aforementioned numerical comparisons, because death was a direct consequence of the complications noted.

Six (33%) of the 18 patients in the MPa group did not

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TABLE 1

Demographic data

<table>
<thead>
<tr>
<th>Group</th>
<th>MVA</th>
<th>Fall</th>
<th>GSW</th>
<th>HBC</th>
<th>Blunt</th>
<th>Sports</th>
<th>Diving</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPa</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>MPa+s</td>
<td>29</td>
<td>12</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Blunt = struck by falling object; GSW = gunshot wound; HBC = pedestrian or bicyclist hit by car; MVA = motor vehicle accident.

TABLE 2

Mechanisms of injury*

<table>
<thead>
<tr>
<th>Cause of Injury</th>
<th>MPa</th>
<th>MPa+s</th>
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<tr>
<td>MV A</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Fall</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>GSW</td>
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<td>0</td>
</tr>
<tr>
<td>HBC</td>
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<td>3</td>
</tr>
<tr>
<td>Blunt</td>
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<td>7</td>
</tr>
<tr>
<td>Sports</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diving</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Blunt = struck by falling object; GSW = gunshot wound; HBC = pedestrian or bicyclist hit by car; MV A = motor vehicle accident.

TABLE 3

Percentage of patients in each group classified by ASIA grade determined at initial evaluation

<table>
<thead>
<tr>
<th>ASIA Grade (%)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPa</td>
<td>39</td>
<td>11</td>
<td>33</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>MPa+s</td>
<td>47</td>
<td>15</td>
<td>22</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

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Fig. 1. Bar graphs showing percentage of patients in each group who experienced each of the complications noted (P Sore = pressure sore; PE = pulmonary embolus; Pneum = pneumonia; UTI = urinary tract infection).
experience any of the complications tallied in this study. In the MP$_{+}$ group, 10 (18%) of the 55 patients were free of complications. This intergroup difference in the numbers of cases without complications was not statistically significant (p = 0.18).

We considered the possibility that the higher incidence of complications in the MP$_{+}$ group was a result of overall differences in the injury severity between individuals in the two groups. For example, those with more severe injury might be more likely to require bladder catheterization and be less able to reposition themselves to relieve pressure points than those with greater preservation of neurological function caudal to a spinal lesion. We believe, however, this explanation cannot account for the observed differences, for several reasons. As shown by the graphs in Fig. 2 patients in both groups had very similar durations of hospitalization, with more than 50% in each group being hospitalized for 4 or more weeks following injury. Another indicator of functional capability is that of EMG scores during voluntary muscle contraction; these measures have been shown to relate in a positive and statistically significant manner to manual muscle test scores across multiple upper- and lower-limb muscles.11 In the present study, mean EMG scores were virtually identical between groups for each of the four limbs, as shown in Fig. 3. There was good agreement between mean left- and right-side values, and upper-limb mean scores were somewhat higher than those of lower-limb values. These findings suggest similar degrees of functional disability between the two populations, with the only obvious difference being whether patients received a second administration of MP during surgical stabilization after SCI.

Finally, ASIA classification showed a moderately higher probability of Grades A and B neurological injuries in the MP$_{+}$ group (47% and 15%, respectively) compared with those in the MP group (39% and 11%, respectively). Differences in the distribution of patients by ASIA grade, however, were not statistically different based on results of the Fisher exact testing. Because of the smaller number of patients in the MP group, this intergroup distinction by ASIA grade would have been all but eliminated had the number of cases receiving Grades A and B been higher by a value of one.

**Discussion**

Controversy surrounds use of the drug MP as a neuroprotective agent after SCI. On the one hand, there is evidence derived from animal spinal cord lesion studies demonstrating MP-associated benefit with respect to tissue preservation or regeneration.2,12,35 In contrast, the NASCIS II and III trials have been criticized extensively for issues related to study design, data management, and the manner in which data were published.22,23,33,38 Moreover, NASCIS III suffered from an error in randomization that led to a large difference between groups in the numbers of patients with intact motor function (likely leading to a ceiling effect, because motor recovery was the primary outcome variable; see Table 2). Some of these criticisms have been addressed,5,6 yet debate continues over the known risks in comparison with questionable (some assert) benefits of this treatment regimen after human SCI.

We did not attempt to evaluate the role of MP with respect to recovery of neurological function in patients who received one MP dose (MP$_{-}$ group) compared with those who received two doses (MP$_{+}$). Instead, our focus was the prophylactic use of MP in surgical procedures that place the spinal cord at potential risk of injury. This practice is clearly one that has evolved over time, and publication of the NASCIS II appears to provide justification, albeit indirect, for this approach. Steroid therapy for known or suspected SCI actually predates the original NASCIS I publication.3,19,25,39 There are no studies known...
to us in which the authors have directly addressed the risks and benefits of prophylactic use of MP or other steroids for spinal cord neuroprotection during spine surgery. In the present study, the decision of whether to use MP during surgery appeared to be a function of the surgeon’s preference; there was no information derived from any of the medical records that addressed this issue.

Based on analysis of findings in the present study we found a significant risk to be associated with delivery of MP during surgery in patients with acute SCI who already received a large dose of MP during the 1st day postinjury. Not only is the probability of a steroid-based complication significantly higher in this group, but at least some of these complications are likely to be more difficult to treat (and can be life threatening). It is quite possible that, had the second MP dosing protocol been maintained for the recommended 24-hour period in all patients in the MPa group (maintenance doses sometimes being discontinued once patients left the operating room suite), the difference in complications might have been even more marked.

The 6-week time period over which complications were tallied was chosen to be consistent with other studies. This follow-up duration is identical to that reported in the NASCIS II and III trials.8,9 Gerndt, et al.,19 have stated that MP-related complications “...would be most apparent within the first few weeks of administration.” In a prospective trial, Matsumoto, et al.,30 followed patients with steroid-related complications for 2 months postinjury. Based on detailed analysis of blood samples, Galandiuk, et al.,17 reported evidence of immunosuppression for 12 to 14 days following steroid therapy in patients with acute SCI. Longer periods of follow up might artificially implicate steroid use as a contributor to complications that more likely reflect risks associated with prolonged immobility and repeated catheterization.

In our study the two populations, although similar in relative composition, were not perfectly balanced with respect to sample size, injury severity, age range, or level of injury. With this in mind, the partially retrospective nature of the present study cannot, in and of itself, allow one to draw conclusions as to whether MP use causes excessive morbidity among the patients with acute SCI. Only a double-blind, randomized, and placebo-controlled study could be used to address this issue. Published studies along these lines, including the three NASCIS trials, all conclude that the probability of developing specific steroid-related side effects appears to be increased7,9,17,19,30,36 but conclusive statistical corroboration is typically lacking. In the present study, in which we effectively included individuals who underwent extended periods of steroid therapy, the three cases of death all occurred in patients in the MPa group. It is often overlooked that patient recruitment into NASCIS I was halted prematurely because of concerns about a high mortality rate in the group receiving prolonged (10-day) MP administration.7

Conclusions

The present study has several weaknesses in its design. These include the retrospective manner in which complications were tallied and the imbalance between study groups (arising from a failure to randomize). In light of these weaknesses, our goal is simply to provoke spine surgeons into reconsidering the practice of prophylactic, systemic delivery of MP during surgery in patients with acute SCI in whom MP was already administered on hospitalization. Surgical administration of MP in such patients might be warranted in those cases in which the surgical team has clear evidence that surgically associated central nervous system damage has occurred, which might be demonstrated by intraoperative electrophysiological monitoring.44 Other than this rare case, however, and if the acknowledged weaknesses in this study are found to be acceptable, our findings indicate that prophylactic delivery of MP during surgery should be avoided in individuals with recent SCI who have already received MP at the time of their initial hospitalization.

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References


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