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ARTICLE

High-dose methylprednisolone for acute traumatic spinal cord injury

A meta-analysis

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Abstract

Objective

Due to the continuing debates on the utility of high-dose methylprednisolone (MP) early after acute spinal cord injury (ASCI), we aimed to evaluate the therapeutic and adverse effects of high-dose MP according to the second National Acute Spinal Cord Injury Study (NASCIS-2) dosing protocol in comparison to no steroids in patients with ASCI by performing a meta-analysis on the basis of the current available clinical trials.

Methods

We searched PubMed and Cochrane Library (to May 22, 2018) for studies comparing neurologic recoveries, adverse events, and in-hospital costs between ASCI patients who underwent high-dose MP treatment or not. Data were synthesized with corresponding statistical models according to the degree of heterogeneity.

Results

We enrolled 16 studies (1,863 participants) including 3 randomized controlled trials (RCTs) and 13 observational studies. Pooled results indicated that MP was not associated with an increase in motor score improvement (RCTs: $p = 0.84$; observational studies: $p = 0.44$) and incidence of recovery by at least one grade on the American Spinal Injury Association Impairment Scale or Frankel ($p = 0.53$). Meanwhile, MP did not lead to better sensory recovery ($p = 0.07$). However, MP was associated with a significantly higher incidence of gastrointestinal hemorrhage ($p = 0.04$) and respiratory tract infection ($p = 0.01$). The difference in the overall in-hospital costs between MP and control groups was not statistically significant ($p = 0.78$).

Conclusions

Based on the current evidence, high-dose MP treatment, in comparison to controls, does not contribute to better neurologic recoveries but may increase the risk of adverse events in patients with ASCI. Therefore, we recommend against routine use of high-dose MP early after ASCI.

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Glossary

ACM = acute corticosteroid myopathy; **ASCI** = acute spinal cord injury; **CI** = confidence interval; **GIH** = gastrointestinal hemorrhage; **ICU** = intensive care unit; **MP** = methylprednisolone; **NASCIS-2** = second National Acute Spinal Cord Injury Study; **RCT** = randomized controlled trial; **SCI** = spinal cord injury.

Spinal cord injury (SCI) can be a life-changing catastrophe. The WHO reported in 2013 that 250,000 to 500,000 people had a SCI each year, and 90% of the cases were traumatic.[1] In 2018, the estimated prevalence has almost doubled.[2] People with SCIs are 2–5 times more likely to die prematurely, as a result of the associated physical, psychological, and financial burdens.[1]

In the second National Acute Spinal Cord Injury Study (NASCIS-2) in 1990, Bracken et al.[3] reported a small benefit effect of high-dose methylprednisolone (MP) for neurologic recovery in patients with traumatic SCI if given within 8 hours postinjury. However, the conclusion was drawn from post hoc subgroup analysis, which challenged the level of the evidence.[4] Meanwhile, the inefficacy and potential adverse effects of MP have been reported overwhelmingly by most of the published studies during the last decades.[5–8] Recently, there are a variety of up-to-date guidelines on pharmacologic therapy for acute SCI (ASCI). While most of them do not recommend steroids,[9–11] the latest 2017 AOSpine guideline suggests the use of high-dose MP,[12] on the basis of a meta-analysis with such rigid inclusion criteria that only a very limited number of prospective studies were included.[13] Therefore, the early use of high-dose MP for ASCI remains controversial.

Here, on the basis of the current available studies, we aim to comprehensively evaluate the therapeutic and adverse effects of high-dose MP in comparison to nonsteroid treatment on patients within 8 hours of ASCI to update the evidence for clinical practice.

Methods

We followed the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA)[14] and carried out the study based on a prospective protocol (PROSPERO CRD42018106342) according to the recommendations of the Cochrane Collaboration.

Data sources and search strategies

We searched the online databases of PubMed and Cochrane Library for all the available randomized controlled trials (RCTs) as well as observational studies published up to May 2018. For better quality control, we only enrolled articles published in journals included in the Science Citation Index, which had undergone a rigorous selection process before publication. Detailed strategy was as follows: (methylprednisolone [title/abstract] or pharmacologic [title/abstract] or steroid [title/abstract] or steroids [title/abstract]) and (spinal cord injur* [title/abstract]) for PubMed and (methylprednisolone:ti,ab, kw or pharmacologic:ti,ab, kw or steroid: ti,ab,kw) and (spinal cord injury:ti,ab,kw) for Cochrane Library. Conventional searches were supplemented by manual searches of the reference lists of all the relevant studies, review articles, and conference abstracts.

Inclusion and exclusion criteria

Studies were included if they met the following inclusion criteria: (1) articles were published in Science Citation Index journals; (2) patients were diagnosed with ASCI and interventions were initiated within 8 hours after the injury; (3) in treatment group, high-dose MP was given to the patients according to the NASCIS-2 protocol[3]; (4) in control group, no steroids were administrated to the patients; (5) no significant difference in the mean age between groups was reported; (6) significant clinical outcomes such as neurologic score improvements, incidence of adverse events, or in-hospital costs were compared. Studies failing to comply with all the inclusion criteria were excluded. No exclusions were made based on complete/incomplete injuries, open/closed injuries, or the age of patients.

Standard protocol approvals, registrations, and patient consents

No additional ethical approval was required for this meta-analysis.

Study selection and data extraction

Two literature reviewers, blinded from each other, evaluated the eligibility of potential titles and abstracts independently. Included studies were reassessed as full text rigorously by the inclusion criteria. We solved disagreement first by discussion and further by adjudication of a third reviewer if the disagreement remained. The following data were then extracted from each included study: the first author's name, year of publication, demographic information, number of patients, percentage of patients with complete SCI, percentage of patients received surgeries, length of follow-up, and outcomes (neurologic scores, adverse events, and in-hospital costs). Outcomes for extraction were considered of clinical significance to the patients, determined by consensus of 2 experienced medical practitioners.

Quality assessment of the included studies

We performed risk of bias assessment for RCTs according to the Cochrane Handbook for Systematic Reviews and Interventions (version 5.1). A risk of bias table was constructed with all the included RCTs, containing a risk of bias judgment for each individual study. We evaluated the risk of bias for

observational studies using the Newcastle-Ottawa Scale, in which each study was judged on 8 items, categorized into 3 groups: the selection of the groups, the comparability of the groups, and the ascertainment of the outcomes.[15] A score of 0–9 was allocated to each observational study. Studies scored 6 or more were considered of high quality. Again, 2 reviewers carried out the assessment independently and disagreement was solved by discussion or further adjudication of a third reviewer.

Statistical analysis

We compared the pooled outcomes between treatment and control groups using Review Manager (RevMan 5.3) software. Heterogeneous data between studies were indicated by $p \leq 0.10$ or $I^2 \geq 50\%$; otherwise the data are homogeneous. We used a random effects model for heterogeneous data and a fixed effect model for homogeneous data. We reported continuous variables with mean differences and 95% confidence interval (95% CI) and dichotomous variables as risk ratios and 95% CI. The test of overall effect with a $p < 0.05$ was statistically significant. For data presented as medians and ranges, the values of means and SD were calculated using the formula described by Hozo et al.[16] Collected data were carefully inputted, and then rechecked by 2 reviewers respectively. We performed stratified analysis according to different study designs (RCTs or observational studies). We also performed subgroup analyses according to the time points of follow-ups (≤2 months or >2 months), categories of the sensory scores (light touch, pinprick, or others), as well as specific adverse events.

Data availability

Data can be made available to qualified investigators on request to the corresponding author.

Results

Study selection

The study selection process is demonstrated in figure 1. We identified 1,574 articles, carefully reviewed 86 full texts, and finally enrolled 16 studies for the analyses. All of the enrolled studies were published in English, including 3 RCTs (431 participants)[3,7,17,18] and 13 observational studies (1,432 participants).[5,6,8,19–28]

Study characteristics

Characteristics of the included studies are summarized in the table. Most of the patients were male. Two studies included patients younger than 18 years.[20,22] Five studies did not specify the mean age in each comparison group.[3,8,24,25,27] One study reported gunshot injury[25] and another reported penetrating injury.[28] The number of patients who underwent stabilizing surgeries was reported in most of the studies. Single or multiple time points of follow-ups varied from weeks to years in different studies. Significant clinical outcomes, including neurologic recoveries, incidence of adverse events, and in-hospital costs (mainly length of stay), were compared between groups at follow-ups.

Study quality assessment

All the observational studies scored ≥6 points (table) and RCTs were of modest risk of bias (figure e-1, doi.org/10.5061/dryad.7d837c6).

Outcomes comparison between treatment and control groups

Motor function improvement

Most studies compared improvement in motor score. We used a random effects model for data synthesis due to significant heterogeneity between studies. There was no significant difference in either RCTs ($p = 0.84$) or observational studies ($p = 0.44$) for the pooled motor score improvement at the last follow-up between treatment and control groups (figure 2). Also, no significant difference in motor score improvement was found at short-term (≤2 months) ($p = 0.15$) (figure 3A) or long-term (>2 months) follow-ups ($p = 0.57$) (figure 3B), respectively. The pooled result was not influenced after we removed 2 data sets from Sunshine et al.[19] and Tsutsumi et al.[22] reporting significant difference in the percentage of complete injury (data not shown).

Five observational studies[6,8,21,25,27] compared the percentage of patients with an improvement by one or more grades on the American Spinal Injury Association Impairment Scale or Frankel at final follow-up. Again, MP was not associated with a significant motor recovery ($p = 0.53$) (figure 4).

Sensory score improvement

Four studies compared sensory recovery.[17,18,24,28] MP was not associated with a better improvement in light touch ($p = 0.17$), pinprick ($p = 0.42$), or other categories of sensory scores ($p = 0.31$) (figure 5).

Incidence of adverse events

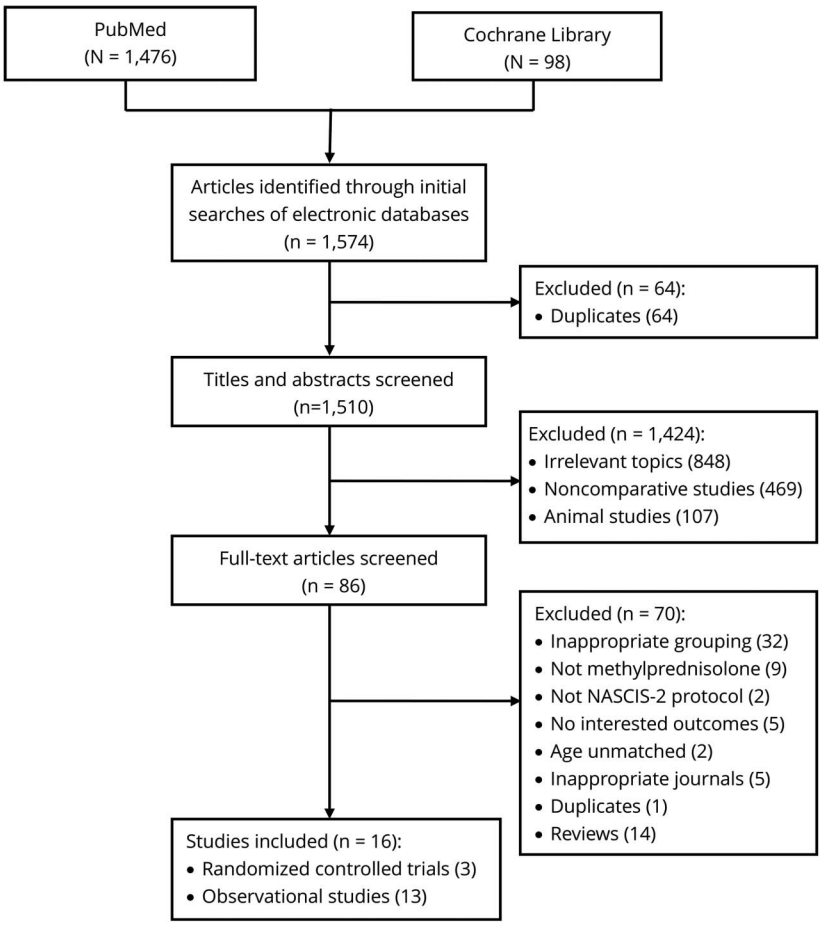
We pooled the common adverse events reported in different studies, including death, gastrointestinal hemorrhage (GIH), respiratory tract infection, urinary tract infection, wound infection, sepsis, decubiti, and deep vein thrombosis/pulmonary embolism. In addition, we included acute corticosteroid myopathy (ACM) after high-dose MP treatment, which was specifically reported in one study.[23]

MP treatment was associated with a significantly higher incidence of adverse events ($p = 0.02$), especially for GIH ($p = 0.04$) and respiratory tract infection ($p = 0.01$) (figure e-2, doi.org/10.5061/dryad.7d837c6). The pooled GIH incidence could be slightly influenced (from $p = 0.04$ to $p = 0.05$) after removing the data set of Tsutsumi et al.[22] reporting a significant difference in the percentage of complete injury between groups.

In-hospital costs

Based on the limited evidence from the few studies reporting in-hospital costs, MP was associated with significant

Figure 1 Flow diagram of studies identified, included, and excluded



NASCIS-2 = second National Acute Spinal Cord Injury Study.

decreased days in general care ($p < 0.0001$) and rehabilitation ($p = 0.03$), but increased days of mechanical ventilation ($p = 0.04$) and in the intensive care unit (ICU) ($p = 0.05$). No significant difference in the overall in-hospital costs was found between groups ($p = 0.78$) (figure e-3, doi.org/10.5061/dryad.7d837c6).

Discussion

Based on the current eligible evidence from RCTs and observational studies, our meta-analysis revealed that high-dose MP, given according to the NASCIS-2 protocol within 8 hours after ASCI, was not associated with better neurologic recoveries. Although limited data suggested administration of high-dose MP did not decrease in-hospital costs, more robust analyses indicated it was associated with a higher incidence of adverse events, particularly GIH and respiratory tract infection.

Different from Bracken[29] and Fehlings et al.,[13] who enrolled only a very limited number of prospective studies in their meta-analyses, Evaniew et al.[30] systematically reviewed all the eligible studies evaluating the therapeutic and adverse effects of MP in 2016. Evaniew's findings supported most of the current guidelines against routine use of MP. However, they did not consider differences in age and ASCI severity (complete vs incomplete) between groups and whether MP was administered according to the NASCIS-2 protocol. In addition, they did not compare sensory recoveries.

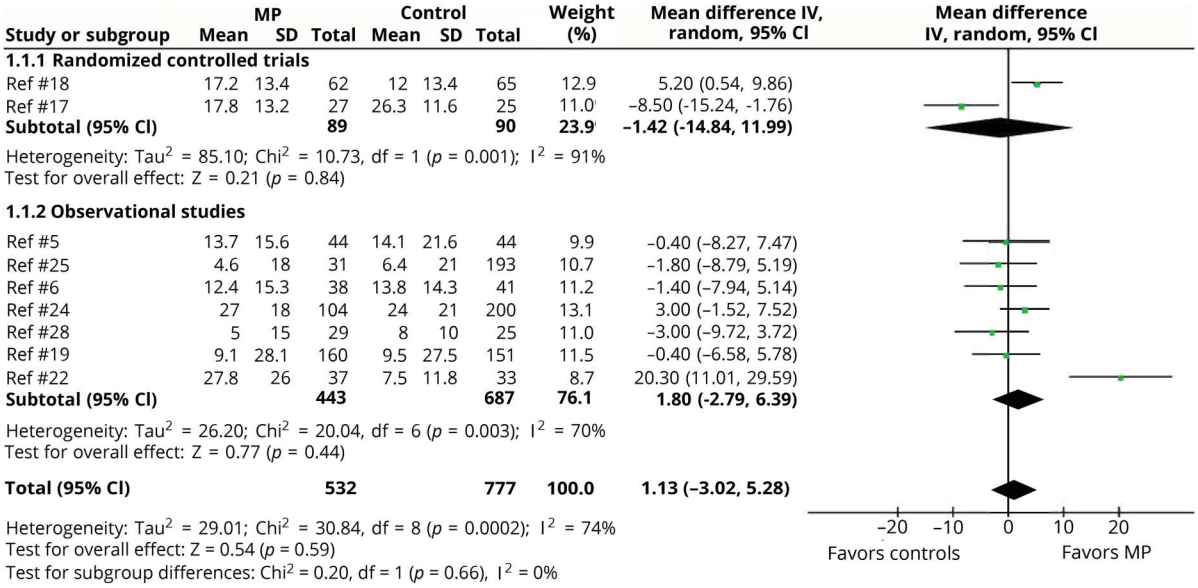
Similar to most of the guidelines and Evaniew's meta-analysis, we recommend against the NASCIS-2 regimen for ASCI based on our current meta-analysis. We included new eligible studies published recently and comprehensively evaluated neurologic recoveries by comparing both motor and sensory scores. As the current debates mainly focus on the dosing protocol of NASCIS-2, studies failing to comply with the above-mentioned protocol weighted little on the balance of the debates and were excluded from our meta-analysis.[31,32] Meanwhile, age has been reported to associate with the prognosis of ASCI,[7,24] which might be a confounder of the outcome comparison between MP and control groups. Therefore, we excluded the studies reporting significant difference in the mean age between groups.[33,34] In

Table Included studies

Authors	Year	Size		Mean age, y, mean (SD)		Surgery, n (%)		Complete injury, n (%)		Follow-up, mo	Outcomes				Quality assessment[a]
		MP	P/C	MP	P/C	MP	P/C	MP	P/C		Motor recovery	Sensory recovery	Adverse events	Costs	
Sunshine et al.[19]	2017	160	151	42 (15.2)	44.8 (16.0)	133 (83.1)	111 (73.5)[b]	72 (45)	40 (26.5)[c]	2	√		√		8
Evaniew et al.[5]	2015	44	44	45.4 (16.2)	45.5 (16.6)	40 (90.9)	36 (81.8)	21 (47.7)	19 (43.2)	4	√		√		9
Khan et al.[20]	2014	216	134	44.8 (21.7)	47 (20.2)	216 (100)	134 (100)	94 (43.5)	56 (41.8)	NR			√		9
Ito et al.[6]	2009	38	41	55	60	29 (76.3)	28 (68.3)	10 (26.3)	11 (26.8)	3	√		√		9
Suberviola et al.[21]	2008	59	23	40.8 (20.1)	46.7 (17.3)	15 (25.4)	2 (8.7)	32 (55)	10 (43)	<1	√		√		8
Tsutsumi et al.[22]	2006	37	33	50.2 (17.3)	51.5 (21.1)	NR		18 (48.6)	25 (75.8)[b]	1.5, 6	√		√		8
Qian et al.[23]	2005	5	3	35 (17.4)	28 (9.5)	5 (100)	3 (100)	2 (40)	2 (66.7)	<1			√		6
Pollard and Apple[24]	2003	104	200	NR		NR		NR		2	√	√			6
Matsumoto et al.[7]	2001	23	23	60.9 (12.4)	60.4 (18.6)	0 (0)	0 (0)	9 (39.1)	6 (26.1)	2			√		RCT
Pointillart et al.[17]	2000	27	25	32 (5.5)	28 (5.2)	40 (76)		NR		12	√	√		√	RCT
Heary et al.[25]	1997	31	193	26 (18.6)		1 (3.2)	27 (14)	25 (80.6)	147 (76.2)	56.3	√		√		8
Gerndt et al.[26]	1997	93	47	34 (19.3)	30 (13.7)	73 (78)	35 (75)	NR		NR			√	√	9
Levy et al.[27]	1996	55	181	25.6 (15.1)		16 (6.7)		5 (9)	18 (10)	6	√		√		8
Gerhart et al.[8]	1995	175	76	NR		NR		NR		"Short term"	√				7
Prendergast et al.[28]	1994	29	25	32.6	39.4	13 (44.8)	16 (64)	14 (48.3)	11 (44)	2	√	√		√	6
Bracken et al.[3,18]	1990/1992	162	171	NR		160 (98.8)	170 (99.4)	105 (64.6)	101 (58.8)	1.5, 6, 12	√	√	√		RCT

Abbreviations: MP = methylprednisolone; P/C = placebo/control; NR = not reported; RCT = randomized controlled trial.
[a] Newcastle-Ottawa Scale for quality assessment of observational studies. Range: 1–9 points. Studies achieving 6 or more points are considered of high quality.
[b] $p < 0.05$.
[c] $p < 0.01$.

Figure 2 Motor score improvement in methylprednisolone (MP) vs control groups

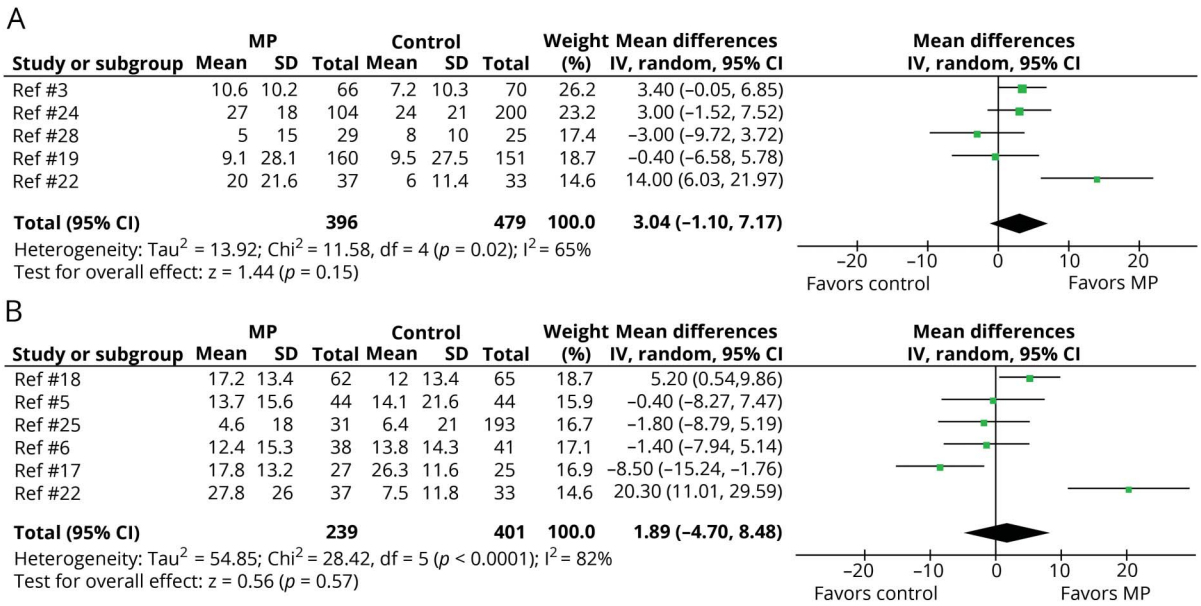


CI = confidence interval.

contrast, we included all the ASCI participants without special restriction to age (adolescents or adults) or mechanism of injury (blunt injury, penetrating injury, or gunshot injury), as none of the above conditions was an evidence-based contraindication of MP therapy. We divided short-term and long-term outcomes by the time point of 2 months because (1) 6 weeks and 6 months after injury, lying on both sides of 2 months, were most frequently used in studies with multiple follow-ups; and (2) 2 months after injury was reported to divide SCI into acute and chronic phases.[35–37]

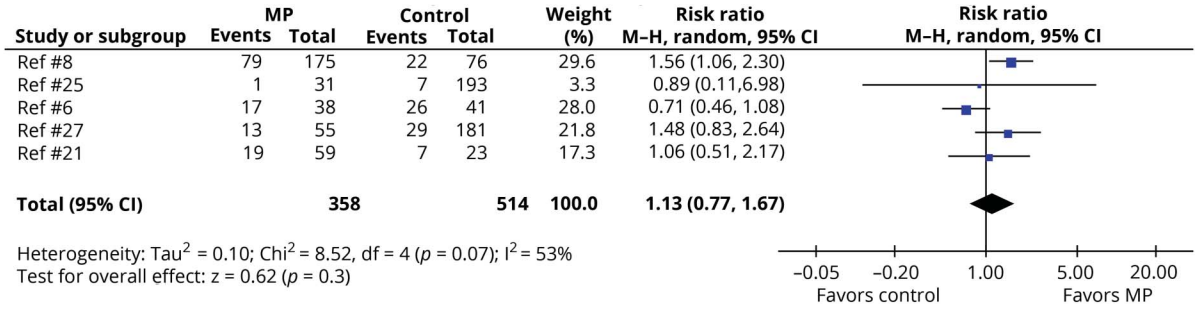
Several limitations in this meta-analysis should be addressed. First, we only performed stratified analysis separating RCTs from observational studies in the pooled overall motor score improvement, due to a limited number of RCTs. Second, younger age, less severe injury, as well as early surgical

Figure 3 Motor score improvement in methylprednisolone (MP) vs control groups at short-term and long-term follow-ups



(A) Short-term and (B) long-term follow-ups. CI = confidence interval.

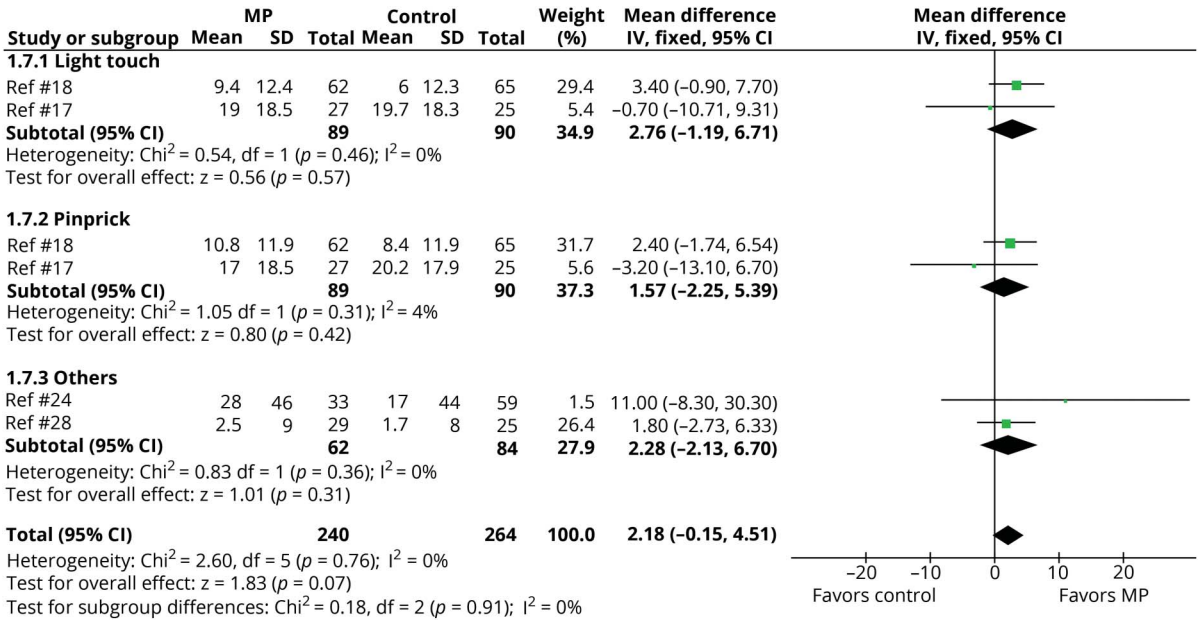
Figure 4 Incidence of at least 1 grade American Spinal Injury Association Impairment Scale/Frankel improvement in methylprednisolone (MP) vs control groups



CI = confidence interval; M-H = *Mantel-Haenszel*.

intervention (<24 hours postinjury) were reported to associate with better prognosis of ASCI[7,17,24,38] and therefore were potential confounders to influence the outcomes. Although we controlled the mean age and the percentage of complete injury between the comparison groups, the time to surgical intervention varied a great deal between and within studies; we therefore could not control the surgical confounding factor. Instead, we listed the percentage of patients who underwent stabilizing surgery (with no time restriction) for reference in the table. Third, relevant details of the common care and treatment that might also influence neurologic recoveries and incidence of complications were not clearly illustrated in most of the studies. For example, standard care like maintenance of mean arterial pressure between 85 and 90 mm Hg for the first 7 days following an ASCI is recommended to improve neurologic outcomes,[39] but few studies introduced information on their acute cardiopulmonary management for the patients involved. Only 2 studies reporting GIH mentioned the administration of acid suppressant such as an H2 blocker or proton pump inhibitor to both comparison groups, which is crucial for GIH prevention. Few studies reporting respiratory tract infection compared percentage of patients who underwent mechanical ventilation (a definite risk factor of ventilator-associated pneumonia) between groups upon admission to the ICU. Similarly, urethral catheterization was not mentioned in most of the studies reporting urinary tract infection. Although most of the current included studies might have controlled the above-mentioned methods for common care and treatment between groups, description

Figure 5 Sensory score improvement in methylprednisolone (MP) vs control groups



CI = confidence interval.

of these relevant details is highly recommended in future studies. Finally, some studies presented data as medians and ranges, and the values of means and SDs were not original data but calculated using the formula. Nevertheless, synchronized data conversion of both comparison groups within the same study would not significantly change the result.

MP, although theorized to inhibit inflammatory reactions and lipid peroxidation of the neurons early in the secondary injury cascade after ASCI, was found to suppress the proliferation of neural stem cells both in vitro[40] and in vivo.[41] In addition, Qian et al.[23] reported that administration of high-dose MP according to the NASCIS-2 protocol might cause ACM with a natural healing process of 6–8 months, and hypothesized that the neurologic recovery showed in NASCIS might partly result from the natural recovery of ACM, rather than the therapeutic effect of MP. Nevertheless, steroids are powerful drugs; they are just looking for an indication. It has been reported that with emerging drug delivery techniques such as MP-loaded ibuprofen-modified dextran-based nanoparticles[42] and dexamethasone acetate–loaded polymeric micelles,[43] steroids could be delivered to the spinal cord lesion more efficiently at a lower dose to increase treatment efficiency and decrease side effects in SCI rats. Scientific and technological development will likely help steroids find a better indication for ASCI treatment in the future.

Based on the current evidence, high-dose MP treatment, in comparison to no steroid therapy, does not contribute to better neurologic recoveries but increases the risk of adverse events in patients with ASCI. Therefore, we recommend against routine use of high-dose MP within 8 hours of ASCI. Detailed methodology and better control of potential confounders like age, severity of injury, and time to surgical interventions are necessary if further research is forthcoming to confirm and update our current findings.

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Disclosure

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