

Pharmacological Therapy for Acute Spinal Cord Injury

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RECOMMENDATIONS

Level I

- Administration of methylprednisolone (MP) for the treatment of acute spinal cord injury (SCI) is not recommended. Clinicians considering MP therapy should bear in mind that the drug is not Food and Drug Administration (FDA) approved for this application. There is no Class I or Class II medical evidence supporting the clinical benefit of MP in the treatment of acute SCI. Scattered reports of Class III evidence claim inconsistent effects likely related to random chance or selection bias. However, Class I, II, and III evidence exists that high-dose steroids are associated with harmful side effects including death.
- Administration of GM-1 ganglioside (Sygen) for the treatment of acute SCI is not recommended.

RATIONALE

The search for an effective neuroprotective strategy to prevent secondary injury in the setting of acute SCI remains a priority for basic scientists and clinicians alike. Despite promising results for a number of compounds tested in the laboratory,¹ only 5 pharmaceutical agents have been evaluated in humans with the purpose of improving function after acute SCI. All 5 pharmacological treatments have been evaluated in controlled,

randomized, blinded clinical trials of human patients who have suffered acute SCI. Three substances, naloxone, thyrotropin release hormone, and tirilazad, have been studied less extensively.^{2–4} Further research to define their therapeutic roles in SCI is necessary but because of modest results is unlikely to occur. In 2002, the guidelines author group of the Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) published a medical evidence-based guideline⁵ on the use of MP and GM-1 ganglioside in the setting of acute cervical spinal cord injury. The purpose of the current review is to build on that foundation, adding pertinent new evidence accumulated over the past decade. There have been no new pharmacological agents formally tested for clinical use in SCI through this time period.

SEARCH CRITERIA

A National Library of Medicine (PubMed) computerized literature search from 1966 to 2011 was undertaken using Medical Subject Headings of “steroids,” “methylprednisolone,” and “GM-1 ganglioside” in combination with “spinal cord injury” and “neurological deficit.” Approximately 680 000 citations were acquired. Non-English-language citations were excluded, as were nonhuman experimental studies. Titles and abstracts of 641 manuscripts were reviewed, 589 on the topic of steroids and human SCI and 52 on the topic of GM-1 ganglioside and human spinal cord injury. Additional publications were cross-referenced from the citation lists of the remaining papers. Finally, the members of the author group were asked to contribute articles known to them on the subject matter that were not found by other search means. Duplications,

ABBREVIATIONS: ASIA, American Spinal Injury Association; MP, Methylprednisolone; NASCIS, National Acute Spinal Cord Injury Study; SCI, spinal cord injury

case reports, pharmacokinetic reports, general reviews, editorials, critiques, and manuscripts with mention of one agent or another but without original data were eliminated. Twenty-seven studies on MP and 2 studies on GM-1 ganglioside provide the basis for this review and are summarized in Evidentiary Table format (Tables 1-2).

SCIENTIFIC FOUNDATION

Methylprednisolone

The most research into pharmacotherapy for SCI has been generated by investigation of the potential benefit of MP administration. Certainly the most widely recognized studies are the National Acute Spinal Cord Injury Study (NASCIS) II and III published between 1990 and 1998.^{2,4,6,7} The original NASCIS I trial reported negative results in comparing “high-dose” to “low-dose” MP in 306 patients with acute SCI.⁸ High-dose patients received an MP loading dose of 1000 mg followed by the same dose daily thereafter for a period of 10 days. Low-dose patients received a loading dose of 100 mg followed by a further 100 mg each day for 10 days. Six-month follow up available on 54% of patients demonstrated no difference in motor or sensory outcomes in the high-dose group compared to low-dose patients. Wound infection was 3 times more frequent in the high-dose group ($P = .01$), and 3 times as many patients receiving high-dose MP died within the first 2 weeks of treatment (6% vs 2% mortality). One-year follow up confirmed the absence of a neurological difference between the 2 groups.⁹

The second of the 3 NASCIS studies investigated the effect of MP and naloxone administration in 487 patients with acute SCI.² In this study MP was administered in an initial loading dose of 30 mg/kg followed by 5.4 mg/kg/hour for 23 hours. While the naloxone data was uniformly uninformative, the authors reported a mean improvement of 5 points in motor score (total possible score = 50) and 4 points in sensory scores (total possible score = 58) for patients treated with MP compared to controls at 6 months, as long as they received the drug within 8 hours of injury. Improved motor scores persisted at 1 year ($P = .03$), but the difference in light touch and pinprick sensation between MP and placebo groups was lost.⁷

Although the NASCIS II cohort totaled 487 patients, beneficial effects from MP administration were discernable only after a post-hoc 8-hour therapeutic window was imposed. The rationale for this 8-hour cutoff has never been substantiated.¹⁰ Two hundred and ninety-one patients randomized later than 8 hours from injury were therefore excluded from the analysis, eliminating over half of the study population. The final conclusions from the study were based on a cohort of 66 MP-treated patients compared to 69 controls. Only neurological scores from the right half of the body were reported, although bilateral neurological testing was performed. As mentioned above, sensory improvements were the same in MP and placebo-treated patients 1 year after injury.

Analysis of patients treated beyond the 8-hour window demonstrated MP to have a detrimental effect on neurological outcome. It makes mathematical sense that if (1) an average result encompassing an entire population shows no change and (2) analysis of a subpopulation shows benefit, that (3) the remainder of the population must therefore show harm. As it applies to MP administration in acute SCI, it is at least as likely that these observations represent random chance rather than the possibility a study drug could be of benefit for 8 hours but then have the exact opposite effect over the next 4 hours.

Further post-hoc analyses suggested that MP administration improved neurological function below the level of injury in patients with incomplete SCI, noting that patients with complete SCI demonstrated very little long-tract recovery irrespective of treatment.¹¹ Only 17 patients with incomplete spinal cord injuries received MP within 8 hours of injury and only 22 such patients received placebo.⁷ Hence, while long-tract (as opposed to segmental) recovery was reported in NASCIS II, it was identified in a very small subgroup of patients.

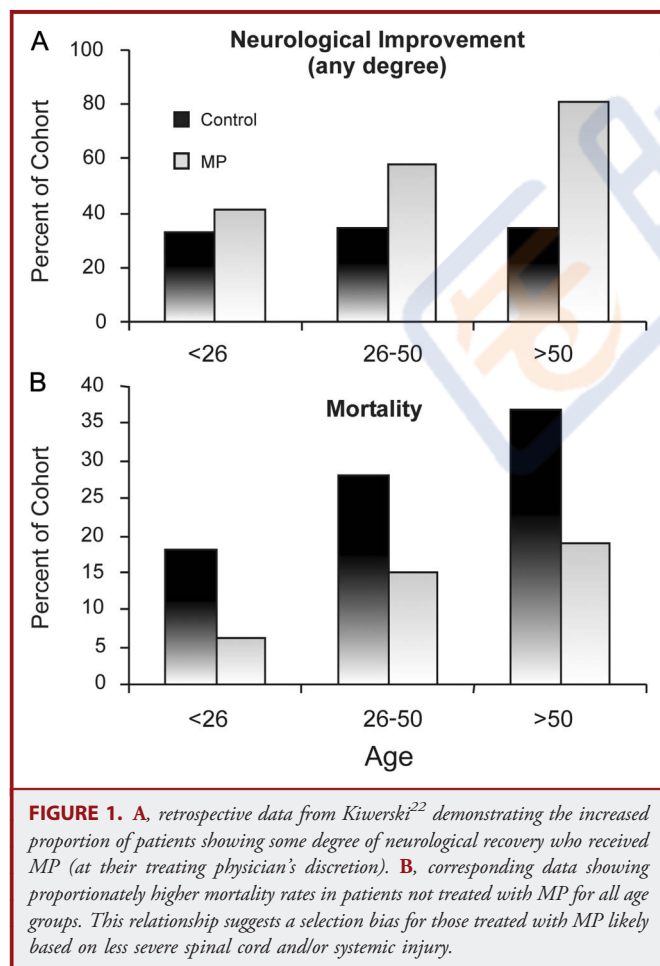
Complications were reasonably distributed between the treatment groups except for a 1.5 times higher incidence of gastrointestinal (GI) hemorrhage, 2 times higher incidence of wound infection, and 3 times higher incidence of pulmonary embolus in MP-treated patients compared to controls. There was a 2.5 times higher incidence of thrombophlebitis in control patients compared to those who received MP. None of these findings were reported as statistically significant, but none of these comparisons were properly powered to avoid Type II error.

NASCIS II was designed as a randomized, controlled, double-blinded clinical study to generate Class I medical evidence on the efficacy of MP and naloxone in the treatment of acute spinal cord injury. However, the strength of medical evidence generated is weakened by omission of data from publication, the arbitrary assignment of an 8-hour therapeutic window, the inconsistency of reported benefit, and the absence of functional outcome measures. The primary positive finding of a 5-point improvement in motor score associated with MP administration compared to placebo control was discovered only in a post-hoc analysis of a partial dataset, constituting a retrospective analysis. Accordingly, the beneficial results of NASCIS II are downgraded to Class III medical evidence. A trend towards more serious complications associated with steroid use is indicated from the original Class I medical evidence dataset.

In 1993, Galandiuk et al¹² reported on 32 patients with cervical or upper thoracic ASCI managed in an urban trauma center. Fourteen patients who received NASCIS II doses of MP within 8 hours of SCI were compared to 18 patients with similar injuries managed without steroids. Forty-seven percent of the cohort was studied retrospectively while 53% were studied prospectively. No difference was observed in neurological outcome for patients treated with MP compared to those untreated. However, patients receiving MP exhibited significant immune response alterations evidenced by a lower percentage and density of monocyte class II antigen expression and lower T-cell helper/suppressor cell ratios.

In addition, MP-treated patients experienced a higher rate of pneumonia (79% vs 50%) and longer hospital stays (44.4 days compared to 27.7 days) compared to their non-MP counterparts.

The same year, Kiwerski et al¹³ published the largest retrospective review of patients with acute SCI to date. Six-hundred and twenty patients were treated over a 15-year period beginning in 1976. Of these, 290 patients were administered MP and 330 were not, based on the discretion of the treating physician. The dose varied according to age, weight, and medical condition, and also at the preference of the attending physician. The most usual dose was 8 mg 3 times a day for several days up to 1 week. Consistently, more patients in the MP group were reported to show some degree of improvement compared to controls. The mortality rate was at least double for patients in the control group compared to those treated with MP, ranging from 18% to 38% depending on age (Figure 1). The authors did not explore the reasons for such high mortality, but the data suggest the control group was more severely injured and therefore less likely to recover.



Otani et al¹⁴ reported a prospective randomized (nonblinded) clinical trial investigating the administration of MP at NASCIS II doses within 8 hours of SCI from 11 centers in Japan. Eighty-two MP patients were compared to 76 observational controls (no placebo), randomized over a 14-month period from January 1992 to March 1993. Interestingly, "In the control group, however, use of a corticoid other than MPSS was allowed up to the dose equivalent to 100 mg/day MP for a maximum of 7 days in total. . .if it was judged necessary by the attending physician for the purpose of treating the spinal cord injury."¹⁴ Of the patients entered into the study, only 70 in the treatment group and 47 in the control group were analyzed due to protocol violations. Primary preplanned comparisons of change in motor and sensory scores failed to yield significant differences (Figures 2A and 2B). Post-hoc analyses suggested that significantly more MP patients recovered some degree of sensory function compared to controls ($P = .016$ pinprick; $P = .021$ light touch) (Figure 2C).

However, as discussed in the setting of NASCIS II, mathematical balance dictates that (1) if primary comparisons within the study population show no difference and (2) a subanalysis suggests a treatment effect, then (3) there must be an equal and opposite effect in the remaining patients. In this circumstance, the authors' observation that significantly more MP patients showed sensory recovery is only balanced by considering that within the fewer recovering control patients—magnitude (not frequency) of sensory recovery must have exceeded that observed in the MP-treated group. Taken together, both observations render each other meaningless and irrelevant.

Prendergast et al¹⁵ retrospectively compared patients with SCI before 1990 (the year NASCIS II was published) to patients with SCI after 1990. The latter group ($n = 29$) received MP in NASCIS II doses, whereas the earlier group ($n = 25$) received no steroids (historical control). Of 31 patients who suffered penetrating trauma, 16 received steroids while 15 did not. Throughout a 2-month follow-up period there was no difference in motor or sensory scores for patients with blunt SCI irrespective of steroid administration. However, in those suffering penetrating SCI, MP use was associated with deterioration in motor and sensory function compared to baseline scores on admission. In contrast, recovery was observed in controls. Motor scores were significantly better in control patients compared to those who received MP ($P = .03$).

Gerhart et al¹⁶ retrospectively identified a concurrent cohort of 363 acute SCI patients managed in 1990, 1991, and 1993. Within the study population, 188 (52%) were treated according to NASCIS II protocol, 90 (25%) received no methylprednisolone, and 85 (23%) received other steroid (eg, dexamethasone), an incorrect dose of MP, or had insufficient data. The authors found no significant difference in the outcome assessed by Frankel grade at the time of hospital discharge comparing those who received protocol MP (appropriate dose and timing) to those who did not receive any MP during treatment.

One-hundred and thirty patients suffering acute SCI between 1989 and 1992 were retrospectively analyzed, comparing patients

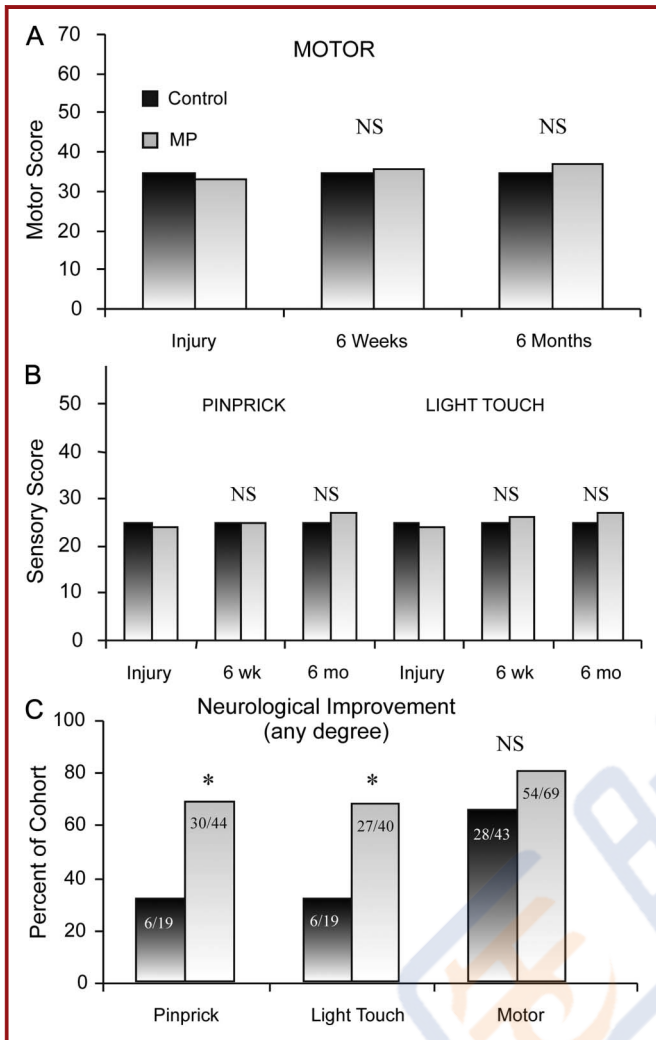


FIGURE 2. A, Otani et al observed no significant difference in motor score recovery at 6 weeks or at 6 months when patients receiving MP were compared to controls. B, similarly there was no difference between the groups in sensory (pinprick and light touch) scores. Note: Graphs A and B depict relative changes between groups only; total (mean) motor and sensory scores were not reported, only the differences between them. C, in post-hoc analyses, the number of patients showing some degree of sensory improvement was greater in the MP patients than in controls ($P = .016$ pinprick; $P = .021$ light touch). However, to keep the mathematical balance reported in primary comparisons (A and B above) the greater number of MP patients with sensory improvement had to be offset by a greater magnitude of recovery in the fewer control patients who demonstrated it (not reported).

who received MP to those who did not.¹⁷ Similar to the Prendergast paper, George et al based their comparison on 55 patients treated prior to 1990 (historical controls) and 75 patients treated with MP after 1990 according to NASCIS II dosing within 8 hours of injury. Neurological function was assessed by a 6-point mobility score and through the Functional Independence Measure scale. Mobility was no different between the

groups on admission, but on discharge, despite a lower mean age and lower injury severity score, the MP group fared significantly worse by one-half point compared to controls ($P < .05$). Functional Independence Measure scores did not differ between the 2 groups on discharge or throughout the rehabilitation period.

Medical complications were retrospectively examined by Gerndt et al¹⁸ in 140 SCI patients who received MP according to NASCIS II protocols and compared to a historical control group of 47 patients who received no steroid during treatment. The authors found a 4-fold increase in the incidence of acute pneumonia ($P = .03$), a 3-fold increase in pneumonia of any type ($P = .02$), as well as an increase in ventilated days ($P = .04$) and Intensive Care Unit (ICU) length of stay ($P = .045$) in the MP patients compared to controls. Control patients had a higher incidence of urinary tract infections ($P = .01$). MP patients spent fewer days in regular hospital wards ($P = .02$) and in the rehabilitation unit ($P = .035$). Overall, hospital stay was not different between the 2 groups, leading the authors to conclude that MP may predispose SCI patients to pneumonia, but had no adverse effect on long-term outcome.

Poynton et al¹⁹ retrospectively identified 71 consecutive SCI patients admitted to their rehabilitation facility between June 1991 and December 1994. American Spinal Injury Association (ASIA) motor and sensory scores were recorded at the time of injury, time of transfer to the rehabilitation center, and in follow up after discharge. Thirty-eight patients received NASCIS II MP dosing within 8 hours of injury. Thirty-three patients did not receive MP therapy because they presented beyond the 8-hour cutoff. Outcome was not related to treatment with MP, nor was it related to surgical intervention, although decompression was not distinguished from stabilization.

The third NASCIS study involved 14 centers across the United States and 2 in Toronto, Canada. Six-month and 1-year follow up were published in separate manuscripts.^{4,6} Patients presenting within 8 hours of SCI were enrolled in a prospective double-blind manner and randomized to 1 of 3 treatment arms: (1) MP infusion 5.4 mg/h \times 24 hours; (2) MP infusion 5.4 mg/h \times 48 hours; and (3) tirilazad mesylate 2.5 mg/kg every 6 hours \times 48 hours. Tirilazad mesylate was included as a chemically engineered “super-steroid,” created to possess greater antioxidant properties than methylprednisolone. All patients received a loading dose of MP (30 mg/kg) prior to randomization. A placebo control group was not included because of the reported therapeutic effect of MP in NASCIS II. Four hundred ninety-nine patients were entered into the study, 166 in the 24-hour MP group, 166 patients in the 48-hour MP group, and 167 in the 48-hour tirilazad mesylate group.

Within all preplanned comparisons, there were no significant differences in neurological recovery between any groups. Neither tirilazad mesylate nor 48-hour MP showed evidence of a neuro-protective effect compared to 24-hour MP administration; NASCIS III was a negative Class I medical evidence study. Post-hoc analyses suggested motor function to be at least temporarily

improved in patients who received 48-hour MP (n = 80) compared to 24-hour (n = 71) administration, provided the drug was initiated within 3 to 8 hours of injury. A difference of 5 ASIA motor points was found to be significant in favor of 48-hour MP at 6 weeks ($P = .04$) and 6 ASIA points at 6 months ($P = .01$). However, the 5-point ASIA difference became statistically questionable at 1 year follow up ($P = .053$). Even in the post-hoc analysis there was no notable difference between the 3 study groups in ASIA sensory scores, Functional Independence Measure outcomes, or presumably in the unreported left-sided ASIA motor scores. Post-hoc ASIA motor score changes are depicted for both NASCIS II and III in Figure 3.

Similar to NASCIS II, a higher incidence of severe complications seemed to be proportional to steroid administration. There was a 2 times higher incidence of severe pneumonia and a 4 times higher incidence of severe sepsis in the 48-hour MP group compared to patients on MP for 24 hours. Although these differences were not statistically significant, conclusions from statistical testing cannot be drawn, as sample sizes in the order of 600 patients per group would be required to avoid Type II error assuming $\alpha = 0.05$ and $\beta = 0.2$. There were 6 times more deaths observed in the 48-hour group due to pneumonia, respiratory distress syndrome, and respiratory failure ($P = .056$).

Like its predecessors, NASCIS III was designed as a randomized, controlled, double-blinded clinical study to generate Class I medical evidence on the efficacy of MP (and tirilazad mesylate) in the treatment of acute spinal cord injury. However, the strength of the medical evidence generated is weakened by omission of data

from publication, the arbitrary assignment of a 3- to 8-hour therapeutic window, the inconsistency of reported benefit, and the absence of improvement in functional outcome measures. The primary positive finding of a 5-point improvement in motor score associated with 48-MP administration compared to 24-MP was discovered only in a post-hoc analysis of a partial dataset, constituting a retrospective analysis. Accordingly, the beneficial results of NASCIS III are downgraded to Class III medical evidence. A trend towards more serious complications associated with prolonged steroid use is indicated from the original Class I medical evidence dataset.

Three years later, Pointillart et al²⁰ reported a single-institution, prospective, randomized clinical trial from France that compared the effect of nimodipine, MP (NASCIS II dosing protocol), and nimodipine + MP against no pharmacological therapy in 106 patients with acute SCI. Blinded neurological assessment evaluated ASIA scores on admission and at 1-year follow up. Time from injury to surgical decompression (where indicated and within 24 hours) was tracked as a confounding variable. One hundred patients were available to assess at 1 year because of 5 deaths and 1 loss to follow up.

Neurological improvement was observed in each group at 1 year compared to admission ($P < .0001$). However, there were no significant differences in ASIA motor or sensory scores between the 4 individual treatment arms. Only the completeness of SCI was linked to prognosis; patients with incomplete injury showed significantly more recovery than those who were complete ($P < .0001$). Improvement among complete injury patients was generally restricted to the level of the lesion and the 2 adjacent caudal levels. Eighty patients underwent surgery within 24 hours, of which 49 had surgery within 8 hours of injury. Neither surgery nor timing of surgery was associated with neurological recovery.

Infectious complications occurred more frequently among patients treated with MP (66%) compared to those who did not receive steroids (45%), which was not statistically significant. Two MP patients suffered upper GI hemorrhage due to ulceration. There were no similar events in patients who did not receive MP. Hyperglycemia requiring insulin administration for up to 3 days was documented in 46% of MP patients but in only 1 of the control patients ($P < .05$).

In 2001, Matsumoto and colleagues reported on 46 patients with acute cervical SCI who were prospectively randomized in a double-blind manner to receive either MP at NASCIS II doses or placebo.²¹ Patients were admitted to a single institution from April 1993 to August 1999. Twenty-three patients received MP, while 23 received placebo. The purpose of the study was to compare complications between the 2 groups from the time of admission throughout the 2-month follow-up period. Despite the prospective nature of the protocol, neurological scores were not reported. However, admission Frankel grades were the same for both groups. MP-treated patients demonstrated a higher propensity towards complications compared to placebo-treated controls (56.5% vs 34.8%; $P = .14$). Eight patients who received MP developed respiratory complications (pneumonia n = 3,

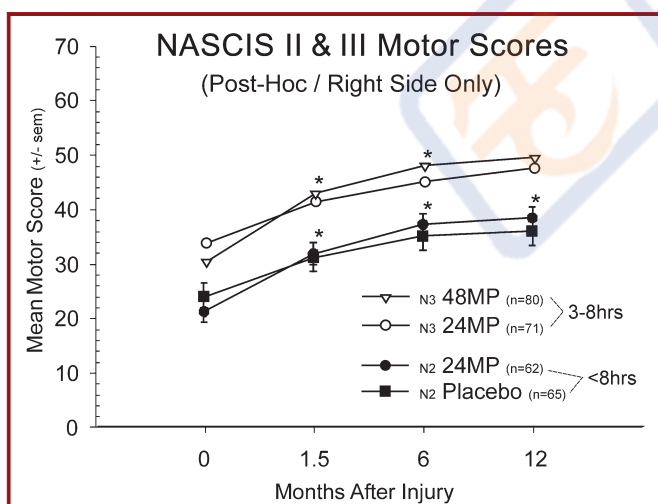


FIGURE 3. Combined 6-week, 6-month, and 1-year post-hoc right-sided motor scores from NASCIS II (N2) and III (N3) reported as favoring 24 MP administration within 8 hours and 48 MP administration between 3 and 8 hours after SCI. Y-axis represents motor function from total quadriplegia (0 points) to normal neurological function (70 points). No difference in post-hoc sensory scores was present at 1 year. **Note:** All primary (preplanned) comparisons negative. Standard error values not published for NASCIS III. * $P < .05$ multiple t-testing.

atelectasis $n = 1$) compared to 1 placebo patient ($P = .009$). Four MP patients developed gastrointestinal complications (GI bleed $n = 3$; ileus $n = 1$). No similar complications were observed in control patients ($P = .036$).

Pollard et al²² retrospectively identified patients who suffered an incomplete cervical SCI and were admitted to a single rehabilitation facility within 90 days of injury over an 18-year period spanning 1982 to 2000. Data were part of a federally funded national database (model systems). Five hundred and forty seven patients were identified, of which 412 met inclusion criteria based on completeness of records and absence of confounding comorbidity (eg, head injury). An analysis of sex, race, age, high vs low energy mechanism of injury, fracture type, cord syndrome, steroid protocol, and definitive surgery less than 24 hours after injury was undertaken to determine which factors were associated with greater improvement in ASIA motor and sensory scores.

Improved neurological recovery was noted in younger patients ($P = .002$) and those with a central cord or Brown-Sequard syndrome ($P = .019$). Administration of MP was not associated with improvement in final ASIA motor score at latest follow-up (MP $n = 104$; No-MP $n = 200$; $P = .66$) or change in ASIA motor score from time of injury (MP $n = 104$; No-MP $n = 201$; $P = .26$). Final mean ASIA sensory scores were no different between patients who received MP and those who did not (MP $n = 86$; No-MP $n = 87$; $P = .904$). An analysis of change in ASIA sensory score suggested steroid-treated patients recovered 11 more points compared to those who did not receive MP ($P = .027$). However, without explanation, the number of patients available for this comparison was a fraction of the original cohort (MP $n = 33$; No-MP $n = 59$).

Patients with SCI sustained from diving accidents were retrospectively reviewed by Aito et al²³ within the experience of a single institution between 1978 and 2002. The primary purpose of the review was to correlate neurological outcome with the level and type of spinal fracture. Sixty-five patients were included in the study, of which 95% were male. Factors associated with improved neurological outcome were: surgical intervention (timing not specified), younger age of the patient, and incomplete SCI. In a subanalysis of 30 patients admitted between 1994 and 2002 (after incorporation of the NASCIS II protocol), 20 patients who received MP within 8 hours of injury were compared to 10 patients who did not receive steroids. Data are not provided, but the authors report their analysis based on the presence or absence of some type of neurological recovery (not specified) in favor of those patients who received MP (Fisher exact test on proportions, $P = .005$). Recovery was mainly restricted to 9 of 10 patients with incomplete SCI, all of whom received MP.

Quian et al²⁴ prospectively analyzed a cohort of 8 SCI patients who were assessed for evidence of acute corticosteroid myopathy (ACM) from 1 to 7 days after their injury. The diagnosis was established directly through muscle biopsy and indirectly through electromyography (EMG) studies sampled above the level of SCI.

Five patients received MP treatment according to NASCIS II dosing. Three patients did not receive MP due to penetrating trauma ($n = 2$) or presentation more than 8 hours from the time of injury ($n = 1$). ACM occurred in a time-dependent manner between 3 to 7 days in the MP group: 1 patient biopsied within 24 hours of injury had normal muscle; 2 patients biopsied 3 days after injury showed mild evidence of ACM; 2 patients biopsied on day 5 and 7, respectively, showed changes compatible with severe ACM. Patients in the control group were biopsied within 24 hours of injury ($n = 2$) and on day 5 ($n = 1$). Muscle biopsies and EMG activity were normal in all 3 control patients. Acknowledging the natural history of ACM improvement within 6 to 8 months from time of onset, the authors speculated that some of the motor improvement observed in the NASCIS II and III studies may have been due to resolution of an iatrogenic myopathy.

From 1998 through 2002, Tsutsumi et al²⁵ identified 278 consecutive admissions to their institution for acute mid to lower cervical SCI. From this group, 70 patients admitted within 7 days of injury and with 6 months of follow up were discovered. Thirty-seven received MP at NASCIS II doses within 8 hours of injury, while 33 received no drug, according to the preference of the treating physician at the time of injury. Neurological function was assessed through ASIA motor scores. Sensory function was not tested.

The study group was further subdivided into complete (ASIA A) and incomplete (ASIA B, C, D) patients. No difference in motor improvement was seen in MP patients ($n = 18$) compared to controls ($n = 25$) in those with complete injuries ($P = 0.48$). Incomplete patients treated with MP ($n = 19$) improved on average 18 more motor points than those who did not receive MP ($n = 8$) ($P = .005$). However, 84% ($n = 16$) of the 19 MP patients were ASIA grade C or D on admission compared to 75% ($n = 6$) of the 8 control group patients. Mean admission and follow-up ASIA motor scores were not published, making it impossible to further discern within this small retrospective group how much selection bias towards less severe injuries (and hence recovery) favored those who received steroids.

Lee et al²⁶ retrospectively analyzed 111 patients with SCI admitted to a single institution over the 2-year period spanning from January 2002 until December 2003 with respect to MP administration, surgical intervention, and complication rates. Neurological outcome was assessed according to the Frankel grading system, where improvement was defined as a change in 1 or more Frankel grades. Fifty-eight patients (52%) received MP according to either NASCIS-II or NASCIS-III dosing protocols, while, for reasons not specified, 53 patients did not. Potential neuroprotective effects of MP were not reported. Instead, the analysis compared patients who had both MP and surgery to those who did not have either. "Significant" changes in Frankel score were observed in 11 of 16 complete SCI patients treated with MP and surgery, compared to zero of 7 patients treated with surgery alone. Twenty-one of 31 incomplete SCI patients who underwent surgery and MP administration also showed "significant" Frankel grade improvement compared to 4 of 8 patients

treated with surgery alone. Unfortunately, neither statistical methodology nor P -values were reported. If one calculates Fisher exact test for 2-tailed significance on 2 independent samples, the significance of improvement seen in the complete group who received MP was $P = .005$, whereas in the incomplete group receiving MP it was $P = .42$. In the subanalysis it remains unclear why 47 MP patients were treated surgically (81% of the entire cohort of MP patients) compared to only 15 patients (28%) in the non-MP group, perhaps suggesting the latter to be a more severely or chronically injured patient group (Figure 4).

Complications ascribed to MP administration were observed in 24 of 58 patients treated with MP (41%), including peptic ulcer, upper GI hemorrhage, perforated peptic ulcer, and urinary tract infection. One patient with a complete SCI died as a result of sepsis from GI perforation. The incidence of complications was proportional to the completeness of the SCI. It is not specified whether there were any non-MP patients who suffered similar morbidity.

Leypold and colleagues reported a radiographic study comparing cord edema and hemorrhage in 82 patients with ASIA A (complete) cervical SCI.²⁷ Thirty-four of the patients were treated prior to 1994 and did not receive MP as part of their treatment. Forty-eight patients were treated after 1997 and received MP according to NASCIS II protocol. An unspecified number of patients treated in the 4 years spanning 1994 to 1997 were excluded to "avoid the possibility of assignment to the wrong group." Magnetic resonance sequences (T1 and T2, dual echo SE, or gradient echo) were acquired in a 1.5T magnetic resonance unit within 3 days of injury. No images were available prior to

administration of MP in those patients treated with steroids. Neurological outcomes were not reported.

The mean age of the MP group was 16 years older than that of the historical controls (47 years vs 31 years; statistically significant P -value not provided). The incidence of spinal cord hemorrhage was higher in historical controls compared to MP-treated patients, but the difference was not statistically significant (91% vs 67%; $P = .162$). There was no difference in rostro-caudal length of edema within the spinal cord (4.0 vs 3.3 spinal segments; $P = .9$). However, length of hemorrhage was greater in controls compared to MP patients (1.5 vs 0.8 spinal segments; $P = .04$). Potential differences in mechanism of injury (eg, between a 50-year-old MP patient with central cord syndrome and a 30-year-old non-MP patient with fracture dislocation) were not explored. Of equal or more important concern, however, is the lack of a baseline (pre-MP) magnetic resonance imaging and the concurrent assumption that the extent of SCI hemorrhage within 3 days of injury was independent of the initial SCI. There have been no previous studies defining the temporal sequence of acute hematoma evolution in the spinal cord as a result of SCI.

In 2008, Suberviola et al²⁸ published a review of all adult patients admitted to their institutional ICU with acute SCI over a 12-year period. A total of 82 patients were identified, of which 59 received MP (NASCIS II protocol) and 23 did not. Patient demographics including admission Frankel grade did not differ between the groups except that the non-MP patients had a higher injury severity score compared to those who received steroids (31 vs 22; $P = .006$). Accordingly, the length of ICU stay was also longer for the non-MP patients (20 days vs 12 days; $P = .031$).

At time of ICU discharge, approximately 31% of patients in both groups improved by 1 or more Frankel grades. There was no difference in ICU mortality rate attributable to steroid administration or lack thereof. Similarly, wound infections, septicemia, and urinary tract infections were comparable between groups. However, MP patients suffered a higher rate of respiratory infections ($P = .02$), total infections ($P = .004$), and early hyperglycemia requiring insulin drip for up to 4 days ($P < .01$).

Ito et al²⁹ compared a consecutive series of acute SCI patients who received MP against a subsequent consecutive series of SCI patients who were not given steroids. The study was performed in a prospective nonrandomized manner over a 4-year period: from August 2003 through July 2005, 38 patients were given MP according to the NASCIS II protocol, while from August 2005 through July 2007 41 were treated for acute SCI without MP. Patients were excluded from the study if they presented more than 8 hours after injury. Neurological assessments were made on admission and 3 months later. Adverse events were recorded during the hospital stay.

An improvement by 1 or more ASIA grades was observed in 45% of those who received MP compared to 63% of those who did not ($P > .05$). On average, ASIA motor scores improved by 12 points in the MP group and 14 points in control group patients ($P > .05$). Similarly, there was no therapeutic benefit to MP if

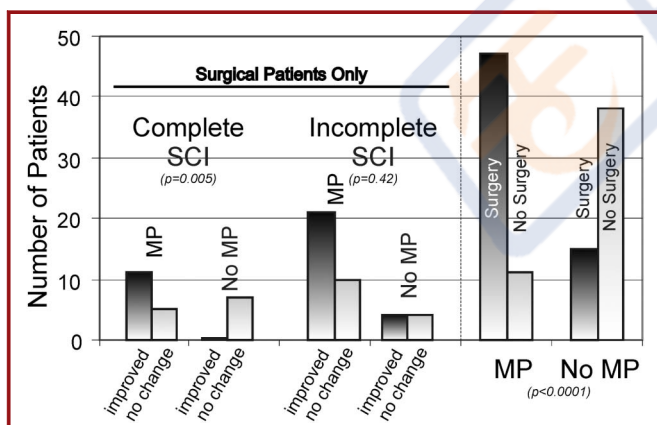


FIGURE 4. Left, graphical representation of MP effect reported by Lee et al⁶ in their retrospective review of 111 patients with acute SCI. A steroid benefit was reported only in patients who also underwent surgical intervention. Of those who had surgery and harbored neurologically complete injuries, improvement in Frankel grade was observed more frequently in the 16 patients who received MP compared to the 7 that did not ($P = .005$, Fisher exact test). This difference was not significant in 31 MP and 8 non-MP patients with incomplete injuries. Right, however, data from the entire cohort demonstrates that 81% of the MP-treated patients received surgery compared to only 28% of the non-MP patients ($P < .0001$) suggesting the latter to have more severe or more chronic injuries, presumably more resistant to treatment.

patients were compared on the basis of motor complete and motor incomplete injuries. ASIA sensory scores were not reported. Infections (pneumonia, urinary tract infection, wound infection) were observed in 68% of the MP group but in only 44% of control group patients ($P = .028$). Sixteen percent of MP-treated patients suffered GI hemorrhage compared to 5% of controls, but the difference was not statistically significant.

A rare complication of corticosteroid-induced acute tumor lysis syndrome was detailed in a case report published by Tsao et al³⁰ in 2009. A 37-year-old woman was treated with MP (NASCIS-II protocol) for an acute incomplete cervical SCI. She received MP treatment within 8 hours of injury but with concurrent (undiagnosed) intravascular diffuse large B-cell lymphoma. Sixteen hours after infusion, the patient developed ventricular fibrillation and acute renal failure. Resuscitation was successful and the patient responded to hemodialysis, but succumbed to her disease 8 months later.

Based on data from a small number of randomized head injury trials and the success reported in NASCIS II and III, a prospective randomized placebo-controlled trial investigating the effect of MP on head injury was undertaken in 239 hospitals across 49 countries.³⁰ Over a 5-year period, patients were enrolled into the Corticosteroid Randomization After Significant Head injury (CRASH) study, receiving either a 48-hour MP infusion according to NASCIS III dosing or a 48-hour placebo infusion of normal saline. The research hypothesis was constructed to evaluate the neuroprotective efficacy of high-dose steroids in cranial trauma. Primary outcome measures were: (1) death from any cause at 2 weeks, and (2) death or disability at 6 months. Sample-size calculations suggested that 20 000 patients were required to detect a 2% difference in the study groups.

Patients were eligible for enrollment if they were 16 years of age or older, were within 8 hours of injury, and had a Glasgow Coma Score ≤ 14 . Interim data of in-hospital mortality, complications, and 6-month outcome were supplied by each institution on an annual basis to an independent data monitoring and ethics committee. The committee was responsible for unmasking the results if the randomized comparisons provided proof beyond reasonable doubt of a difference in outcome between the study and control groups AND evidence that would be expected to substantially alter the choice of treatment for patients.

In May 1994, the trial was terminated prematurely as a result of interim analyses by the data monitoring and ethics committee. A total of 10 008 patients had been enrolled, just over 5000 patients in each treatment arm. Within the MP group, 1052 (21.1%) deaths were observed within the first 2 weeks of injury compared to 893 (17.9%) in control patients representing a relative risk for death of 1.18 (95% confidence interval [CI] 1.09-1.27; $P = .0001$). There was no difference in the severity of head injury between the 2 groups ($P = .22$). Six-month data were published a year later by the same group.³¹ The risk of death remained higher in the MP group (1248 deaths; 25.7%) compared to placebo (1075 deaths; 22.3%) ($P = .0001$). In other words, for every 29 patients treated with MP, 1 died from drug-associated morbidity.

The second outcome measure of death and disability at 6 months was also higher in the MP group (relative risk 1.05; 95% CI 0.99-1.10; $P = .079$). The authors concluded that corticosteroids should not be used routinely in the treatment of head injury.

SUMMARY

Methylprednisolone

Despite 4 prospective blinded randomized controlled trials investigating the effect of MP in acute SCI, there exists no Class I medical evidence of any beneficial effect.^{2,4,8,20} Two prospective Class II trials also failed to demonstrate the therapeutic efficacy of MP in SCI.^{14,29} In total, over 980 patients have received steroids for SCI and over 280 have participated as control subjects within the protocol of a prospective clinical trial—in which, universally, all primary comparisons to establish efficacy have been negative.

A variety of Class III medical evidence has been published supporting the neuroprotective effect of MP in SCI.^{6,7,13,14,22,23,25,26} In general, these studies suffer from 1 of 2 significant limitations: limited sample size derived retrospectively from much larger study populations^{6,7,14,22,23,25,26} and/or incomplete data reporting in which omitted data are likely to have negated the proposed beneficial effect.^{6,7,13,14,22,23,25,26} Additionally, the beneficial effects claimed related to MP administration in the setting of acute SCI have been inconsistent. Patients are reported to have demonstrated improvement in sensory but not motor function,^{14,22} motor but not sensory function,^{6,7,25} or some other (undefined) type of neurological recovery.^{13,23} It is important to note that none of these retrospective data analyses have claimed neurological improvement of a meaningful functional or behavioral nature. In light of both significant methodological errors and inconsistent neurological outcomes, the beneficial effects of MP can as easily be ascribed to random chance as to any true therapeutic effect.

Harmful side effects of MP administration in the setting of acute SCI have been reported as significant in 3 Class I studies,^{8,20,21} including wound infection, hyperglycemia requiring insulin administration, and GI hemorrhage. Although not statistically significant, similar trends were observed in Class I medical evidence from NASCIS II and III, including GI hemorrhage, sepsis, pneumonia, and death due to respiratory failure.^{2,4} In addition, Class II medical evidence shows a significantly higher risk of infection (respiratory, urinary, wound) and steroid-induced myopathy in patients treated with MP compared to controls.^{24,29} Several Class III medical evidence studies describe similar adverse events of statistical significance including pneumonia, respiratory failure, peptic ulcer disease, GI hemorrhage, and hyperglycemia requiring insulin administration.^{12,18,26,28} Most compelling is the Class I medical evidence from over 10 000 patients with head injury, indicating that high-dose MP administration leads to significantly higher mortality independent of injury severity.³¹

In summary, there is no consistent or compelling medical evidence of any class to justify the administration of MP for acute SCI. Both consistent and compelling Class I, II, and III medical evidence exists suggesting that high-dose MP administration is

TABLE 1. Evidentiary Table: Pharmacological Therapy: Methylprednisolone

Citation	Description of Study	Evidence Class	Conclusions
Ito, ²⁹ <i>Spine</i> , 2009	Prospective nonrandomized consecutive case series of 38 patients with SCI treated with MP (2003-2005) compared to a subsequent consecutive series of 41 who did not receive MP (2005-2007). Change in ASIA grade and motor scores determined by difference from admission to 3 months.	II	No difference in neurological improvement as defined by ASIA grade or ASIA motor score when total cohort of each group compared or when motor complete or motor incomplete injuries compared. Significantly higher incidence of infection (respiratory, urinary, and wound) in MP patients vs controls ($P = .028$).
Tsao, ³⁰ <i>Lancet</i> , 2009	Case report	III	Rare complication of corticosteroid-induced acute tumor lysis syndrome causing ventricular fibrillation and renal failure in a 37-year-old patient treated with MP for acute SCI.
Suberviola, ²⁸ <i>Injury, Int J Care Injured</i> , 2008	Retrospective review of ICU stay in 59 SCI patients who received MP (NASCIS II) and 23 who did not between 1994 and 2005.	III	No difference in neurological outcome based on Frankel grade at time of ICU discharge. MP patients had significantly higher rates of respiratory infection, total infections (all types) and early hyperglycemia requiring insulin drip.
Lee, ²⁶ <i>Surg Neurol</i> , 2007	Retrospective review of 111 patients with SCI, 58 treated with MP and 53 not. Recovery defined as improvement of 1 grade or more in Frankel classification. MP associated complications defined as peptic ulcer, upper GI hemorrhage, and urinary tract infection.	III	No neurological comparisons reported on primary cohort. Subanalysis of complete SCI patients who underwent surgery showed 11/16 treated with MP improved whereas none of the 7 non-MP patients improved. In the MP-treated group no one improved enough to ambulate independently. Incomplete patients undergoing surgery NS. In the entire cohort ($n = 111$) 41% of MP patients developed an MP-related complication.
Leybold, ²⁷ <i>Spine</i> , 2007	Retrospective review of magnetic resonance spinal cord signal changes in 48 MP-treated patients compared to 34 historical controls (all ASIA A).	III	MP group significantly older than historical controls (47 vs 31 yrs). No difference in incidence of spinal cord hemorrhage or rostro-caudal length of edema. Length of hemorrhage 0.8 spinal segments in MP patients compared to 1.5 in controls ($P = .04$). No accounting of mechanism. No baseline (pre-MP) magnetic resonance imaging.
Tsutsumi, ²⁵ <i>Spine</i> , 2006	Retrospective review of 70 cervical SCI patients treated over 5 years in which 37 received MP and 33 did not. Two hundred and eight patients excluded because of incomplete follow up, incomplete data, or steroids given outside of NASCIS II protocol.	III	ASIA sensory scores not assessed. No difference in ASIA motor recovery from MP in patients with complete SCI ($n = 43$). Recovery of 18 more ASIA motor points in MP patients ($n = 19$) compared to controls ($n = 8$) at 6 months ($P = .005$). Possibility of selection bias identified in MP administration for less severe SCI predisposing to greater recovery.

(Continues)

TABLE 1. Continued

Citation	Description of Study	Evidence Class	Conclusions
Aito, ²³ <i>Spinal Cord</i> , 2005	Retrospective review of 65 patients over 24 years with complete and incomplete injuries. Subanalysis of 30 patients treated from 1994 to 2002 with and without MP.	III	Presence of any neurological improvement more likely in 20 patients treated with MP compared to 10 who did not receive steroids ($P = .005$). Most improvement seen in 9 of 10 incomplete patients all of whom received MP.
Qian, ²⁴ <i>Spinal Cord</i> , 2005	Prospective case-control cohort of 5 patients with SCI treated with MP and 3 patients not eligible to receive MP looking for evidence of acute corticosteroid myopathy.	II	Muscle biopsy and EMG above the level of SCI used to confirm diagnosis. Time-dependent ACM demonstrated in patients who received MP. No similar changes observed in controls.
Pollard, ²² <i>Spine</i> , 2003	Retrospective review of 412 patients with incomplete SCI from 1982 to 2000. Data available in 104 patients who received MP and 200 who did not.	III	Final ASIA motor score and change in ASIA motor score from admission not improved by MP administration. No difference in final ASIA sensory score from MP. Eleven-point improvement in ASIA sensory score compared to admission in MP-treated patients ($P = .027$) but only 33 MP and 59 control patients available for analysis.
Matsumoto, ²¹ <i>Spine</i> , 2001	Prospective, randomized, double-blind study in 46 SCI patients for the purpose of comparing medical complications. Half were randomized to 24 MP and half to placebo.	I	Methylprednisolone patients had higher incidence of complications (56.5% vs 34.8%, NS). Respiratory complications ($P = .009$) and GI bleed ($P = .036$) were significantly higher in MP patients.
Pointillart, ²⁰ <i>Spinal Cord</i> , 2000	Multicenter, prospective, randomized clinical trial of 106 SCI patients treated with MP ($n = 27$), nimodipine ($n = 27$), MP + nimodipine ($n = 27$), or no pharmacological agent ($n = 25$).	I	No difference in neurological outcome between groups at 1 year (small sample size). Infection and GI bleed, and hyperglycemia higher in MP patients (NS, no power analysis). Hyperglycemia requiring insulin significantly higher in MP patients.
Bracken, ⁶ <i>J Neurosurg</i> , 1998	NASCIS III: One-year follow up	I* (reported positive results III)	All primary (preplanned) comparisons negative. Post-hoc analyses showed improved ASIA motor scores of questionable significance in 48 MP patients compared to 24 MP ($P = .053$). 48 MP associated with higher rates of sepsis, pneumonia, and death (NS, no power analysis).
Gerndt, ¹⁸ <i>J Trauma Inj Inf Crit Care</i> , 1997	Retrospective review of 140 SCI patients. Comparison of medical complications among 93 who received NASCIS II MP compared to 47 historical controls who received no steroid.	III	MP treated patients had significant increases in pneumonia, acute pneumonia, ventilated days, and ICU stay. No adverse effects on long-term outcome.
Poynton, ¹⁹ <i>Injury</i> , 1997	Retrospective case control review of 71 consecutive SCI admissions. Thirty-eight patients treated with MP within 8 hours were compared to 25 referred more than 8 hours after injury who received no methylprednisolone.	III	No effect of MP or surgery on outcome after SCI.

(Continues)

TABLE 1. Continued

Citation	Description of Study	Evidence Class	Conclusions
Bracken, ⁴ <i>JAMA</i> , 1997	NASCIS III: Multicenter randomized, double-blind trial comparing 24-hour MP administration to 48-hour MP and 48-hour tirilazad mesylate administration in the treatment of 499 SCI patients.	I* *(reported positive results III)	No difference between groups in all primary (preplanned) comparisons. Post-hoc analyses showed improved ASIA motor scores at 6 weeks and 6 months in 48 MP patients compared to 24 MP.
Gerhart, ¹⁶ <i>Paraplegia</i> , 1995	Retrospective concurrent cohort comparison of 363 SCI patients managed in 1990 to 91 and 1993. 188 patients received NASCIS II MP dosing compared to 90 patients without MP.	III	No difference in neurological outcome between groups based on Frankel classification.
George, ¹⁷ <i>Amer Surg</i> , 1995	Retrospective review of 145 SCI patients, 80 treated with MP, and 65 who did not receive MP.	III	No difference in mortality or neurological outcome between groups despite younger age and less severe injury in MP patients.
Otani, ¹⁴ <i>Sekitsui Sekizui</i> , 1994	Prospective randomized (nonblinded) multicenter study evaluating NASCIS II MP dose given to 82 patients within 8 hours compared to 76 observational controls enrolled between January 1992 and March 1993.	II* *(reported positive results III)	Only 70 MP patients and 47 controls analyzed. No difference in motor or sensory function between groups. Post-hoc analysis suggested some degree of sensory recovery to occur more frequently in MP patients, possibly cancelled out by greater degree of improvement in controls.
Prendergast, ¹⁵ <i>J Trauma Inj Inf Crit Care</i> , 1994	Retrospective review of 29 acute SCI patients treated with NASCIS II MP dosing after 1990 compared to 25 patients treated without MP before 1990. Thirty-one patients suffered penetrating SCI.	III	No difference in neurological recovery between MP or control groups. Patients with penetrating SCI who received MP showed deterioration in motor and sensory scores compared to improvement observed in controls.
Kiwerski, ¹³ <i>Injury</i> , 1993	Retrospective review of 620 SCI patients from 1976 to 1991. Discretionary MP administration and discretionary dose based on physician assessment.	III	Some degree of recovery reported more frequently in MP patients. Mortality rates 2X higher in patients who did not receive MP, suggesting more severe and life-threatening injuries.
Galandiuk, ¹² <i>Ann Surg</i> , 1993	Prospective assessment of 15 patients from 1990 to 1993 and retrospective review of 17 patients from 1987 to 1990. Fourteen patients given MP within 8 hours of SCI compared to 18 patients not treated with MP.	III	No difference in neurological outcome. MP patients had immune response alterations, higher rate of pneumonia and longer hospital stay compared to control patients (NS).
Bracken, ⁷ <i>J Neurosurg</i> , 1992	NASCIS II: One-year follow-up.	I* *(reported positive results III)	All primary (preplanned) comparisons negative. Post-hoc analyses showed improvement in motor but not sensory scores at 1 year in patients given MP within 8 hours of injury ($P = .030$). Wound infections, GI hemorrhage, and pulmonary embolus more common in MP vs placebo (NS, no power analysis).
Bracken, ² <i>NEJM</i> , 1990	NASCIS II: Multicenter randomized, double blind, placebo-controlled trial comparing MP to naloxone and placebo in 487 patients with acute SCI.	I* *(reported positive results III)	No difference between groups in all primary (preplanned) comparisons. Post-hoc analyses showed improvement in motor and sensory scores at 6 months in patients given MP within 8 hours of SCI.

(Continues)

TABLE 1. Continued

Citation	Description of Study	Evidence Class	Conclusions
Bracken, ⁹ <i>J Neurosurg</i> 1985	NASCIS I: One-year follow up.	I	No significant difference in neurological recovery of motor or sensory function 1-year post-injury.
Bracken, ⁸ <i>JAMA</i> , 1984	NASCIS I: Multicenter, double-blind randomized trial comparing MP(1000 mg/d vs 100 mg/d for 11 days) in treatment of 330 patients with acute SCI.	I	No treatment effect at 6 weeks and 6months post injury. No control group. Wound infections significantly higher in high-dose group ($P = .01$). Death in first 14 days 3X more common in high-dose group (NS, no power analysis).

ASIA, American Spinal Injury Association; ICU, intensive care unit; MP, methylprednisolone; NASCIS, National Acute Spinal Cord Injury Study; NS, not statistically significant; SCI, spinal cord injury.

associated with a variety of complications including infection, respiratory compromise, GI hemorrhage, and death. MP should not be routinely used in the treatment of patients with acute SCI.

GM-1 Ganglioside (Sygen)

Found indigenously in cell membranes of mammalian central nervous system tissue, GM-1 ganglioside is a compound thought to have antiexcitotoxic activity, promote neuritic sprouting, potentiate the effects of nerve growth factor, and prevent apoptosis. In 1991, Geisler et al³² reported promising results of a pilot study investigating its use in acute SCI. All patients received a 250 mg bolus of MP followed by 125 mg every 6 hours for 72 hours. GM-1 patients were administered 100 mg of GM-1 per day for 18 to 32 days, with the first dose provided within 72 hours of injury. Neurological assessment was accomplished with ASIA motor score assessments and the Frankel scale.

Of 37 patients entered into the study, 34 were available for 1-year follow up (16 GM-1 patients, 18 placebo). GM-1

ganglioside-treated patients showed significant improvement in Frankel grade from baseline to 1-year follow up ($P = .034$) and significantly greater improvement in ASIA motor scores compared to placebo-treated patients ($P = .047$). The recovery of motor function in GM-1 ganglioside-treated patients was felt to be due to recovery of strength in paralyzed muscles rather than strengthening of paretic muscles. There were no adverse effects attributed to the administration of the study drug. The authors concluded that GM-1 ganglioside enhanced neurological recovery in human patients following SCI and deserved further study.

The subsequent multicenter study involved 28 neurotrauma institutions and randomized 797 patients within 72 hours of injury to receive either GM-1 ganglioside (100 or 200 mg i.v./day) or placebo for a total of 56 days³³. All patients received NASCIS II doses of MP within 8 hours of injury. The duration of follow up was 1 year. Although patients with ASIA grade C and D SCI treated with Sygen demonstrated statistically significant improvement in modified Benzel grade compared to placebo-treated

TABLE 2. Evidentiary Table: Pharmacological Therapy: GM-1 Ganglioside

Citation	Description of Study	Evidence Class	Conclusions
Geisler et al, ³³ <i>Spine</i> , 2001	Prospective randomized, double blind, stratified multicenter trial of GM-1 ganglioside in 760 acute SCI patients. All received MP per NASCIS II protocol. (Placebo group)	I	No significant differences in neurological recovery identified between GM-1 treated patients and MP treated patients at 26-week follow up. Trend for earlier recovery in GM-1 treated patients. No true placebo group.
Geisler et al, ³² <i>NEJM</i> , 1991	Prospective, randomized, double blind trial of GM-1 ganglioside in 37 human SCI patients. All received 250 mg MP bolus followed by 125 mg/Q6H x72 hours before randomization (placebo group).	I	GM-1 ganglioside enhances recovery of neurological function, significant difference in recovery compared to MP group ($P = .047$). Insufficient numbers of patients to draw meaningful conclusions. No true placebo group.

NS, not statistically significant



patients at 4 and 8 weeks after injury, the advantage was lost at subsequent follow up visits. No difference between actively treated and placebo-treated patients was noted in any of the outcome measures at 1 year. There have been no further studies to confirm or refute these results in the last decade. Consequently, GM-1 ganglioside is not recommended for use in the routine management of patients with acute SCI at this time.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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