Controversies in Cervical Spine Trauma: The Role of Timing of Surgical Decompression and the Use of Methylprednisolone Sodium Succinate in Spinal Cord Injury. A Narrative and Updated Systematic Review

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Abstract

Traumatic spinal cord injuries (SCIs) have devastating physical, social, and financial consequences for both patients and their families. SCIs most frequently occur at the cervical spine level, and these injuries are particularly prone to causing debilitating functional impairments. Unfortunately, no effective neuroregenerative therapeutic approaches capable of reversing lost neurologic and functional impairments exist, resulting in a large number of patients living with the persistent disability caused by a chronic cervical SCI. Over the past decades, a multitude of nonpharmacologic and pharmacologic neuroprotective strategies have been intensely investigated, including the timing of surgical decompression and the role of methylprednisolone sodium succinate (MPSS) in patients with acute SCI. These strategies have been the source of vibrant debate surrounding their potential risks and benefits. Our aim in this combined narrative and updated systematic review is to provide an assessment on the timing of surgical decompression as well as the role of high-dose MPSS treatment in patients with traumatic SCIs, with a special emphasis on the cervically injured subpopulation. Based on the current literature, there is strong evidence to support early surgical decompression within 24 h of injury to promote enhanced neurologic recovery. Meanwhile, moderate evidence supports the early initiation of a 24-h high-dose MPSS treatment within 8 h of injury, particularly in patients with a cervical SCI.

Keywords: Methylprednisolone sodium succinate, MPSS, spinal cord injury, surgical decompression, systematic review, timing

Introduction

Traumatic spinal cord injury (SCI) occurs over a brief instant yet has far-reaching physical, social, and financial consequences for both patients and their families. Although the worldwide incidence ranges between 10.4 and 83 cases per million per year,[1] there are currently more than one million people living with a SCI in North America alone. With the cervical spinal cord being the most commonly affected level of injury, patients are particularly prone to suffer from debilitating impairments such as quadriplegia, respiratory compromise, and dependence for activities of daily living. In accordance with the degree of physical impairment, direct lifetime costs are substantially higher in those with quadriplegia, reaching a staggering $2.3–5.1 million US dollars (USD) per patient, as compared to patients with paraplegia, where estimates are calculated at $1.6–2.5 million USD per patient.[2]

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Unfortunately, no effective neuroregenerative therapies capable of restoring lost neurological functions currently exist. Current therapeutic strategies are largely targeted towards damage control, with the goal of mitigating the negative effects of the secondary injury mechanism[3] on neurological deficits and outcomes.[4,5] Importantly, patients with SCIs report that even modest improvements in motor function would enhance their quality of life by providing greater daily independence.[6] A multitude of therapeutic approaches have been investigated over the past decades, with some of them being intensely debated. Historically, concerns were expressed around the possibility that early surgery might exacerbate secondary injury, although this concern is no longer valid given the extensive basic science and clinical evidence that indicates the safety of early surgical intervention in the setting of acute SCI. It is particularly critical to maintain mean arterial blood pressures higher than 85–90 mmHg during all phases of surgery for acute SCI.[7]

In this article, we review two of the most discussed controversies in the therapeutic management of patients with acute traumatic SCI: (i) the role of timing of surgical decompression and (ii) the use of methylprednisolone sodium succinate (MPSS). First, clinical data regarding the optimal timing of surgical decompression have been mixed, with some studies showing an effect of timing of surgery whereas others have not. Differing time thresholds and heterogeneous patient populations have further limited the development of definitive evidence. This is being complicated since the execution of randomized controlled trials (RCTs) is a methodological challenge in the setting of acute traumatic SCI. Second, current knowledge on the use of MPSS strongly relies and builds on the results of historical, large-scaled RCTs.[8-11] The interpretation of these results and their implementation into clinical practice has been the source of vibrant debate over the past decades. Subsequent studies have attempted to review the evidence with the aim of providing clinicians with specific recommendations regarding the use of MPSS in traumatic SCI.[12,13] However, despite a similar evidence base, these guidelines have resulted in differing recommendations, further complicating practical decision making in the setting of acute SCI.

In addition to an evidence-based narrative review, we provide an updated systematic review of the literature. This analysis provides compelling evidence to support a strong role for early decompressive/reconstructive surgery in the setting of acute SCI. Moreover, our analysis of the literature supports the 2017 AO Spine guidelines, which support the use of MPSS as a valid treatment option for acute SCI—in particular, those individuals with an acute cervical SCI.

Materials and Methods

Electronic literature search

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and conducted a systematic search in PubMed for systematic reviews and meta-analyses, RCTs, and observational studies published between January 2017 and March 3, 2021, on patients with acute traumatic cervical SCIs treated with MPSS or where the timing of surgical decompression was analyzed. The review methods were established before conducting the review. The detailed search strategy included the following terms: (sci [text word] or spinal cord injury [all fields]) and (methylprednisolone [all field] or steroid [all field] or surgery [all fields] or surgical decompression [all fields] or decompression [all fields] or operation [all fields]).

Two investigators (NH, BR) independently evaluated the eligibility of potential titles and abstracts. After an initial assessment, full texts were again independently reviewed according to the inclusion and exclusion criteria, as defined in the next section. Disagreements were solved by discussion and where needed, a third reviewer (MGF) was consulted.

Inclusion and exclusion criteria

Articles were included if (1) Participants: Cohorts included patients with acute traumatic SCI with ≥50% of patients being affected at the cervical level. (2) Intervention, *MPSS*: The effects of MPSS treatment encompassing any therapeutic regimen were compared with non-MPSS treatment. Intervention, *Surgical Timing:* A cohort that underwent early surgery was compared with a cohort undergoing late surgery. (3) Outcomes: The effects of MPSS treatment or the timing of surgical decompression were investigated with adequate outcome measures (e.g. the third version of the spinal cord independence measure [SCIM-III], American Spinal Injury Association [ASIA] motor scores, or American Spinal Injury Association Impairment Scale [AIS] grades). (4) Due to a paucity of updated data in the field of MPSS treatment for acute SCI, we also included systematic reviews and meta-analyses, in addition to RCTs and observational studies, into our systematic search. (5) Publication: Only articles published or translated into English in peer-reviewed journals were included.

Exclusion criteria included the following: (1) Participants: Patients <12 years old, penetrating SCIs, cohorts focusing on patients with specific spine diseases (ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis [DISH], cord compression due to tumor, degenerative disease), no evidence of spinal fractures or dislocations, patients without neurological deficits after trauma, studies only investigating non-cervical SCIs. (2) Outcomes: Studies not reporting on functional or clinical outcomes, studies not reporting neurologic assessment on admission, and studies with outcome follow-ups of ≤3 months. (3) Study design: Experimental studies, case reports. (4) Publication: Abstracts, editorials, letters, narrative reviews, and systematic reviews without meta-analyses.

Data extraction

From the included articles we extracted the following data: author name, publication year, study design, demographic information, number of patients, level of injury, treatment details, study inclusion/exclusion criteria, injury severity on admission, follow-up duration, rates of follow-up, outcomes assessed, and whether funding was received.

Quality assessment of included studies

NH and BR independently assessed the risk of bias of the observational studies using the Newcastle-Ottawa Scale Quality Assessment Scale. The scale rates the studies in three domains: selection of the groups (0–4 points), comparability of the groups (0–2 points), and the ascertainment of outcomes (0–3 points).[14] The quality of systematic reviews was assessed by the second version of the Assessment of Multiple Systematic Reviews (AMSTAR-2) evaluation tool.[15]

Results

Study selection

Our bibliography search yielded 6475 citations. Of these, 6378 were excluded based on the information provided in the title or abstract. Ninety-seven articles were carefully reviewed in full text. We excluded 72 articles for the following reasons: not assessing outcomes of interest (*n* = 41), systematic reviews without meta-analysis or narrative reviews (*n* = 20), cohorts without SCI or cervical SCI (*n* = 3), studies excluded due to short follow-up periods (*n* = 2), no AIS or ASIA assessment on admission (*n* = 2), studies applying multiple interventions in the same group of patients (*n* = 1), data previously published (*n* = 1), studies solely focusing on patients with DISH (*n* = 1), or groups with mixed dexamethasone and MPSS treatment (*n* = 1) [Figure 1]. Among the remaining 25 studies, 21 were included in the qualitative synthesis on the timing of surgical decompression and four studies were included

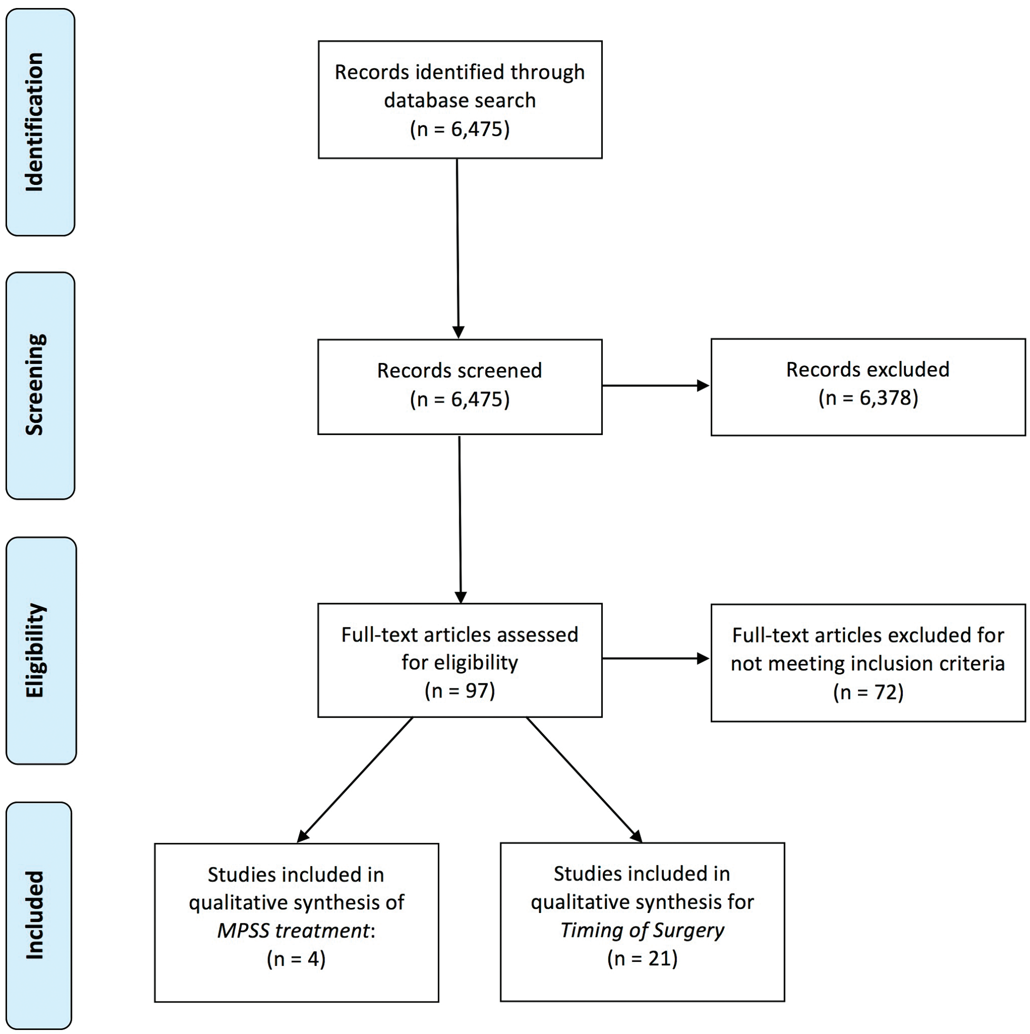

Figure 1: Flow diagram of literature search

on the role of MPSS treatment in the management of acute SCI.

Timing of surgery

Of the 21 studies investigating the role of the timing of surgical decompression, five studies were systematic reviews and meta-analyses published between 2018 and 2020. The systematic reviews had differing inclusion criteria, methodologies, and conclusions [Table 1]. The quality of the systematic reviews ranged from critically low to moderate quality, as assessed by the AMSTAR-2 evaluation tool. Among the remaining 15 studies meeting our inclusion criteria, three were prospective cohort studies, one was a pooled analysis of four previously independently published prospective cohort studies, and 11 were retrospective cohort studies [Table 2].

Treatment with MPSS

Four studies were included in the qualitative analysis of MPSS treatment in acute SCI. Three articles were systematic reviews and meta-analyses published between 2017 and 2020 [Table 3]. Their quality ranged from low to high. The other study meeting the inclusion criteria was a RCT published in 2019 [Table 4].

Timing of surgical decompression

After the primary injury, persistent spinal cord compression due to blood, dislodged bone, or disc fragments may impair spinal cord perfusion and lead to localized ischemia, which puts the perilesional penumbric zone at risk of progressive loss of neural tissue. Timely surgical decompression affords the opportunity to relieve the pressure on the spinal cord vasculature and to thus restore spinal cord blood flow as well as to mitigate the harmful biochemical effects of the secondary injury cascade.[16] A meta-analysis of preclinical studies confirmed the beneficial effects of early surgical decompression and found it to be key to improving neurobehavioral outcomes.[17] From a clinical perspective, early surgical treatment and internal fixation of the potentially unstable spine favors early mobilization, thereby reducing immobilization-associated complications, length of hospital stay, and, ultimately, costs of patient care.[18-20]

A number of clinical studies investigating the impact of timing of surgery on outcomes have emerged over the past decades. Among these, differing time thresholds have been used to define "early" vs. "late" surgical decompression. Only a few studies have investigated 8–12 or 48–72 h thresholds, whereas a cutoff of 24 h has been studied most frequently.[21] However, evidence has shown mixed results for the timing of surgery on outcomes, therefore complicating the development of strong recommendation guidelines.[22]

In 1982, an observational study of 44 cases of cervical SCI failed to show significant differences in neurologic recovery for patients undergoing early surgery, defined as <8 h from injury, as compared with late decompression (9–48 h).[23] A prospective study of 283 mixed-level patients who had experienced a SCI, which followed in 1987, determined an association between neurologic deterioration of patients suffering from cervical SCIs and those who underwent early surgery within five days, therefore advocating for delayed surgery in these patients.[24] And yet, a survey of 971 spine surgeons revealed that more than 80% preferred surgical decompression within 24 h of injury.[25] Due to the ambiguity of the risks and benefits of early vs. delayed surgical management of patients with acute traumatic SCIs, high-quality studies were warranted.

The largest prospective cohort study investigating the role of timing in a cervical-only SCI population was the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS, n = 313), which was published in 2012.[26] The study evaluated the effectiveness of early (<24 h after injury) vs. late (≥24 h) surgical decompression on neurological outcomes, as defined by the changes in AIS grades at six months post-injury. Of the 222 patients with follow-up data available at six months post-injury, 19.8% of patients undergoing early surgery showed at least a two-grade improvement in AIS, as compared with 8.8% in the late surgery group (odd ratio [OR] = 2.57, 95% confidence interval [CI]: 1.11–5.97). Moreover, there was a nonsignificant trend toward less in-hospital complications in the early surgery group. Bourassa-Moreau *et al*.[27] found the improved rates of AIS conversion of 20 patients with cervical AIS grade A to be associated with early surgical decompression within 24 h of injury.

Although there has been a paucity of studies only focusing on patients with cervical SCIs, several other studies with mixed-level SCI populations have been published. Another Canadian-based prospective cohort study published in 2012 (n = 84, cervical = 52.4%) with follow-ups at rehabilitation discharge found a significantly greater proportion of patients with at least a two-grade AIS improvement when operated within 24 h of injury.[28] The study published by Dvorak *et al*.[20] (n = 888, cervical = 62.3%) showed that SCI patients with incomplete AIS grades B to D profited from an additional 6.3 points of motor score recovery when undergoing surgical treatment within 24 h from injury. Although these results have not been observed in patients with AIS grade A, patients with AIS grade A and B experienced shorter lengths of stay.

Updates since 2017

The significance of strengthening the current evidence on the role of the timing of surgical decompression has been reflected in ongoing efforts of 21 studies published since 2017. Among the five systematic reviews and meta-analyses, differing cutoffs of 8, 24, and 72 h have been used to define early vs. late surgical treatment, with cutoffs of 8

Table 1: Overview of previous systematic reviews and meta-analyses assessing the timing of surgical decompression in the treatment of acute SCI

Assessment (year)	Literature search dates	Purpose	Inclusion and exclusion criteria	Timing	Evidence base available	Follow-up range	Primary conclusions	AMSTAR-2 score
El Tecle *et al*.[29] (2018)	After January 1992, Embase, MEDLINE, PubMed, Scopus, CINAHL, Cochrane	To analyze data reporting on patients with ASIA-A and evaluating factors affecting the natural history of complete SCI	*Inclusion:* Papers reporting outcomes using ASIA Clinical trials Observational studies *Exclusion:* Animal studies Articles not in English	Early (<24 h) vs. late (>24 h)	Three RCTs (*N* = 141)	Two months to 12 months	Early surgery (defined as surgery within 24 h of injury) is predictive of a higher conversion rate of patients with ASIA-A SCI	Critically low
Lee *et al*.[30] (2018)	Up to 2016, MEDLINE, EMBASE, Cochrane, Web of Science, SCOPUS	To evaluate whether early (<8 h) surgical decompression is better in improving neurologic outcomes than late (>8 h) surgical decompression for traumatic SCI	*Inclusion:* Patients with acute SCI Studies comparing clinical outcomes of early (<8 h) vs. late (>8 h) surgical decompression *Exclusion*: NR	Early (<8 h) vs. late (>8 h)	Three RCTs, four non-randomized studies (*N* = 650)	Six months to 67 months	Early surgical decompression within 8 h after traumatic SCI was beneficial in terms of neurologic improvement compared with late surgery	Moderate
Ma *et al*.[31] (2020)	Until December 2019, PubMed, MEDLINE, EMBASE, Cochrane	To determine the beneficial effects of surgery within 8 h for patients with traumatic SCI	*Inclusion:* RCTs, cohort or cross-sectional studies Patients with traumatic SCI receiving surgery Studies had to report comparative clinical outcomes between early and late surgery Reporting of baseline and follow-up neurologic status Reporting of outcomes (≥1) by ASIA, Frankel, LOS, length of ICU stay, complications, and mortality *Exclusion:* Case reports/series Repeated reports Single-arm studies Studies focusing on pediatric patients Studies with less than six months of follow-up	Early (<8 h) vs. late (>8 h)	Two RCTs, seven non-randomized studies (*N* = 716)	Six months to 67 months	Urgent decompression (<8 h) for patients with traumatic SCI is associated with benefits in terms of neurologic recovery	Low

Table 1: Continued

Assessment (year)	Literature search dates	Purpose	Inclusion and exclusion criteria	Timing	Evidence base available	Follow-up range	Primary conclusions	AMSTAR-2 score
Ter Wengel *et al.*[32] (2019)	Until November 2017, PubMed, EMBASE	To address neurological improvement after early and late surgery for complete and incomplete cervical traumatic SCI	*Inclusion:* Cervical traumatic SCI containing baseline ASIA, Frankel, Benzel, and Larson classification Timing of surgical decompression Neurological examination at follow-up *Exclusion:* Studies with <10 patients <15 years of age Traumatic CCS, AS, DISH, OPLL	Early (<24 h) vs. late (>24 h)	15 non-randomized studies (N = 1126)	Two months to 131 months	Surgical decompression within 24 h is more frequently associated with clinically meaningful improvement in patients with complete cervical traumatic SCI. In those with incomplete cervical traumatic SCI, neurological outcome is similar between early and late surgery	Low
Yousefifard *et al.*[33] (2020)	January 2000 to October 2015, MEDLINE, EMBASE, CENTRAL, SCOPUS, Web of Science, ProQuest	To compare the effects of early and late spinal decompression surgery on neurologic improvement and postsurgical complications in patients with traumatic SCI	*Inclusion:* Studies comparing the effects of early with later surgical decompression on outcomes of SCI Studies assessed outcomes based on ASIA and Frankel score *Exclusion:* Age <14 years Nontraumatic SCI Temporal cutoff of more than 72 h Patient follow-up of less than six months	Studies with mixed cutoffs: >8 h/<8 h >24 h/<24 h >72 h/<72 h	Two RCTs, two quasi-RCTs, 18 non-randomized studies (N = 6803)	Six months to 24 months	Early spinal decompression can improve neurologic recovery and reduce postsurgical complications with an optimum efficacy within 12 h of injury	Low

AMSTAR = A MeaSurement Tool to Assess systematic Reviews, AS = ankylosing spondylitis, CCS = central cord syndrome, ICU = intensive care unit, LOS = length of stay, NR = not reported, OPLL = ossification of the posterior longitudinal ligament

Table 2: Study characteristics of cohort studies assessing the timing of surgical decompression in the treatment of acute SCI

Author (year), design, and risk of bias	Sample and characteristics	Inclusion and exclusion criteria	Severity (on admission)	Type of intervention	Surgical timing	Outcome measures	Follow-up time (%)	Funding
Aarabi *et al*.[34] (2020), Prospective cohort, NOS: 4–2–3	*N* = 72 Male: 83.3% Age, mean (SD): 46 (±17.6) Level of injury: Cervical: 72/72 (100%)	*Inclusion:* Age > 16 years GCS ≥14 No life-threatening injury or disease Subaxial cervical spine fracture dislocations Available preoperative and postoperative CT and MRI indicating complete spinal decompression after surgery Follow-up ≥6 months *Exclusion:* Non-testable patient Penetrating SCI Upper cervical SCI Postop-MRI indicating inadequate spinal cord decompression Nonoperative management Dying or lost to follow-up Poor-quality imaging studies	AIS grade: A: 27/72 (37.5%) B: 23/72 (31.9%) C: 22/72 (30.6%) D: 0/72	ACDF: 10/72 (13.9%) ACDF and Laminectomy: 25/72 (34.7%) ACCF and Laminectomy: 11/72 (15.3%) Laminectomy: 17/72 (23.6%)	<12 h: 32/72 (44.4%) 12–24 h: 25/72 (34.7%) 24–138.5 h: 15 (20.8%)	*AIS grade:* A: Complete B: Sensory Incomplete C: Motor Incomplete, 50% of key muscle grade <3/5 D: Motor Incomplete, 50% of key muscle grade ≥3/5	Six months or more (100%) to >12 months	No competing financial interests
Badhiwala *et al*.[22] (2021), Pooled analysis of four prospective cohorts, NOS: 4–2–3	*N* = 1548 Male: 79.9% Early surgery group (*N* = 528): Age, mean (SD): 39.5 (±16.9) Male: 79% Level of injury: *Cervical*: 459/528 (86.9%) *Thoracic*: 54/528 (10.2%) *Lumboscaral*: 15/528 (2.8%) Late surgery group (*N* = 1020): Age, mean (SD): 38.9 (± 17) Male: 79.9% Level of injury: *Cervical*: 816/1020 (80%) *Thoracic*: 175/1020 (17.2%) *Lumbosacral*: 29/1020 (2.8%)	*Inclusion:* Data from December 1991 to March 2017 Patients who underwent decompressive surgery for acute SCI within the data set ≥12 years of age AIS grades A-D Level of injury: Any *Exclusion:* [a]NR	*Early surgery group:* AIS grade: A: 260/528 (49.2%) B: 82/528 (115.5%) C: 88/528 (16.7%) D: 98/528 (18.6%) *Late surgery group:* AIS grade: A: 506/1020 (49.6%) B: 117/1020 (11.5%) C: 181/1020 (17.7%) D: 216/1020 (21.2%)	NR	<24 h: 528/1548 (34.1%) ≥24 h: 1020/1548 (65.9%)	*AIS grade* *AIS motor score:* 0–5 (no contraction to normal function) for 14 muscles (range from 0 to 70) *AIS light touch and pin prick score:* 1–3 (absent, dysfunction, or normal) in 29 segments (range from 29 to 87)	One year (66.6%)	No funding received

Table 2: Continued

Author (year), design, and risk of bias	Sample and characteristics	Inclusion and exclusion criteria	Severity (on admission)	Type of intervention	Surgical timing	Outcome measures	Follow-up time (%)	Funding
Cao *et al.*[35] (2019), Retrospective cohort, NOS: 4–2–3	N = 55 Male: NR Age: Nonfunctional restoration group (N = 25), mean (SD): 31.9 (± 5.7) Functional restoration group (N = 30), mean (SD): 29.4 (± 6.7) Level of injury: Cervical: 55/55 (100%)	*Inclusion:* Subaxial cervical SCI with fracture dislocation confirmed by MRI and CT from April 2013 to April 2018 Underwent surgical treatment Age: 18–60 Signed informed consent *Exclusion:* Previous history of cervical spine surgery Compression fracture of the cervical vertebra, cervical tumor, and cervical spondylosis Lost during follow-up Incomplete prognosis condition and treatment data Lack of signed informed consent, refusal of surgery	AIS grade: A: 25/55 (45.5%) B: 17/55 (30.9%) C: 8/55 (14.5%) D: 5/55 (9.1%)	ACDF (NR) ACCF (NR)	Nonfunctional restoration group (days): 4.4 ± 2 Functional restoration group (days): 1.2 ± 0.5)	*AIS grade*	12–74.5 months (100%)	NR
Dakson *et al.*[36] (2017), Retrospective cohort, NOS: 4–2–2	N = 94 Male: 79% Age, mean (SD): 47.6 (± 20.7) Level of injury: Cervical: 66/94 (70%) Thoracolumbar: 28/94 (30%)	*Inclusion:* Patients coded as traumatic SCI, presenting between 2006 and 2010 *Exclusion:* NR	AIS grade: A: 31/94 (33%) B: 12/94 (13%) C: 16/94 (17%) D: 29/94 (31%) NA 6/94 (6%)	NR	<24 h (13.4±5): 23/56 (41.1%) >24 h (24.1±212.5): 33/56 (58.9%)	*AIS grade*	Cervical: 26.7 days: 39/66 (59.1%) 115 days: 31/66 (47%) 252 days: 31/66 (47%)	NR

Table 2: Continued

Author (year), design, and risk of bias	Sample and characteristics	Inclusion and exclusion criteria	Severity (on admission)	Type of intervention	Surgical timing	Outcome measures	Follow-up time (%)	Funding
Du *et al*.[37] (2019), Prospective cohort, NOS: 4–2–3	*N* = 402 Male: 69.9% Age, mean (SD): 46.8 (± 15.3) Level of injury: Cervical 402/402 (100%)	*Inclusion:* Age 16–80 years AIS grades A–D Spinal cord compression or injury confirmed by MRI or CT-myelography Informed consent present Level of injury: C3–C7 SLIC Score ≥4 Treatment with decompression, fusion and fixation surgery *Exclusion:* Penetrating injuries Major neurological deficits or illness before injury Serious, life-threatening injury prohibiting early surgery Arrival at the trauma center ≥72 h Surgery more than seven days after injury Cervical vertebral infection, tumors, AS with cervical spinal stenosis Cervical SCI combined with thoracolumbar fractures or multiple system injuries	AIS grade (early surgery): A: 31/173 (17.9%) B: 55/173 (31.8%) C: 53/173 (30.6%) D: 34/173 (19.7%) AIS grade (late surgery): A: 52/211 (24.6%) B: 71/211 (33.6%) C: 65/211 (30.8%) D: 23/211 (10.9%)	Anterior: 270/402 (67.2%) Posterior: 87/402 (21.6%) A-P combined: 45/402 (11.2%)	<72 h: 187/402 (46.5%) >72 h: 215/402 (53.5%)	*AIS grade*	12 months (early surgery): 173/187 (92.5%) 12 months (late surgery): 211/215 (98.1%)	No funding received
Facchinello *et al*.[38] (2018), Prospective cohort, NOS: 4–2–2	*N* = 42 Sex: NR Age, median (IQR): 43 (30–61) Level of injury: Cervical 42/42 (100%)	*Inclusion:* Motor-complete, cervical traumatic SCI between January 2010 and June 2016 Signed informed consent Level of injury between C1 and T1 Initial AIS grade A or B Minimum follow-up of six months *Exclusion:* Consent not obtained	AIS grade: A: 71% B: 29%	NR	<19 h: 20/42 (47.6%) >19 h: 22/42 (52.4%)	*AIS grade* *SCIM-III Score* (0–100): Self-care (0–20) Respiration and sphincter management: 0–40 Mobility (0–40)	Six months or more (100%)	U.S. Army Medical Research and Material Command, Rick Hansen Institute

Table 2: Continued

Author (year), design, and risk of bias	Sample and characteristics	Inclusion and exclusion criteria	Severity (on admission)	Type of intervention	Surgical timing	Outcome measures	Follow-up time (%)	Funding
Jug *et al.*[39] (2017), Prospective cohort, NOS: 4–2–3	$N = 64$ Male: 80% Age, median (IQR): 49 (29.5–74) Level of injury Cervical 64/64 (100%)	*Inclusion:* Age 16–85 years Fracture or dislocation at C3–C7 Spinal cord compression confirmed by MRI Neurological level of injury between C3 and C8 Initial AIS grades A–C Spinal cord compression ≥25% Surgery <24 h *Exclusion:* Neurological deficits prior to injury No evidence of fracture or dislocation Life-threatening injuries preventing early surgical decompression Cognitive impairment preventing accurate neurological assessment	AIS grade: A: 41/64 (64%) B: 9/64 (14%) C: 14/64 (22%)	OR and APDF: 4/64 (6%) CR and ADF: 37/64 (58%) CR and PDF: 7/64 (11%) CR and APDF: 16/64 (25%) Laminectomy: 7/64 (13%)	Median time to surgery, SD (IQR), hours: 7.0 (5–11)	*AIS grade*	Six months (100%)	Ministry of Health of the Republic of Slovenia,Slovenian Research Agency
Kim *et al.*[40] (2018), Retrospective cohort, NOS: 4–2–3	$N = 86$ Male: 78% Age, mean (SD): 40.23 (± 15.04) Level of injury: Cervical 46/86 (53.5%) Thoracic 12/86 (13.95%) Thoracolumbar 19/82 (22.1%) Lumbar 9/86 10.5%)	*Inclusion:* Cases of acute traumatic SCI from February 2005 to December 2016 Cervical, thoracic, thoracolumbar, and lumbar Vertebrae requiring surgical decompression *Exclusion:* GCS score <14 Evidence of TBI History of neurologic deficit AIS E Patients lost to follow-up by six months	AIS grade: A: 42/86 (48.84%) B: 15/86 (17.44%) C: 13/86 (15.12%) D: 16/86 (18.6%)	NR	≤48 h: 31/86 (36%) >48 h: 55/86 (64%)	*AIS grade*	Six months (100%)	No financial relationship declared

Table 2: Continued

Author (year), design, and risk of bias	Sample and characteristics	Inclusion and exclusion criteria	Severity (on admission)	Type of intervention	Surgical timing	Outcome measures	Follow-up time (%)	Funding
Lee *et al*.[41] (2018), Retrospective cohort, NOS: 4–2–2	*N* = 56 Male: 62.5% Age, mean (SD): Early surgery group (< 8 h): 50.9 (± 17.1) Late surgery group (8–24 h): 54.5 (±15.4) Level of injury: Cervical 28/56 (50%) Thoracic 13/56 (23.2%) Lumbar 15/56 (26.8%)	*Inclusion:* Traumatic SCI with AIS grades A–D Lesions between C1 and L2 No spinal shock, or patients who had improved from spinal shock Stable medical condition Surgical spinal cord decompression <24 h Follow-up of 6 months or more Adult patients No systemic or life-threatening injury *Exclusion:* Absence of neurological deficits No surgical procedure Decompression > 24 h Cognitive impairment rendering neurological assessment impossible OPLL, unstable medical condition	AIS grade: A: 15/56 (26.8%) B–D: 41/56 (73.2%)	Fusion: 43/56 (76.8%) Laminectomy: 5/56 (8.9%) ACDF: 8/56 (14.3%)	<8 h: 26/56 (46.4%) >8–24 h: 30/56 (53.6%)	*AIS grade*	Six months (100%)	NR
Mattiassich *et al*.[42] (2017), Retrospective cohort, NOS: 4–2–3	*N* = 49 Male: 78% Age, mean (SD): 50 (± 20) Level of injury: Cervical 49/49 (100%)	*Inclusion:* Newly diagnosed traumatic cervical SCI Age 15–85 years Initial neurological level between C2-T1 CT or MRI to verify spinal cord compression Initial AIS grade A–D Six months or more of follow-up *Exclusion:* Nontraumatic SCI Severe craniocerebral injury (GCS <14) Preexisting major neurological deficits, dementia or reduction of intelligence leading to reduced cooperation Pregnancy Surgery >24 h Severe polytrauma (ISS ≥25)	AIS grade: A: 20/49 (41%) B: 5/49 (10%) C: 12/49 (24%) D: 12/49 (24%)	NR	<5 h: 33/49 (67.3%) ≥5 h: 16/49 (32.7%)	*AIS grade*	2.61 years ± 2.32 (mean ± SD; range 0.5–10.88 years)	Research grant from the Austrian Insurance for Occupational risks, Paracelsus Medical University, Austrian Society of Traumatology

Table 2: Continued

Author (year), design, and risk of bias	Sample and characteristics	Inclusion and exclusion criteria	Severity (on admission)	Type of intervention	Surgical timing	Outcome measures	Follow-up time (%)	Funding
Mayol *et al*.[43] (2019), Retrospective cohort, NOS: 4–2–2	*N* = 62 Male: 84% Age, average: 38.6 Level of injury: Cervical 62/62 (100%)	*Inclusion:* Decompression and/or spinal cord stabilization surgeries for cervical spine trauma from January 2010 to December 2014 Age > 18 Surgery at the author's facility At least one follow-up visit *Exclusion:* NR	AIS grade: A: 20/62 (32%) B: 11/62 (18%) C: 14/62 (23%) D: 17/62 (27%)	NR	<24 h: 13/45 (28.9%) 25–48 h: 3/45 (6.7%) 49–72 h: 2/45 (4.4%) >72 h: 27/45 (60%)	*AIS grade*	NR, 45/62 (72.6%)	NR
Nasi *et al*.[44] (2019), Retrospective cohort, NOS: 4–2–2	*N* = 81 Male: 71.6% Age, mean (SD): 57.81 (± 21.26) Level of injury: Cervical 81/81 (100%)	*Inclusion:* Patients presented with traumatic cervical SCI from 2010 to 2017 *Exclusion:* NR	AIS grade: A: 26/81 (32.1%) B: 12/81 (14.82%) C: 19/81 (23.45%) D: 24/81 (29.62%)	Anterior: 52/81 (61.4%) Posterior: 13/81 (21.05%) Combined: 16/81 (17.55%)	<12 h: 40/81 (49.4%) >12 h <48 h 41/81 (50.6%)	*AIS grade*	Three, six, and 12 months (100%)	None
Park *et al*.[45] (2017), Retrospective cohort, NOS: 3–2–2	*N* = 73 Male 79.5% Age, mean (range): 44.23 (14–83) Level of injury: Cervical 73/73 (100%)	*Inclusion:* One-level decompression and fusion surgery January 2015 to December 2013 Cervical traumatic SCI Only surgically treated patients Initial AIS grades A–D MRI evidence of cervical spinal cord compression *Exclusion:* Patients with multilevel compressive lesions Presence of other potentially lethal organ injuries	AIS grade: A: 36/73 (49.3%) B: 6/73 (8.2%) C: 12/73 (16.4%) D: 19/73 (26%)	Single-level decompression and fusion surgery 73/73 (100%)	≤24 h: NR >24 h: NR	*AIS grade*	Three months (100%)	No financial interests declared
Sewell *et al*.[46] (2018), Retrospective cohort, NOS 3–2–3	*N* = 95 Male: 66.3% Age, median (range): 45 (16–83) Level of injury: Cervical 95/95 (100%)	*Inclusion:* Age ≥ 16 years Traumatic cervical SCI GCS >13 Concomitant chest injuries necessitating ICU admission *Exclusion:* Head injuries (GCS ≤13)	AIS grade: A: 28/95 (29.5%) B: 36/95 (37.9%) C: 17/95 (17.9%) D: 14/95 (14.7%)	NR	<24 h: 40/95 (42.1%) >24 h: 55/95 (57.9%)	*AIS grade*	Six months 94/95 (98.9%)	Declaration of absence of financial relationships

Table 2: Continued

Author (year), design, and risk of bias	Sample and characteristics	Inclusion and exclusion criteria	Severity (on admission)	Type of intervention	Surgical timing	Outcome measures	Follow-up time (%)	Funding
Tian *et al.*[47] (2020), Retrospective cohort, NOS: 4–1–2	N = 304 Male: 84.5% Age, mean (SD): 49.81 (±13.03) Level of injury: Cervical 269/304 (88.5%) Thoracic 11/304 (3.6%) Lumbar 24/304 (7.9%)	*Inclusion:* Age >18 Initial assessment based on ASIA score AIS grades A–D Surgical intervention during hospital stay *Exclusion:* Acute cerebrovascular disease	AIS grade: A: 78/304 (25.7%) B: 33/304 (10.9%) C: 66/304 (21.7%) D: 127/304 (41.8%)	NR	≤72 h: 133/304 (43.8%) >72 h: 172/304 (56.3%)	*AIS grade*	12 months (100%)	NR
Wichmann *et al.*[48] (2020), Retrospective cohort, NOS: 4–2–2	N = 143[b] Male: 78% Age, median (IQR): 56 (32–67) Level of injury: Cervical 98/143 (68%) Thoracic 38/143 (27%) Lumbar 7/143 (5%)	*Inclusion:* Subjects with acute traumatic SCI Between 2012 and 2019 All levels of traumatic SCI *Exclusion:* Age <13 years Concomitant TBI Missing baseline ASIA scores Missing follow-up SCIM-III scores	AIS grade: A: 55/143 (38%) B: 16/143 (11%) C: 37/143 (26%) D: 35/143 (25%)	NR	≤24 h (64%) >24 h (36%)	*SCIM-III Score*	Six months 63/143 (44%), 12 months 80 (56%)	NR

ACCF = anterior cervical corpectomy and fusion, ACDF = anterior cervical discectomy and fusion, ADF = anterior decompression and fusion, APDF = anterior and posterior decompression and fusion, AS = ankylosing spondylitis, CR = closed reduction, CT = computed tomography, GCS = Glasgow Coma Scale, ICU = intensive care unit, ISS = injury severity score, IQR = interquartile range, LOS = length of stay, MRI = magnetic resonance imaging, NOS = Newcastle Ottawa Scale, NR = not reported, OPLL = ossification of the posterior longitudinal ligament, OR = open reduction, PDF = posterior decompression and fusion, SD = standard deviation, SLIC = subaxial cervical spine injury classification, TBI = traumatic brain injury,

[a]A detailed description of the inclusion as well as exclusion criteria is included within the supplementary appendix

[b]Ten patients were treated nonoperatively

Table 3: Overview of previous systematic reviews and meta-analyses assessing the effects of MPSS in the treatment of acute SCI

Assessment (year)	Literature search dates	Purpose	Inclusion and exclusion criteria	Evidence base available	Follow-up range	Primary conclusions	AMSTAR score
Fehlings *et al.*[54] (2017)	January 1956 to 17 June 2015 PubMed, Cochrane	To assess the comparative effectiveness and safety of high-dose MPSS vs. no pharmacological treatment in patients with traumatic SCI	*Inclusion Criteria* Adults with traumatic SCI Comparison of MPSS with placebo or standard care without pharmacologic intervention Efficacy outcomes assessed by changes in motor scores and changes in sensation Safety assessed by complications, AEs, and deaths Comparative studies (RCTs and observational studies with controls) Follow-up rate ≥50% $N \geq 10$ per group Observational studies must control for SCI severity as evaluated by motor status at baseline and/or complete/incomplete injury English articles *Exclusion:* Age <13 years, pregnancy, penetrating SCI, cord compression due to tumor, hematoma, or degenerative disease, patients without neurological deficits Nonclinical outcomes Animal studies, nonclinical studies, follow-up rates <50%, $n < 10$ per group, no control for injury severity	Four RCTs, two non-randomized studies, seven systematic reviews (Total *N*: NR)	Six weeks to one year	When commenced within 8 h of injury, a high-dose 24-h regimen of MPSS confers a small positive benefit on long-term motor recovery and should be considered a treatment option for patients with SCI	High

Table 3: Continued

Assessment (year)	Literature search dates	Purpose	Inclusion and exclusion criteria	Evidence base available	Follow-up range	Primary conclusions	AMSTAR score
Liu *et al*.[55] (2019)	Till 22 May 2018 PubMed, Cochrane	To evaluate the therapeutic and adverse effects of high-dose methylprednisolone according to the NASCIS-2 dosing protocol in comparison to no steroids in patients with acute SCI	*Inclusion:* Studies published in Science Citation Index journals Patients diagnosed with acute SCI and intervention initiated within 8 h In the treatment group, high-dose methylprednisolone was given according to the NASCIS-2 protocol No steroids in the control group No significant difference in the mean age between groups Significant clinical outcomes were compared. *Exclusion:* Studies failing to comply with all the inclusion criteria	Three RCTs, 13 non-randomized studies (N = 1863)	Six weeks to one year	High-dose methylprednisolone treatment, in comparison to controls, does not contribute to better neurologic recoveries but may increase the risk of AEs in patients with acute SCI	Moderate

Table 3: Continued

Assessment (year)	Literature search dates	Purpose	Inclusion and exclusion criteria	Evidence base available	Follow-up range	Primary conclusions	AMSTAR score
[a]Sultan *et al*.[56] (2020)	Till 30 June 2019 PubMed, EMBASE, Cochrane	To reassess and update the safety and potential short-term and long-term efficacy of steroids after acute SCI as compared with controls not treated with steroids among a homogeneous patient population	*Inclusion:* Clinical studies, RCTs, and observational comparative studies (including cohort or case control studies Age ≥ 13 years with acute SCI being treated with steroids within 8 h of injury Intervention: MPSS or dexamethasone Control: placebo or any other, non-steroid therapeutic agents Studies with five patients or more Measurable outcomes: motor and/or neurological function assessments and/or AEs associated with steroid use *Exclusion:* Steroids not administered within 8 h of injury Injury involving only nerve roots or cauda equina Patients suffering from other life-threatening morbidities History of narcotic addiction, malignancy, pregnancy, and gunshot wounds Review articles, case reports, guidelines, case series, conference papers, editorials, animal studies, treatment of steroids in combination with non-steroidal agents, articles not in English	Five RCTs, seven non-randomized studies (Total *N*: NR)	NR	Methylprednisolone therapy within the first 8 h after acute SCI failed to show a statistically significant short-term or long-term improvement in a patient's overall motor, or neurological scores compared with controls who were not administered steroids	Low

AE = adverse event, NR = not reported

[a]Although dexamethasone has been included into the search strategy, only articles evaluating methylprednisolone treatment have been identified and included in this review

Table 4: Study characteristics of the single study assessing the effects of MPSS therapy in the treatment of acute SCI

Author (year), design	Sample and characteristics	Treatment	Inclusion and exclusion criteria	Severity (on admission)	Outcome measures	Follow-up time (%)	Funding
Wang *et al.*[57] (2019), RCT	N = 78 *MPSS:* Male: 84.6% Age (SD): 46.8 (±8.1) *Control:* Male: 79.5% Age (SD): 47.2 (±7.9) Level of injury: Cervical (100%)	*MPSS: n* = 39 <3 h from injury IV bolus of 30 mg/kg body weight over a 15-min period followed by a 30-min pause, and then a 23-h maintenance infusion of 5.4 mg/kg/h >3–8 h from injury 48-h IV infusion of 30 mg/kg/h Control: *n* = 39	*Inclusion* Cervical SCI Incomplete paraplegia August 2015 to December 2017 Age 20 to 70 years Diagnosis confirmed MRI Single-segment injury *Exclusion:* Cervical SCI with pamplegia Long bone fracture Peripheral nerve injury of four limbs Craniocerebral injury Coagulation disorders	ASIA motor score: *MPSS, Score (±SD)*: 56.47 (±10.62) *Control, Score (±SD)*: 55.47 (±10.88)	*ASIA motor score* [a]*JOA score:* 16 and 17 (normal function) 12–15 (grade 1) 8–11 (grade 2) 0–7 (grade 3) [b]*Spinal cord functional state evaluation method:* Range 0–40 (subscoring not specified)	NR	None

IV = intravenous, JOA = Japanese Orthopedic Association Score, NR = not reported, SD, standard deviation

[a]The choice of a tool developed to assess the severity of clinical symptoms in patients with degenerative cervical compressive myelopathy has not been justified

[b]It is unclear whether the authors refer to the SCIM-III

and 24 h being studied most frequently [Table 1].[29-33] Only one meta-analysis (n = 1126) has been published solely focusing on patients with cervical SCIs.[32] Ter Wengel *et al*.[32] demonstrated that surgical decompression within 24 h of injury was more likely to result in ≥2 grades AIS improvements in patients with complete cervical SCIs as compared with incomplete cervical SCIs (OR = 2.6, 95% CI: 1.4–5.1). Likewise, in their ASIA A-only SCI study population, El Tecle *et al*.[29] (n =141) showed higher conversion rates in patients treated with early surgery within 24 h (46.1% vs. 25%, OR = 2.31, 95% CI: 1.08–4.96, P = 0.03).

Two meta-analyses specifically assessed the effects of very early surgery as defined by a cutoff of 8 h on outcomes.[30,31] Although Lee *et al*.[30] (n = 650) did not perform a sub-analysis based on the level of injury, they found improved rates of neurologic recovery in their mixed population of patients with complete and incomplete SCI who underwent surgery within 8 h of injury, as compared with patients operated between 8 and 24 h of injury (OR = 1.77, 95% CI: 1.24–2.42). On the other hand, Ma *et al*.[31] (n = 716) could only demonstrate the positive effects of very early surgery (<8 h) in patients suffering from complete SCI (relative risk [RR] = 3.96, 95% CI: 2.02–7.76, P < 0.05).

Of the 16 included cohort studies with a study population comprising between 42 and 1548 patients [Table 2],[34-48] 10 studies included patients with cervical SCIs only.[34,35,37-39,42-46] Their respective study population ranged between 42 and 402 patients, with follow-ups ranging from three months to 10.88 years. Of the remaining six studies with mixed-level SCIs, the study population varied between 56 and 1548 patients, with the majority of patients suffering from cervical SCIs (range: 50–86.9%).[22,36,40,41,47,48] Follow-ups among these ranged between 252 days and one year. In the following, we report these results categorized by the level of injury.

Cervical-only SCIs

Most included studies with a cervical-only cohort used a cutoff of 24 h to differentiate between early and late surgery. However, only a few of these studies were able to support the aforementioned benefits of early surgical decompression. Sewell *et al*.[46] studied the effect of early (<24 h) vs. late (>24 h) surgery on neurological outcomes in a patient population (n = 95) with cervical SCI and concomitant chest injuries. Although they were not able to show significant differences in neurologic outcomes between the two groups, their sub-analysis of patients with incomplete cervical SCI demonstrated significant improvements of at least one AIS grade (OR = 14.0, 95% CI: 3.1–72.4, P <0.01) when operated early. Similarly, by choosing a cutoff of 19 h, Facchinello *et al*.[38] (n = 42) demonstrated higher proportions of patients with ≥1 AIS grade improvements when operated early (75% vs. 41%, P = 0.0257). Conversely, other studies failed to show beneficial effects on neurologic outcomes for patients receiving early surgical decompression within 24 h.[34,43,45] In their cohort of 72 patients, where adequate surgical decompression was confirmed by postoperative imaging studies, Aarabi *et al*.[34] did not detect significant differences in neurologic outcomes between patients undergoing ultra-early (<12 h), early (12–24 h), or late (>24–138.5 h) surgical decompression.

Several studies have gone further and stratified the early post-injury period by investigating cutoffs between 5 and 12 h after injury.[39,42,44] Nasi *et al*.[44] (n = 81) found that surgery within 12 h of injury was associated with significantly greater neurological improvement (72.5% vs. 43.9%, P = 0.009). The differences became even more distinct when only analyzing the results of patients with complete cervical SCIs (61.53% vs. 7.69%, P = 0.003). In support of very early surgeries, Jug *et al*.[39] (n = 64) examined the optimal time point of surgical decompression within the first 24 h of injury and found significant neurologic improvements in AIS grades to occur within 4 h of injury (95% CI: 4–9 h). And yet again, Mattiassich *et al*.[42] (n = 49) did not show any significant additional neurological benefits for patients undergoing surgical decompression within 5 h of injury.

The study with the largest prospective cohort (n = 402) investigated the effects of a late surgery cutoff of 72 h on the neurologic outcomes of patients with cervical SCI.[37] Patients undergoing surgery within 72 h of injury were found to have significantly higher rates of ≥1 and ≥2 AIS grade improvements (P < 0.0001 and P = 0.003, respectively).

Mixed-level SCIs

The highest-quality results to date were recently published and examined a pooled analysis of four individual, high-quality, prospective multicenter acute SCI datasets. In their pooled cohort of 1548 patients (cervical = 86.9%), Badhiwala *et al*.[22] demonstrated improved ASIA motor scores of 23.7 (95% CI: 19.2–28.2) vs. 19.7 points (95% CI: 15.3–24; P = 0.0006), ASIA light touch scores of 19.0 (15.1–23.0) vs. 14.8 points (11.2–18.4; P = 0.0021), pin prick scores of 18.3 (13.7–22.9) vs. 14.2 points (9.8–18.6; P = 0.0019), as well as improved AIS grades (crude odds ratio [cOR] = 1.48; 95% CI: 1.16–1.89; P = 0.0019) for patients undergoing surgery within the first 24 h after injury. Two previously published retrospective cohort studies (n = 94 and n = 143, cervical: 70% and 68%) demonstrated comparable results of improved neurologic recoveries and functional outcomes for patients receiving surgical treatment within 24 h.[36,48]

Capturing earlier cutoffs, Lee *et al*.[41] (n = 56, cervical: 50%) suggested improved neurologic outcomes in patients surgically treated within 8 h of injury (OR = 0.128, 95% CI: 0.031–0.521; P = 0.004).

On the other hand, two retrospective cohort studies investigated later cutoffs of 48 h (n = 86, cervical: 53.5%) and 72 h (n = 304, cervical: 88.5%).[40,47] Both studies showed that despite choosing later cutoffs, patients were still profiting from improved neurologic recoveries when operated within 48 or 72 h.

Despite the heterogeneity of the literature, which largely reflects the mixed quality of the available evidence, a growing body of evidence underlines that the timing of decompression within 24 h of injury is beneficial in terms of neurologic recovery. Future work needs to tackle the heterogeneity of SCI, thereby identifying specific subpopulations of SCI patients with the greatest potential to benefit from early surgical decompression. The importance of personalized treatment becomes all the more critical in areas with limited resources. Moreover, although a cutoff of 24 h has been studied most frequently, earlier time points need further attention. Certainly, the recent paper by Badhiwala *et al*.[22] provides compelling evidence to suggest a time-dependent effect of the role of surgical decompression within the first 24 h after SCI.

The role of MPSS

MPSS, a potent synthetic glucocorticoid, is believed to upregulate anti-inflammatory cytokines and to block lipid peroxidation of neuronal cell membranes, thereby counteracting the inflammatory response encountered during the secondary injury phase of traumatic SCI.[49,50] Studies of intravenous administration of MPSS in animal models of acute SCI have shown enhanced tissue sparing and neuronal survival, resulting in greater neurologic recovery.[49,50] Based on these exciting preclinical findings, several large-scale clinical trials followed over the past three decades, providing us with a source of intense debate on the role of MPSS in the early management of SCI.

In 1984, a multicenter, double-blind, RCT, also known as the National Acute Spinal Cord Injury Study (NASCIS, n = 330), studied the efficacy of MPSS treatment given over a period of 10 days in a high-dose group (1000 mg bolus and 250 mg every 6 h) and compared it with low-dose MPSS administration (100 mg bolus and 25 mg every 6 h).[8] Although the authors did not find any differences in neurologic outcomes at six weeks or six months after injury, the rates of both surgical site and trauma site infections were more prevalent in the high-dose group (RR = 3.6, P = 0.01).[8] Considering that concurrent animal studies have found significantly higher doses of MPSS to be necessary to reach therapeutic thresholds, the dosing was discussed as a major limiting factor in the NASCIS trial.[8]

Subsequently, the double-blind RCT, termed NASCIS II (n = 487, quadriparetic or quadriplegic: 57.2%), was initiated to address the higher dose of MPSS.[9] The 1990 study examined the efficacy and safety of a higher dose of MPSS (bolus of 30 mg per kg bodyweight, followed by 5.4 mg per kg per hour for 23 h), as compared with placebo. The overall comparison of the two groups revealed no significant differences in terms of neurologic outcomes. However, based on an a priori hypothesis, that the effects of MPSS are influenced by injury-to-treatment time, the authors performed a subgroup analysis by using an 8-h cutoff. Patients receiving high-dose MPSS treatment within 8 h of injury had significant improvements in AIS motor scores (changes of 16.0 vs. 11.2 points, $P = 0.03$), sensation to pinprick (change of 11.4 vs. 6.6 points, $P = 0.02$), and touch (change of 8.9 vs. 4.3, $P = 0.03$). In terms of safety, a trend toward an increased incidence of pulmonary embolism and gastrointestinal hemorrhage in patients treated with MPSS was observed; however, this did not reach statistical significance. Meanwhile, prolonged administration of MPSS over a period of 48 h in an upper lumbar SCI model in cats showed significantly enhanced tissue preservation and improved neurobehavioral outcomes.[51]

In light of this, the third NASCIS trial ($n = 499$, quadriparetic or quadriplegic: ~48.6%), published in 1997, compared the efficacy of 24 h vs. 48 h of MPSS treatment (bolus of 30 mg per kg bodyweight followed by 5.4 mg per kg per hour for 24 or 48 h).[10] Patients treated with a 48 h regimen of MPSS were shown to benefit from improved neurologic grades when treatment was initiated within 3 to 8 h after injury ($P = 0.03$). As these data add weight to the NASCIS II results, in that early treatment within 8 h of injury is of importance for long-term neurologic improvements to occur, it is of particular note that patients who were receiving a 48 h regimen of MPSS showed higher rates of severe sepsis ($P = 0.02$) and pneumonia ($P = 0.07$). Therefore, the risks may outweigh the benefits as compared with an early initiated 24 h regimen. A prospective, double-blind RCT ($n = 46$) investigated the complications in patients with acute cervical SCIs when MPSS treatment was administered within 8 h of injury.[52] The authors observed significantly higher rates of pulmonary (34.8% vs. 4.34%, $P = 0.009$) and gastrointestinal complications (17.4% vs. 0%, $P = 0.036$), with aged patients older than 60 years being particularly prone to pulmonary complications ($P = 0.029$).

Yet another RCT ($n = 106$, tetraplegic: 54.7%) and a propensity-matched prospective cohort study ($n = 88$, cervical: 72.7%), including sub-analyses of cervically injured patients, could not find any benefits when MPSS was administered within 8 h of injury and given over a period of 24 or 48 h according to the NASCIS-II regimen.[11,53]

Updates since 2017

As a consequence of early evidence provided by some of the largest RCTs in the history of SCI research, few subsequent efforts have been made to further investigate the effects of MPSS on the treatment of acute SCI. Despite this, three published systematic reviews meeting our inclusion criteria have shown differing results.[54-56] Of particular note, none of the aforementioned trials provided a sub-analysis based on the level of injury.

In their meta-analysis of four RCTs and two non-randomized cohort studies, Fehlings *et al*.[54] provided moderate evidence that patients who received MPSS treatment within 8 h of injury were able to achieve an additional 3.2 points (95% CI: 0.1–6.33; $P = 0.04$) of motor score recovery compared with patients receiving placebo or no treatment. Moreover, they found no statistically significant differences in the pooled risk of death, wound infection, gastrointestinal hemorrhage, sepsis, pulmonary embolism, urinary tract infection, pneumonia, or decubiti between the groups of patients receiving MPSS treatment within 8 h of injury as compared with no treatment.

Conversely, Sultan *et al*.[56] did not demonstrate the beneficial effects of an early (<8 h) initiation of MPSS on neurologic scores in patients with acute traumatic SCI. Of particular note, differing control groups and a lack of precise dosing and duration of MPSS treatment significantly complicated the analysis and interpretation of their results. Similarly, Liu *et al*.[55] did not show the beneficial effects of an early (<8 h) initiation of MPSS treatment according to the NASCIS II protocol. Yet again, the heterogeneity of the included studies, the inclusion of penetrating SCIs, as well as a high proportion of study cohorts with a maximum follow-up duration of ≤2 months limit the validity of their study results.

There has been only one RCT meeting our inclusion criteria. Wang *et al*.[57] investigated the effects of early (<8 h) MPSS treatment on neurologic outcomes in a single-level cervical SCI cohort ($N = 78$). Both their treatment and control group underwent vertebral body decompression, bone grafting, and internal fixation according to the severity of spinal cord compression. Unfortunately, their treatment arm consisted of two distinct therapeutic regimens where patients admitted within 3 h of injury were treated according to the NASCIS II protocol and patients admitted between 3 and 8 h after injury received a 48-h infusion of MPSS at 30 mg/kg/h. Interestingly, although the authors observed significantly higher rates of ASIA score improvements in the treatment arm, there were no significant differences in terms of adverse events.

In summary, due to the paucity of new high-quality evidence since 2017, there is currently no rationale to significantly deviate from the 2017 clinical practice guidelines developed by Fehlings *et al*.,[58] which recommended a 24-h infusion of high-dose MPSS to adult patients within 8 h of acute SCI as a treatment option. Importantly, the heterogeneity of the SCI patient population requires critical and individual evaluation of whether high-dose MPSS treatment is at risk of causing more potential harm than benefits.

Limitations

It is important to note that this review has several limitations. First, the systematic part of this review captured only the publications from recent years (2017 to March 2021). However, in addition to providing an update, the narrative portion of this study addresses the most relevant advancements before 2017. Second, this review aimed to provide a qualitative assessment of the literature. A statistical pooling of data was not performed, thereby restraining the significance of the results to the individual studies. Third, substantial clinical variabilities, differing methodologies, as well as the risk of bias limited the overall strength of evidence in several of the studies. Lastly, given that MPSS has been the most studied steroid, we excluded studies evaluating other steroids from our analysis, knowing that in some centers the administration of other steroids, for example dexamethasone, is preferred.

Conclusions and Future Directions

The current body of research provides strong evidence that early surgical decompression within 24 h of injury promotes enhanced neurologic recovery. Considering the heterogeneity of SCI, future studies are needed to more precisely stratify patients with the largest potential to benefit from early surgery. This becomes all the more important, as logistical hurdles in the management of patients with traumatic SCIs complicate access to treatment in a timely fashion. Therefore, future work is needed to evaluate health systems and transport methods to ensure an optimized path to early intervention. In addition, further work needs to be done to define the optimal approaches to surgically achieve decompression. For example, the role of intraoperative ultrasound to assess surgical decompression intraoperatively, the potential role of duroplasty to allow for further cord decompression, and the routine use of postoperative MRI to evaluate the status of the decompression require further study.

Early initiation of a 24 h high-dose MPSS treatment within 8 h of injury has been shown to hold the potential to improve motor recovery, particularly in those with cervical SCI. Likewise, future studies are warranted to identify subgroups of patients with SCIs who stand to benefit the most from MPSS treatment. Ongoing research efforts are also needed to evaluate the potential synergistic effects of MPSS therapy in conjunction with other exciting neuroprotective or neuroregenerative therapeutic approaches. Of note, there is an urgent need to evaluate other neuroprotective and neuroregenerative strategies, including riluzole, neural stem cells, and approaches to overcome the intrinsic inhibitory environment of the injured cord.[16,59]

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Ethical policy and institutional review board statement

Not applicable.

Conflicts of interest

There are no conflicts of interest.

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