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Modern Medical Management of Spinal Cord Injury

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Abstract

Purpose of Review Spinal cord injury (SCI) shows an incidence of 10.4–83 cases/million/year globally and remains a significant source of morbidity and cost to society. Despite greater understanding of the pathophysiology of SCI, neuroprotective and regenerative approaches to treatment have had limited clinical utility to date. Here, we review the key components of supportive care that are thus the mainstay of therapy and that have improved outcomes for victims of acute SCI in recent decades.

Recent Studies Current management strategies for acute SCI involve early surgical decompression and fixation, the use of vasopressor medications for mean arterial blood pressure (MAP) augmentation to improve spinal cord perfusion, and corticosteroids. We highlight recent literature supporting the role of norepinephrine in acute SCI management and also an emerging neurocritical care strategy that seeks to optimize spinal cord perfusion pressure with the assistance of invasive monitoring.

Summary This review will highlight key pathophysiologic principles and targets for current acute clinical treatments in SCI, which include early surgical decompression, MAP augmentation, and corticosteroids. We discuss anticipated future research in these areas and focus on potential risks inherent to these treatments.

Keywords Spinal cord injury · Decompression · Blood pressure · Corticosteroids · Methylprednisolone · Vasopressor

Introduction

Spinal cord injury (SCI) shows a global incidence of 10.4–83 cases/million/year, and it commonly results in significant long-term disability as it robs many patients of their arm and leg function, bowel, bladder, and sexual function [1, 2]. Injuries remain more prevalent in males, with a peak incidence of 30 years, but a growing proportion of acute SCI is now seen in the elderly because of falls. Direct lifetime costs can range between $1.1 and 4.7 million per person in the USA, and the cost to society is markedly greater [3]. Despite substantial investment in preclinical investigations aimed at better understanding the pathophysiology of acute SCI and developing targeted therapies to improve outcomes from SCI, very few have reached clinical practice. Current clinical approaches toward SCI treatment involve aggressive intensive care measures, early surgical decompression, and stabilization, followed by blood pressure augmentation to reduce secondary injury [4•, 5, 6•]. This review will discuss literature supporting the best current clinical practices for acute SCI and will also discuss therapeutic approaches believed to be on the near horizon.

Recent guidelines have played an important role in delineating best practices and reducing practice variation in acute clinical treatments. These include recommendations from the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS), which were published in 2002 [7, 8] with an update in 2013 [9]. The Paralyzed Veterans of America published "Early Acute Management of Spinal Cord Injury" clinical practice guidelines in 2008 [10], and these were followed by AOSpine's clinical practice guidelines in 2017 [11]. The most recent guidelines for acute SCI were published by the CNS, and they focused on thoracolumbar spine trauma and spinal cord injury [12]. As this chapter will outline, there have been important advances in the clinical management of acute SCI over the last two

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decades. These guidelines have, in turn, undergone rapid change as our understanding of the best care for SCI pathology has progressed. Particularly important advances have come in relation to diagnosis and management of blunt cerebrovascular injury as well as the role of imaging and timing of decompression. Although these guidelines have reached differing conclusions about some aspects of care, all are useful resources for practitioners charged with the care of patients with SCI.

Pathophysiology and Recent Clinical Trials

Allen et al. [13] divided SCI into two timeframes and types of physiological processes. The first are related to the primary injury, involving physical contusions, sheer injury, lacerations to the cord, and microhemorrhages from a trauma. Afterwards, secondary injury ensues, as a delayed and progressive process involving complex interrelated signaling cascades and tissue changes resulting altered hemostasis, apoptosis, and tissue destruction that causes further damage to the spinal cord after the primary injury has ended [13]. The recognition of secondary injury has been a major advance for the field. This concept was initially controversial but is now well accepted and provides a rationale and therapeutic window for interventions, which might interrupt this delayed loss of cells and tissue. Recent research has focused on (1) reduction of secondary injury using adjuvant therapies (aka neuroprotection), and (2) augmentation of SCI regeneration using cellular transplantation and other methods. Of particular importance in secondary injury is the postinjury inflammatory cascade, which has been extensively studied and subject to numerous recent reviews [1, 2, 14–17]. Numerous targeted preclinical agents have been tested in clinical trials for the treatment of acute SCI but very little has crossed the chasm to clinical practice (Table 1, Fig. 1) [6•, 18].

Surgical Decompression

Recent studies provide evidence that there is neurologic benefit to early surgical decompression and have led to recognition that the injured spinal cord should be decompressed urgently. Jug et al. [19] evaluated surgical treatment after cervical trauma in 48 patients ($n = 22$ within 8 h after injury vs. $n = 20$ at 8–24 h after injury) and found that patients who underwent earlier surgery had significantly better rate of improvement of ≥ 2 AIS grade (45.5% vs. 10%, $p = 0.017$). Wilson et al. [20] later completed a prospective multicenter study evaluating 35 patients undergoing cervical, thoracic, or thoracolumbar trauma with early surgery and 49 with late surgery. No difference in AIS motor score improvement was seen for primary outcomes overall; however, after adjusting for preoperative status and neurological level, early surgery yielded a greater improvement. A recent meta-analysis of studies evaluating timing of surgery from 1996 to 2012 evaluated 18 studies [21]. Although there was significant heterogeneity in these studies, early surgery showed significantly better total motor score (weighted mean difference [WMD]: 5.94, 95% confidence interval [CI]: 0.74, 11.15), more neurological improvement (odds ratio [OR]: 2.23, 95% CI 1.35, 3.67), and shorter hospital length of stay (WMD: − 9.98 days,

Table 1 Summary of ongoing clinical trials in spinal cord injury

Agent	Trial	NCT number
Glyburide	The Spinal Cord Injury Neuroprotection with Glyburide [SCING] trial	NCT02524379
Hepatocyte growth factor		NCT02193334
Granulocyte colony-stimulating factor		
Basic fibroblast growth factor	Asubio Spinal Cord Early Neuro-recovery Treatment for Acute Spinal Cord Injury [ASCENT-ASCI]	NCT01502631, NCT03229031
Riluzole	Riluzole in Acute Spinal Cord Injury Study [RISCIS]	NCT01597518
Minocycline	Minocycline in Acute Spinal Cord Injury [MASC]	NCT01828203
C3 transferase	SPinal Cord Injury Rho INhibition InvestiGation [SPRING]	NCT02138110
Bioresprobable polymer scaffolds	Neuro-Spinal Scaffold	NCT02669849
Mesenchymal stem cells		NCT01676441, NCT03308565, NCT03521323; NCT03505034; NCT02481440
Schwann cells		NCT01739023, NCT02354625
Neural stem cells		NCT02163876, NCT01321333, NCT01772810
Functional electrical stimulation		NCT01292811

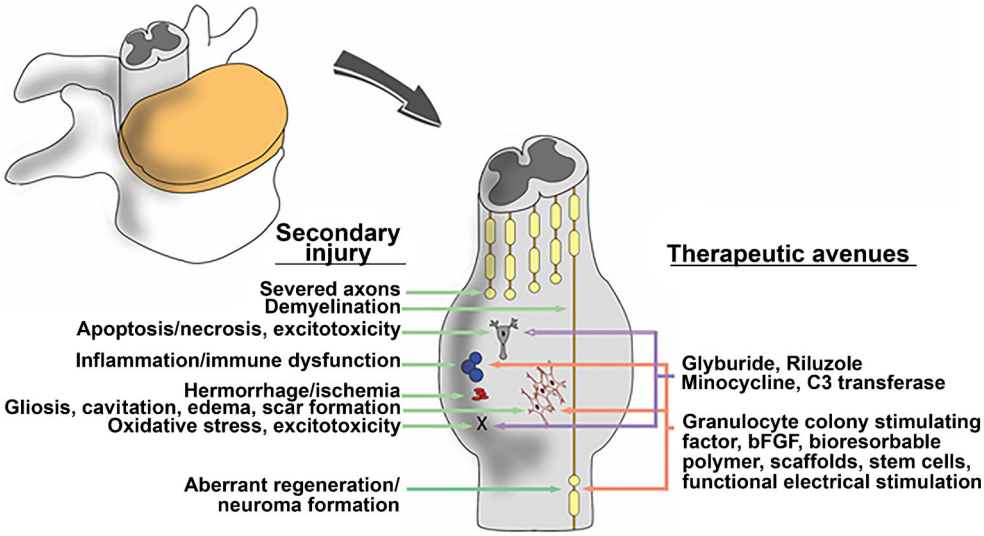

Fig. 1 Overview of secondary spinal cord injury and potential therapeutic avenues

95% CI −13.10, −6.85) than late surgery. The Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) was a prospective multicenter study comparing 6-month surgical outcome after early (< 24 h) or late (≥ 24 h) treatment for cervical SCI [22]. A total of 313 patients were enrolled (182 with early surgery, 131 with late surgery). Patients who underwent early surgery showed a greater likelihood of ≥ 2 improvement in AIS grades (OR 2.57, 95% CI 1.11, 5.97) at 6-month follow-up [23, 24, 25•, 26, 27].

The STASCIS trial has proven itself a landmark study, and perhaps more than any other it bears responsibility for the shift to earlier surgeries for SCI [22]. Given its importance, it is worth considering the criticisms of the study. The STASCIS trial did not mention whether a power calculation was performed and whether this led to recruitment of an adequate sample size. Similarly, it is not clear that the prescribed primary outcome and method of analysis were selected a priori. If one limits analysis to an outcome improvement of ≥ 2 AIS grades and consideration of AIS A, B, and C cases only (cases where a ≥ 2 AIS would be possible), the results of the study are no longer significant (OR 2.335, 95% CI 0.913, 6.134, p = 0.07). Nonetheless, these results have increased the urgency of SCI treatment nationally akin to treatment of myocardial infarction and ischemic stroke. Further study of outcome data, and timing of surgery, will likely be seen in the near future.

Given these demonstrations of early surgical treatment benefitting patients with cervical SCI, recent research efforts have evaluated early decompression after thoracolumbar SCI [24], evaluated methods for earlier transfer of patients for surgical care [23, 25•, 26], explored earlier rehabilitation after surgery (Karsy et al., submitted), and assessed the development of imaging methods to stratify patients and predict prognosis before surgical intervention [28]. Researchers have also aimed to evaluate the effect of "ultra-early surgery," treatment within 12 h of injuries, although data are more limited on this question [27].

Hemodynamic Treatment

Even in the absence of hemorrhagic shock, hypotension can ensue after SCI because of disruption of sympathetic innervation. This is termed "neurogenic shock" and can result in spinal cord hypoperfusion and worsened injury to the spinal cord. Bradycardia is a hallmark of neurogenic shock, but the clinician must maintain a high level of suspicion that other hemodynamic patterns of shock may coexist, especially in the polytrauma patient. Several published reports have suggested that preventing hypotension after SCI and even augmenting mean arterial pressure (MAP) may benefit neurological recovery [29, 30]. This body of evidence has grown, and this therapeutic strategy is now a key tenet of acute SCI care. As a result, hemodynamic support with vasopressor medications to avoid hypotension (defined as a systolic blood pressure < 90 mmHg) and to augment MAPs to > 85–90 mmHg have been suggested in both the 2002 and the 2013 AANS/CNS guidelines [4•, 5, 31]; however, to date, these clinical recommendations remain supported by only low-quality evidence. Newer preclinical and clinical studies have aimed to improve understanding of MAP management.

Several animal studies help to inform vasopressor responses and complications, thus shedding light on what may be the preferred pharmacologic agent; some of these studies also examined cerebrospinal fluid drainage in an effort to increase spinal cord blood flow. Martirosyan et al. [32] evaluated 15 pigs who received a combination of MAP augmentation with or without spinal fluid drainage after acute SCI to assess spinal cord blood flow. After SCI, blood flow decreased by an average of 56% but with artificial MAP elevation, a decrease

of 34% was seen. Similarly with spinal fluid diversion, a 49% decrease in MAPs was seen. With the combination of spinal fluid drainage and MAP augmentation, a 24% increase in cord perfusion was observed, along with increased intrathecal pressure of 5.45 mmHg. Streijger et al. [33] evaluated SCI in a T10 porcine contusion model. Spinal cord perfusion decreased after injury along with decreases in PaO_2 up to 7 days. Lactate/pyruvate ratios increased immediately at the area of injury and distally, suggesting an expanding area of ischemia and hypoxia from the injury site up to 7 days later. A later study comparing norepinephrine and phenylephrine showed limited improvement in cord perfusion proximal to an injury [34]; however, after decompression, norepinephrine increased spinal cord blood flow and PaO_2, unlike phenylephrine. Both norepinephrine and phenylephrine decreased the lactate-to-pyruvate ratio, but phenylephrine was associated with greater injury hemorrhage. These results suggest that differential responses in norepinephrine and phenylephrine occur because of both local effects at the site of injury and regional cord perfusion differences. Similar improvements of the lactate-to-pyruvate ratio support how both of these pressures have shown some clinical responsiveness. Ultimately however, norepinephrine seems to maximize the benefit to the spinal cord compared with phenylephrine. Although dopamine was historically the preferred agent for MAP augmentation, these recent studies have suggested better physiological responses to other vasopressor medications. These studies can certainly be expanded to better understand the pathophysiology of cord injury and MAP augmentation on tissue response and known signaling pathways.

Several recent big-data approaches have sought to address targeted blood pressure management. Hawryluk et al. [35] evaluated MAP values in a series of 100 patients with SCI. A total of 28.8% of measurements within the first 7 days were below target values of 85 mmHg. Patients with AIS grade improvement of 0, 1, and > 1 showed significant differences in mean MAP values of 92, 91, and 96 within 7 days of injury, respectively. Differences in the proportion of MAP values below the 85 mmHg threshold were more marked, however. Most convincing in this study though was the evidence that a notable portion of MAP values after injury are below target despite ordered MAP goals. Capatano et al. [36] studied a subpopulation of the patients reported in Hawryluk et al. In this paper, 62 patients with q1 min MAP measurements after injury showed significant improvements in mean MAPs of AIS A patients ($n = 33$) who improved vs. those that did not (96.6 vs. 94.4 mmHg). Similarly, MAP values < 85 mmHg were significantly lower in patients that did not improve (13.5% vs. 25.6%). Improvement is AIS scores were also seen in B and C grades but not D grade injuries. A recent meta-analysis of 11 studies (9 retrospective, 2 prospective) evaluating MAP measurements in SCI suggested MAP augmentation was achieved in the majority of patients with correlations of lower MAPs with worse outcome [37]. Variation in MAP augmentation goals was seen among studies, ranging from 24 h to 7 days. Dopamine, norepinephrine, and phenylephrine were commonly used agents, but more complications were noted with dopamine than other vasopressors. Limitations of this meta-analysis include the variation in MAP target goals and duration of therapy and the retrospective nature of most studies. In addition, the study lacked reported meta-analysis methodology including methods for analysis of the various studies and adjusting for study heterogeneity.

In light of the recent preclinical and clinical research, vasopressor types have been compared in patients. Inoue et al. [38] evaluated 131 patients with SCI who received dopamine or phenylephrine; they showed a significantly higher rate of major complications with phenylephrine (10%) including ST elevation, troponin elevation, atrial fibrillation, and ventricular tachycardia compared with phenylephrine (3%). No differences in neurological outcomes were seen between pressors. Conversely, Readdy et al. [39] evaluated 34 patients with SCI and found no difference in complication rate or neurological outcomes between phenylephrine and dopamine. However, in a subgroup of patients > 55 years of age, dopamine increased cardiogenic complication rates compared with phenylephrine (83.3% vs. 50%). Limitations of these studies include the heterogeneous, overlapping use of vasopressor medications and heterogeneous patient populations. Another smaller study of 11 patients with SCI showed a significantly higher level of spinal cord perfusion pressure (67 vs. 65 mmHg) after use of norepinephrine rather than dopamine, but the clinical difference in MAPs (~ 2 mmHg) remained negligible [40]. A recent review of vasopressors in SCI evaluated seven reports, showing higher complication rates with dopamine than phenylephrine along with a slight improvement in cord perfusion pressure (~ 2 mmHg improvement) with norepinephrine [41]. Subgroup analysis showed that elderly patients had more complications and that no specific vasopressor correlated with improved outcome. Although no recommendation of a specific type of pressor has been seen from the AANS/CNS Joint Section guidelines [5], the Consortium for Spinal Cord Medicine recommends dopamine or norepinephrine because of the incorporation of both alpha and beta adrenergic agents [10]. Likely, clinicians should monitor multiple hemodynamic endpoints (e.g., heart rate, blood pressure, tissue perfusion) while aiming to reduce the morbidity of pressure use with any vasopressor selected. It is anticipated that future studies will further refine how MAP augmentation is achieved and applied after SCI; we are likely to see direct intrathecal monitors of cord perfusion, more meticulous pre- and post-treatment clinical assessment, and use of multimodal, automated data acquisition.

Corticosteroids

Corticosteroids are a controversial neuroprotective treatment for acute SCI. Several major randomized controlled trials, namely the National Acute Spinal Cord Injury Studies (NASCIS), have evaluated the role of methylprednisolone [42–44]. Although primary endpoints were not improved with the use of steroids, secondary analysis suggested treatment within 8 h yielded an improvement in Functional Independence Measure scores at 1 year [42–44]. Major concerns regarding steroid use include increased risk of wound infection, gastrointestinal hemorrhage, sepsis, pulmonary embolism, and death, suggesting the decision to implement steroid use bears substantial risks. Although the AANS/CNS Joint Section guidelines did not recommend steroid use after SCI citing a lack of supportive level I and II evidence as well as level I–III evidence indicating possible harm [8], recommendations from AOSpine suggested a 24-h infusion of high-dose methylprednisolone may be offered to patients within 8 h of injury [11]. A meta-analysis of the three randomized trials and 1 prospective observational trial evaluating early use of steroids showed a modest improvement of AIS motor scores (mean difference 3.21, 95% CI 0.10, 6.33, $p = 0.04$). A pooled risk analysis also showed no impact of steroids on risk factors when accounting for all studies. Several limitations of this analysis included the low precision of motor scores in the meta-analysis, as well as likely minimal appreciable functional outcome difference with such a low motor score change. Of note, the AOSpine guidelines recommend < 48 h of steroid infusion based on the NASCIS III finding that this dosing more markedly increases risks of steroids than benefits.

Although steroid administration after SCI continues to be controversial, another important benefit that has resulted from the NASCIS studies is insight into how future studies of putative neuroprotective agents could be performed more optimally. First, more sensitive measures of functional outcome can be used to detect small but important changes in neurological function. Second, the NASCIS studies will better inform future studies of anti-inflammatory treatments currently in preclinical and clinical development. Many of the lessons from the NASCIS and meta-analysis studies can be used to improve understanding of these novel anti-inflammatory agents by ensuring treatments are provided early, injury groups are well defined, an adequate control group is available, an objective measure of functional outcome is used, and a realistic follow-up time for recovery is provided.

Invasive Spinal Cord Pressure Monitoring

Multiple recent studies have expanded the role of epidural and intrathecal pressure monitoring to directly evaluate perfusion in order to improve understanding of spinal cord perfusion after various interventions. Here, the difference between MAP and intrathecal pressure can calculate spinal cord perfusion pressure. Drainage of spinal fluid, and thus reduction of intrathecal pressure, has been argued to improve perfusion. Studies from animal models have evaluated the role of spinal cord perfusion during injury from traumatic and vascular etiologies [40, 45]. Studies from animals have implicated the importance of aquaporin-4 in the recovery after SCI, creating potential for intrathecal pharmacological therapy [46, 47]. More recent work has focused on the role of spinal cord perfusion as a clinical metric as well as predictor of patient outcome [48, 49]. Kwon et al. [50] reported on a randomized clinical trial of intrathecal drainage in 22 individuals with SCI. The results demonstrated a reduction of intrathecal pressure after spinal decompression (13.8 mmHg to 7.9 mmHg, $p < 0.0001$) but no difference in pressure for patients with postoperative drainage compared with no drainage (28.1 vs. 30.6 mmHg, $p = 0.15$). These results suggested promise for intrathecal pressure monitoring and intervention but failed to be adequately powered to detect a difference. A more recent study of 92 patients with SCI who underwent intrathecal drainage demonstrated that perfusion pressure was an independent predictor of improved neurological recovery (odds ratio 1.039, $p = 0.002$) [48]. Perfusion pressures < 50 mmHg were more likely associated with failure to improve from baseline neurological impairment. Much further work is needed to better understand the importance of spinal cord perfusion on outcome and recovery after SCI.

Conclusion

A number of newer approaches in the treatment of SCI have sought to better use and understand the use of vasopressor medications, steroids, and anti-inflammatory treatments. Approaches to bridge preclinical findings to SCI patients have been widespread in the field. In addition, methods to improve understanding of spinal cord perfusion have been pursued. SCI will likely remain a challenging disease to study because of its complex pathophysiology, patient heterogeneity, and significant comorbidity. The use of prior results can be helpful for informing future clinical trials and clinical management strategies.

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Compliance with Ethical Standards

Conflict of Interest Michael Karsy and Gregory Hawryluk each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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