SYMPOSIUM: CURRENT CONCEPTS IN CERVICAL SPINE SURGERY

Spinal Cord Injury

A Systematic Review of Current Treatment Options

David W. Cadotte MSc, MD,
Michael G. Fehlings MD, PhD, FRCSC, FACS

Abstract

Background   Spinal cord injury (SCI) is a devastating event often resulting in permanent neurologic deficit. Research has revealed an understanding of mechanisms that occur after the primary injury and contribute to functional loss. By targeting these secondary mechanisms of injury, clinicians may be able to offer improved recovery after SCI.

Questions/purposes   In this review, we highlight advances in the field of SCI by framing three questions: (1) What is the preclinical evidence for the neuroprotective agent riluzole that has allowed this agent to move into clinical trials? (2) What is the preclinical evidence for Rho antagonists that have allowed this group of compounds to move into clinical trials? (3) What is the evidence for early surgical decompression after SCI?

Methods   We conducted a systematic review of MEDLINE and EMBASE-cited articles related to SCI to address these questions.

Results   As a result of an improved understanding of the secondary mechanisms of SCI, specific clinical strategies have been established. We highlight three strategies that have made their way from bench to bedside: the sodium-glutamate antagonist riluzole, the Rho inhibitor Cethrin, and early surgical decompression. Each of these modalities is under clinical investigation. We highlight the fundamental science that led to this development.

Conclusions   As our understanding of the fundamental mechanisms of SCI improves, we must keep abreast of these discoveries to translate them into therapies that will hopefully benefit patients. We summarize this process of bench to bedside with regard to SCI.

D. W. Cadotte, M. G. Fehlings
Division of Neurosurgery, University of Toronto,
Toronto, ON, Canada

M. G. Fehlings (✉)
Neural Repair and Regeneration, Spinal Program,
University Health Network, Toronto Western Hospital,
McLaughlin Pavilion, 12th Floor, Room 407,
399 Bathurst Street, Toronto, ON M5T 2S8, Canada
e-mail: michael.fehlings@uhn.on.ca

Introduction

Epidemiologic research has demonstrated that spinal cord injury (SCI) affects 10 to 40 persons per million population per annum in developed countries such as the United States [53]. This number must be interpreted with reference to a complete picture of this devastating condition: a substantial number of individuals who sustain a SCI die before reaching the hospital; patients who do reach the hospital have complications related to their injury and are at high risk of morbidity and mortality; the economic costs of this injury are estimated in the billions of dollars in developed countries (United States); and the personal and family suffering is incalculable [2, 29, 54]. Those sustaining SCI tend to be either young individuals sustaining traumatic injury at the prime of their personal lives and economic earning potential or

older individuals who sustain falls. In either case, the consequence of neurologic injury is overwhelming and has prompted intense research to understand the pathophysiological mechanisms and discover potential therapeutic strategies.

At the root of such strategies is a clear understanding of the secondary mechanisms of SCI and its distinction from primary injury. Primary SCI refers to damage to the neural elements sustained at the time of trauma. This can take the form of shear forces to axons or blood vessels and results in, to date, irreversible injury. Secondary SCI refers to the body's response to primary injury. A host of cellular cascades has been identified that occurs immediately after injury and may persist for months to years. These events, although integral to the normal cellular machinery, have been demonstrated to exacerbate underlying injury and prevent neurologic recovery. By detailing these cascades, researchers have established specific targets that may mitigate secondary SCI and have the potential to improve patient outcomes. With this foundation, advances have been made in both nonoperative and operative treatment strategies. In the paragraphs that follow, we introduce treatment options for SCI that have received recent attention. After this brief introduction, we systematically review the literature for each of these treatments.

Riluzole is a sodium channel-blocking agent that is approved for use in persons with amyotrophic lateral sclerosis (ALS). It is reported to have neuroprotective properties by blocking voltage-sensitive sodium channels whose persistent activation (excitotoxicity) has been demonstrated to have deleterious effects on neural tissue. In addition, riluzole antagonizes presynaptic calcium-dependent glutamate release, a mechanism that may also reduce the deleterious effects of excitotoxicity.

Rho antagonists act at the level of the neuronal growth cone and play a role in preventing neuronal apoptosis. It is believed that by preventing an apoptotic fate in the setting of SCI, one may be able to promote axonal sprouting and regeneration.

Early surgical decompression after SCI has been a proposed treatment for a number of years with its fundamental principle resting in the notion damaged neural tissue has a propensity to swell, and when the tissue swells in a confined space, ischemic and excitotoxic mechanisms are left uncontrolled.

In this systematic review, we highlight some of the recent developments in the treatment of SCI. Specifically, we have formulated three questions whose evidence stems from preclinical and clinical literature: (1) What is the preclinical evidence for the neuroprotective agent riluzole that has allowed this agent to move into clinical trials? (2) What is the preclinical evidence for Rho antagonists that have allowed this group of compounds to move into

clinical trials? (3) What is the evidence for early surgical decompression after SCI?

Search Strategy and Criteria

This systematic review aims to address the most recent topics in the treatment of acute traumatic SCI as framed in the three questions listed. As such, we have outlined a general search strategy along with individual key words and operators for each question.

Using the OVID interface, we queried the MEDLINE database (1950 to May Week 1, 2010) and the EMBASE database (1980 to 2010, Week 19). We included all original research papers in the English language. We excluded all clinical case reports, in vitro experiments, photochemically induced injury models, and nerve root or peripheral nervous system injury models. Lastly, we read all review articles to ensure that we captured relevant papers but did not include the review papers themselves in the results. After articles were chosen (based on the inclusion and exclusion criteria and key words listed subsequently), we applied the Downs and Black criteria to assess the methodological quality of each study (see subsequently).

For Question 1 we queried "riluzole" AND "spinal cord injury." This search returned 69 results. With application of our inclusion/exclusion criteria and eliminating irrelevant articles, we were left with eight studies. Review articles provided no additional references.

For Question 2 we queried "Rho" AND "antagonist" AND "spinal cord injury." This search returned nine results. With application of our inclusion/exclusion criteria and eliminating irrelevant articles, we were left with six studies. Review articles provided an additional three articles that were not captured by our original search, bringing the total to nine studies.

For Question 3 we queried "timing" AND "decompression" AND "spinal cord injury." This search strategy revealed 66 results. With application of our inclusion/ exclusion criteria and eliminating irrelevant articles, we were left with 38 studies. Review articles provided an additional three articles that were not captured by our original search bringing the total to 41 studies (19 preclinical and 22 clinical studies).

Clinical studies were assessed for methodological quality using the Downs and Black criteria [23]. Their 27-item quality assessment checklist evaluates the quality of reporting, external validity, internal validity (bias and confounding), and power with a maximal quality index (QI) of 32. Quality scores were presented as proportions of the total possible score (ie, 32) of the quality assessment scale (where 100% represents the maximum quality). Studies were not excluded based on the quality of methods.

Both authors (DWC, MGF) reviewed the clinical studies independently for quality. Disagreements were resolved by discussion and consensus between the two authors.

Results

Question 1

Recent advances in our understanding of the pathobiology of SCI continue to drive the development of new therapeutic agents and clinical strategies. The neuroprotective agent riluzole, currently in use to treat patients with ALS, has been the focus of eight preclinical studies (Table 1) [3, 33, 39, 43, 44, 53, 55, 56]. Its neuroprotective properties are the result of blocking voltage-sensitive sodium channels and antagonism of presynaptic calcium-dependent glutamate release. Each of these investigations has been carried out in a rat model of SCI that used the following outcome measures: nonbehavioral: tissue-sparing, reduced MAP-2 loss (MAP-2 is a microtubule-associated protein that decreased lipid peroxidation and improved electrophysiological recordings); behavioral: improved locomotor scores (BBB) and improved performance on inclined plane testing. A single study investigated spasticity. Seven of eight studies reported on nonbehavioral outcome measures.

Table 1. A summary of preclinical animal literature studying the effect of the neuroprotective agent riluzole in spinal cord injury

Reference	Species	Injury model	Riluzole dose and route of delivery	Reported outcomes
Stutzmann et al., 1996 [56]	Rat	Thoracic compression with Fogarty catheter	2 mg/kg IV administered 30 minutes after injury and twice daily for 10 days	Riluzole decreased the amount of necrosis in the gray and white matter; riluzole-treated animals recovered SSEPs (amplitude, duration, and latency), whereas control animals did not; in terms of behavior, treated animals were able to sit upright (using paws), whereas control animals were not
Springer et al., 1997 [55]	Rat	Thoracic impactor	8 mg/kg IP administered 15 minutes before injury and 2 hours after injury	Behavioral outcomes not reported; riluzole decreased the amount of MAP-2 (microtubule-associated protein) loss after SCI
Mu et al., 2000 [44]	Rat	Thoracic impactor	8 mg/kg IP administered 2 hours and 4 hours after injury and then daily for 7 days	Riluzole alone did not affect spinal cord cavitation; however, when combined with methylprednisolone, the combination resulted in decreased spinal cord cavitation; similarly, only the combination was able to improve locomotor scores
Mu et al., 2000 [43]	Rat	Thoracic impactor	8 mg/kg IP administered 15 minutes and 2 hours after injury	Behavioral outcomes not investigated; riluzole treatment resulted in improved mitochondrial function and enhanced glutamate and glucose uptake; lipid peroxidation was decreased with riluzole
Schwartz and Fehlings, 2001 [53]	Rat	Cervicothoracic clip compression	5 mg/kg IP administered at the time of injury; *note: authors compare other neuroprotective agents (see reference for details)	Riluzole resulted in greater retrograde labeled neurons in the brain stem (especially red nucleus); there was also reduced cavitation in riluzole-treated animals; riluzole also improved locomotor scores and incline plane testing
McAdoo et al., 2005 [39]	Rat	Thoracic impactor	2 mM administered through microdialysis fiber at the time of injury; *note: authors compare other neuroprotective agents (see reference for details)	Behavioral outcomes not investigated; riluzole did not decrease glutamate release after SCI
Ates et al., 2007 [3]	Rat	Thoracic contusion (weight drop)	8 mg/kg IP administered at the time of injury; *note: authors compare other neuroprotective agents (see reference for details)	Riluzole resulted in greater myelin and neuronal gray matter sparing and smaller lesion area in comparison to controls; both motor function scores and inclined plane angles were improved with riluzole
Kitzman, 2009 [33]	Rat	Sacral cord transection	8 mg/kg IP administered at 4 weeks after injury and then daily for 3 days; 10 mg/kg IP administered at 4 weeks after injury and then daily for 3 days	Only behavioral outcomes; 8 mg/kg resulted in diminished tail spasticity; 10 mg/kg also resulted in diminished spasticity but also resulted in lethargy and locomotor ataxia in two of three animals

IV = intravenous; IP = intraperitoneal; SSEP = somatosensory-evoked potential; SCI = spinal cord injury.

Ates et al. [3] report greater myelin and neuronal gray matter-sparing and overall smaller lesion areas in riluzole-treated animals. Using retrograde labeling and cell counting techniques, Schwartz and Fehlings [53] reported greater numbers of neurons after injury in riluzole-treated animals. With regard to oxidative stress, Mu and colleagues [43] report that riluzole in combination with methylprednisolone improves mitochondrial function and enhances glutamate uptake. The same group reports increased spared tissue rather than cavitation [44]. Stutzmann et al. [56] report a combination of less white matter hemorrhage and improved somatosensory-evoked potentials in riluzole-treated animals over controls. The only negative study, reported by McAdoo et al. [39], demonstrated that riluzole had no direct effect on glutamate release as measured by microdialysis. In terms of behavioral outcomes, five of eight studies reported this metric with mixed results [3, 33, 43, 53, 56]. Riluzole was reported to demonstrate improved BBB scores and/or inclined plane angles in three studies [3, 43, 53]. Mu et al. [43] only report an improvement in behavioral scores with the addition of methylprednisolone. Finally, Kitzman reported transient improvement in spasticity [33].

Question 2

Rho antagonists (Cethrin is the commercial form currently available) are specific inhibitors of Rho, a signaling molecule for myelin and extracellular matrix inhibitors of regeneration. This compound is directly applied to the dura at the time of surgery after injury. In our systematic review we identified nine preclinical studies that examined the effect of Rho antagonists in the setting of SCI [12, 20, 24, 26, 38, 46, 57, 58, 63]. These investigations made use of a combination of mouse and rat models consisting of dorsal hemisection, impactor injury, transection, and hemisection (Table 2). Outcome measures in these studies can be classified into nonbehavioral (histologic, biochemical, and physiological) and behavioral (locomotor function as measured by the BBB test). In addition, a number of studies compared immediate treatment (within minutes of SCI) or delayed treatment (usually weeks after SCI). Dubreuil et al. [24] provided fundamental proof that endogenous cells within a damaged spinal cord are able to take up and retain the rho antagonist C3 transferase (termed Cethrin in human clinical trials). The outcome of other nonbehavioral investigations can be broadly summarized into those that demonstrate a change in the amount of damaged tissue and those that demonstrate increased sprouting of cell populations and those that affect axonal growth. Five of nine studies report directly on the extent of damaged tissue, each showing reduced spinal cord lesion

after induced trauma [26, 38, 57, 58, 63]. Yamagishi et al. further classified the change as reducing microtubule and neurofilament breakdown suggesting delayed Wallerian degeneration in treated animals [63]. Most recently, Lord-Fontaine et al. [38] showed reduced lesion extent combined with increased spared white matter tracts. Three studies comment on neuronal sprouting: Nishio et al. [46] report sprouting of corticospinal neurons with immediate application of Fasudil (another form of a Rho kinase inhibitor) but not delayed treatment. Similarly, Tanaka et al. [58] report that three different Rho kinase inhibitors (Y-27632, HA-1077, and GST-ΔNLS-p21-PTD-myc protein) led to substantial sprouting. Fournier et al. [26] report that C3 transferase has no effect on sprouting. Lastly, there were two studies that demonstrate axonal regeneration [12, 20] and a single study that showed no effect on regeneration of injured axons [26].

Seven of nine studies reported on behavioral outcomes. The results are mixed with the majority of research groups reporting improved locomotor ability with treatment of Rho kinase inhibitors. Of the negative results, C3-transferase was associated with three severely emaciated rats with a poor behavioral response [57] and low-dose Y27632 was associated with worse neurologic recovery [12]. When given at high doses, Y27632 resulted in improved neurologic outcomes compared with controls [12]. This positive result was echoed by the majority of available studies with the following observations: (1) behavioral improvements tend to appear weeks after drug delivery [26, 38]; (2) immediate treatment results in improved outcomes but not delayed treatment [46]; and (3) improvements in behavioral outcomes occur with different Rho antagonists (C3 transferase, Y-27632, HA-1077, and GST-ΔNLS-p21-PTD-myc protein) [20, 58]. In summary, there is substantial evidence both in terms of nonbehavioral outcomes and behavioral outcomes for the use of Rho antagonists after SCI.

Question 3

Surgical decompression after SCI is founded on a solid basis of animal studies demonstrating improved neurologic outcomes with early decompression. Not surprisingly, human clinical trials, and the complexity of caring for acutely injured patients, have been less convincing. We systematically identified 19 preclinical studies and 22 clinical studies that address the question of early surgical decompression after SCI. (Supplemental materials are available with the online version of CORR.) The timing of decompression in animal models ranges from minutes through the 24-hour mark with earlier decompression usually associated with greater neurologic improvement.

Table 2. A summary of preclinical animal literature studying the effect of Rho antagonists in spinal cord injury

Reference	Species	Injury model	Rho antagonist applied (directly applied unless otherwise stated)	Reported outcomes
Dergham et al., 2002 [20]	Mouse	Thoracic hemisection	1) C3 transferase 2) Y27632	Axons regenerating over long distances show upregulation of GAP-43 mRNA; locomotor function improved within 24 hours of injury in comparison to controls
Sung et al., 2003 [57]	Rat	Thoracic impactor	1) C3 transferase 2) Y27632 (oral) 3) Fasudil	The extent of tissue damage at 5 weeks was reduced in treated animals; the experiment had to be terminated early in three rats 1 week after injury as a result of emaciation (C3 transferase); rats receiving fasudil showed improved locomotor function, whereas rats receiving Y-27632 did not
Fournier et al., 2003 [26]	Rat	Thoracic hemisection	1) C3 transferase 2) Y27632	C3 transferase did not promote axonal sprouting or regeneration but did reduce the amount of scar tissue; Y-27632 did enhance the spouting of corticospinal tract fibers; locomotor scores in both C3-transferase and Y-27632 animals were improved
Dubreuil et al., 2003 [24]	Rat/mouse	Rat: thoracic hemisection or thoracic impactor Mouse: thoracic hemisection	1) C3 transferase	Behavioral outcomes not reported; the authors demonstrate the ability of endogenous cells to take up and retain the C3-transferase compound after SCI
Tanaka et al., 2004 [58]	Rat	Thoracic hemisection	1) Y27632 2) Fasudil 3) Cytoplasmic p21Cip1/WAF1 fusion protein GST-ΔNLS-p21-PTD-myc	All agents increased neuronal sprouting and reduced cavity area; in addition, all compounds improved locomotor scores over control animals
Yamagishi et al., 2005 [63]	Rat	Thoracic transection	1) Y-27632	Behavioral outcomes not reported; microtubule and neurofilament breakdown was reduced with treatment
Chan et al., 2005 [12]	Rat	Cervical dorsal column transection	1) Y-27632 (low dose compared with high dose)	Low-dose animals showed decreased sprouting in dorsal gray matter and had impaired locomotor recovery; high-dose-treated animals showed increased sprouting, increased distance of long axons, and improved locomotor recovery over controls
Nishio et al., 2006 [46]	Rat	Thoracic impactor	1) Fasudil (immediate versus delayed treatment)	Immediate treatment resulted in increased sprouting and improved locomotor scores, whereas delayed treatment was not effective
Lord-Fontaine et al., 2008 [38]	Rat/mouse	Rat: thoracic impactor Mouse: thoracic hemisection	1) BA-210 (Cethrin)	BA-210 resulted in reduced lesion amount and increased spared white matter (only rat data reported); locomotor function was improved in both rat and mouse models; in addition, the authors report no development of mechanical allodynia

SCI = spinal cord injury.

The definition of early surgery in the clinical context is open to interpretation, but most spinal surgeons would agree that early surgery is that which is undertaken within 24 hours. In the paragraphs that follow, we review the evidence available for both preclinical and clinical studies.

The majority of preclinical animal models stated that either the degree of compression (for example, the amount of weight applied during a compression study) or the length of time the spinal cord was compressed directly correlated to the degree of recovery. Keeping in mind that these are animal experiments conducted under ideal circumstances, we review the preclinical literature with regard to the timing of decompression after traumatic SCI in the following three domains: (1) histopathologic correlation between the injury model and the damage caused to the spinal tissue; (2) animal models that did not show a functional benefit of early decompression; and (3) animal models that showed a functional benefit of early decompression.

Histopathologic Correlation

Three studies examined either the electrophysiological or histologic consequences of spinal cord compression with a fixed duration of time [4, 6, 34]. The collective results of these early investigations into SCI suggest direct pressure to the spinal cord, likely resulting in direct damage to the neural cell membranes, combined with hypotension and resultant ischemia result in a loss of neurologic function. Animals that showed recovery after injury demonstrated either a normal microscopic examination of the spinal cord or evidence of central gray necrosis, peripheral demyelinization, or laceration. Animals that failed to recover showed more pronounced evidence of damage to the neuroanatomic circuits of the spinal cord at the level of the anterior horn cells or laceration of either the gray or white matter.

Five studies failed to demonstrate a benefit of early decompression after SCI. This generalized conclusion is closely linked to the experimental design of each of these studies. Of those that compared time of compression with outcome [1, 17, 61], the maximum time of compression was 2 hours. To elaborate, Croft et al. [17] showed that with a graded pressure and time up to a maximum of 58 g for 20 minutes, the electrophysiological changes observed (somatosensory-evoked potentials [SSEPs]) were completely reversible. The weakness of this investigation was that no statistical analysis was carried out. Thienprasit et al. [61] subjected a group of cats to a compression model of SCI and then stratified the animals into those that demonstrated electrophysiological recovery within 6 hours and those that did not. Each group would then be stratified to

receive decompression or decompression + hypothermia. Of the animals that had electrophysiological recovery, there was no difference between the control group and the groups that received decompression or decompression + cooling. Of the animals that had no electrophysiological recovery, there was no difference between the control group and the group that received early decompression; however, the early decompression + cooling group did show better behavioral outcomes suggesting a possible neuroprotective role for hypothermia after SCI. Aki and Toya [1], using a dog model, showed that compression for either 30 minutes or 60 minutes resulted in similar electrophysiological and histologic outcomes. The remaining two studies that failed to demonstrate a correlation between the time of compression and outcome attempted to model cauda equina injury [19] and studied a novel hydrogel [30] with the hypothesis that this agent would act as a scaffold for neural repair after transection. Neither demonstrated an effect of early treatment.

The number of animal studies that showed benefit from early decompression far outweighed those that did not. Using a primate model of SCI, Kobrine and others [35] showed that the duration of compression correlated to the neurologic outcome of these animals and that physical injury to the neuronal membrane could account for a lack of recovery. In a rat model that used five times as many animal subjects, Dolan et al. [22] found the degree of functional recovery was directly proportional to the duration and the force of compression whereby greater recovery was observed with lower forces and less time of compression. Guha et al. [28] further delineated this observation using a rat model and concluded that the major determinant of recovery was the intensity of the compression and that the time of compression was important only with lighter compressive forces. These results were echoed by a similar study conducted 1 year later [47]. Zhang et al. [64] expanded on this notion by measuring concentrations of energy-related metabolites in the spinal cord after injury. They concluded that animals with a larger compressive force had higher concentrations of lactate and inosine in the extracellular compartment of the spinal cord and that these higher concentrations were associated with less neurologic recovery. Delamarter et al. [18] used a canine model to show that compression of the cauda equina for 6 hours or longer resulted in a lack of motor recovery despite decompression. This lack of recovery was associated with central necrosis of the spinal cord. In a set of two experiments using a canine model of SCI, Carlson et al. [9, 10] showed that the duration of compression could be correlated to electrophysiology recordings and spinal cord blood flow whereby a shorter duration of compression was associated with return of blood flow and SSEP recovery. Dimar et al. [21] added the fact that longer duration of

compression was associated with an extension of the injury in a cephalad and caudal direction resulting in more pronounced cavitation and necrosis of the spinal cord. As technology improved, Carlson and others made use of MRI to further our knowledge with regard to lesion volumes relative to the time of spinal compression [8]. They demonstrated a difference in MRI-based lesion volumes between a 30-minute compression group and a 180-minute compression group. Perhaps the most hypothesis-driven study of recent times was carried out by Rabinowitz et al. [50] who compared not only the timing of decompression, but also the use of methylprednisolone. Using a randomized design, the authors demonstrated dogs randomized to surgical decompression, with or without methylprednisolone administration, offers greater neurologic improvement than with the use of methylprednisolone alone. This is an important study that compared two therapies at the forefront of human treatment that have yet been compared head to head. The authors rightfully comment on the value of such a trial. In summary, this collection of animal studies demonstrates a substantial body of evidence, across many species, that both the degree of initial force and the duration of compression are related to the degree of neurologic improvement.

The neurologic outcomes after early decompressive surgery in clinical studies have been less promising than those in animal models. This is somewhat expected given the difficulty of controlling factors associated with acute injury in combination with an inherent rate of clinical improvement with proper medical management. Studies have therefore focused on the safety and feasibility of early surgery in addition to improvement in neurologic function. In the paragraphs that follow, we review the clinical evidence according to the level of evidence of each study. The methodological quality of the studies ranged from 7/32 to 25/32 according to the criteria of Downs and Black [23]. (Supplemental materials are available with the online version of CORR.)

No Level I evidence exists to guide clinicians with regard to the timing of surgical decompression after SCI. We identified two Level II studies [11, 62]. Vaccaro and others [62] studied 62 patients who presented with a spinal injury between C3 and T1. They defined the early surgery group as those who were treated within 72 hours and the late surgery group as those who were treated after 5 days. These authors found no difference between groups with regard to the length of stay in the intensive care unit or inpatient rehabilitation and no difference with regard to the American Spinal Injury Association (ASIA) motor score. In contrast, Cengiz et al. [11] studied 27 patients who sustained a traumatic SCI from T8 to L2. They defined early surgery as that occurring within 8 hours of injury and late surgery as that occurring from 3 to 15 days after

surgery. There were several differences between the groups at followup. The early surgery group showed more improvement on the ASIA Impairment Scale, no complications in-hospital, and a shorter length of stay both in-hospital and in the intensive care unit (ICU). The later surgery group had four complications: three cases of lung failure and one case of sepsis. The authors concluded there are statistical differences between patients treated early and those treated late both with regard to neurologic improvement and overall morbidity. There were no mortalities in either group. The majority of clinical studies that attempt to address the question of timing of decompression after traumatic SCI are Level III evidence. (Supplemental materials are available with the online version of CORR.)

Although space constraints prevent a detailed overview of each study, we provide an overview of investigations that outline the following: (1) length of stay in the hospital; (2) medical complications after SCI; and (3) neurologic outcome. We did not identify any Level IV evidence to guide clinicians with regard to the timing of surgical decompression after SCI.

When attempting to study the effect of early surgery on SCI, a relatively easy metric to follow is the length of time a patient spends in the ICU or inpatient unit. This measurement considers not only the severity of injury, but also the accessibility of the medical system at stabilizing the patient and allowing them to proceed with rehabilitation. Of the 22 clinical studies identified in this review, nine Level III studies measured the length of stay [7, 11, 14, 16, 27, 32, 37, 40, 42, 52]. Early surgical decompression was associated with a shorter hospital length of stay in eight studies [7, 14, 16, 27, 32, 37, 40, 42] (although Guest et al. [27] reported no p values), whereas the other only recorded the length of stay in the ICU [52]. A subset of these studies further divided overall length of stay with the duration of stay in the ICU [14, 16, 27, 32] and found this time point was also less in patients receiving early decompressive surgery. Only one study [32] that measured these values found no correlation between timing of surgical decompression and the length of stay in the ICU. An obvious extension to this measurement is the rate at which patients are readmitted to the hospital. This was measured in only one study [40] and the authors found no difference between the early and late surgical intervention groups.

The following complications were recorded in eight of the 22 studies: respiratory care, wound infections, decubitus ulcers, cardiac complications, urinary tract infections, gastrointestinal hemorrhage, deep vein thrombosis (DVT), and death. Four studies [7, 36, 37, 41] reported no difference in the rate of medical complications between the early and late surgical groups, whereas four studies found overall fewer complications in the persons receiving early surgical decompression. Specifically, Mirza et al. [42] reported

fewer complications in persons receiving surgery within 72 hours of injury; Croce et al. [16] reported lower rates of pneumonia and DVT in persons receiving surgery within 24 hours; Chipman et al. [14] reported a lower frequency of all complications in patients with an Injury Severity Score (ISS) greater than 15 and receiving surgery within 72 hours of injury (although this same group reports equal medical complications in persons with low ISS [less than 15] regardless of the time of decompression); McKinley et al. [40] report higher rates of pneumonia in the late surgery group but equal rates of other complications (DVT, pulmonary embolism, ulcers).

All studies reported whether or not patients recovered neurologic function after surgical intervention and the majority (16 studies) attempted to compare the effect of early treatment on the timing of surgery. Four studies demonstrated early surgical decompression afforded better neurologic outcomes: Clohisy et al. [15] report surgical decompression within 48 hours resulted in improvement in the modified Frankel scale; McLain and Benson [41] report better neurologic improvement (no p value reported) with surgical decompression within 24 hours; Mirza et al. [42] showed surgery within 72 hours resulted in major improvements in the ASIA motor score, whereas surgery after 72 hours resulted in no improvement in the mean motor score; lastly, Papadopoulos et al. [48] found patients who received surgical decompression within 12 hours ($\pm$ 1.3 hours) had better neurologic improvement than those with surgery outside this time window. In a similar fashion, seven of the other studies with the same level of evidence reported no neurologic benefit to early surgical decompression [13, 16, 27, 37, 40, 49, 51]. Four studies showed equivocal results [5, 25, 36, 59].

Discussion

An improved understanding of the secondary mechanisms of SCI has resulted in novel strategies aimed at improving outcome for patients. In this review, we highlight three treatment strategies that have promise to demonstrate improved outcomes: neuroprotection (riluzole), Rho antagonists (Cethrin and other compounds), and early surgical decompression. We formulated specific questions for each and systematically reviewed the literature to answer these questions.

There are two main limitations to this systematic review. The first is we searched only the English language. Without access to scientific work published in other parts of the world we cannot be certain that the most important work in the fields of riluzole, Cethrin, or early surgical decompression has been reviewed. The second limitation of this work is the inherent bias of preselecting three treatment

strategies for a condition in which many more are being studied. We chose to systematically review riluzole, Cethrin, and early surgical decompression because these treatment strategies are at a point in their development where large clinical trials are either being planned or are underway. The aim of this work is to bring clinicians up to date on works that will likely affect patients with SCI over the next several years.

Studies involving the neuroprotective agent riluzole focus on local tissue protection, functional neurologic recovery, and a single study on spasticity. There has not been a dose–response study for the application of riluzole in the setting of SCI, but the agent is FDA-approved for use in the setting of ALS. Based on the available preclinical evidence, riluzole has moved into human clinical trials under the direction of the North American Clinical Trials Network.

Rho antagonists have been studied in rat and mouse models of SCI. Only one animal study involved the cervical spine; all others involved the thoracic spine. A number of compounds exist that are directly applied to the spinal cord after injury. Detailed dosing studies and the establishment of a therapeutic window of application have not been conducted. The commercial form of Rho antagonist is termed Cethrin; this agent is currently undergoing a human clinical trial.

Early surgical decompression is playing an increasing role in the treatment of acute SCI. Although still controversial, evidence is mounting for its safety, clinical, and neurologic outcomes. The definition of early surgery is not fixed, but most consider early to be less than 24 hours. In terms of safety, the treating surgeon must balance the potential benefits of early surgery versus the risk. The benefits include relieving cord compression and therefore limiting secondary injury. The risks include aggravating secondary injury by hypotensive episodes or blood loss. Several studies point out that patients should be treated with early surgery if medically stable to do so [2, 11]. Clinical benefits of early surgery possibly include shorter length of both ICU and overall hospital stay with fewer medical complications (such as pneumonia and DVT) [60]. This claim has been challenged by other studies. In terms of neurologic outcome, the field of SCI research is torn between substantive evidence from preclinical animal models favoring early surgery [29, 31, 48] and mixed evidence from human clinical trials. Recent preliminary results from the Surgical Treatment for Acute Spinal Cord Injury Study (STASCIS) suggest decompression of the spinal cord within 24 hours of injury is associated with improved neurologic recovery in persons with cervical injury [45]. A final report from this multicenter prospective cohort study is expected within the next year after long-term followup is complete.

This systematic review presents some of the recent ideas in SCI research and how these have translated into both clinical trials of biologic compounds and clinical practice. With continued research at the basic science and clinical levels, new strategies will surely evolve to optimize care of this devastating condition.

References

1. Aki T, Toya S. Experimental study on changes of the spinal-evoked potential and circulatory dynamics following spinal cord compression and decompression. *Spine*. 1984;9:800–809.

2. Albin MS, White RJ. Epidemiology, physiopathology, and experimental therapeutics of acute spinal cord injury. *Crit Care Clin*. 1987;3:441–452.

3. Ates O, Cayli SR, Gurses I, Turkoz Y, Tarim O, Cakir CO, Kocak A. Comparative neuroprotective effect of sodium channel blockers after experimental spinal cord injury. *J Clin Neurosci*. 2007;14:658–665.

4. Bohlman HH, Bahniuk E, Raskulinecz G, Field G. Mechanical factors affecting recovery from incomplete cervical spinal cord injury: a preliminary report. *Johns Hopkins Med J*. 1979;145: 115–125.

5. Botel U, Glaser E, Niedeggen A. The surgical treatment of acute spinal paralysed patients. *Spinal Cord*. 1997;35:420–428.

6. Brodkey JS, Richards DE, Blasingame JP, Nulsen FE. Reversible spinal cord trauma in cats. Additive effects of direct pressure and ischemia. *J Neurosurg*. 1972;37:591–593.

7. Campagnolo DI, Esquieres RE, Kopacz KJ. Effect of timing of stabilization on length of stay and medical complications following spinal cord injury. *J Spinal Cord Med*. 1997;20:331–334.

8. Carlson GD, Gorden CD, Oliff HS, Pillai JJ, LaManna JC. Sustained spinal cord compression: part I: time-dependent effect on long-term pathophysiology. *J Bone Joint Surg Am*. 2003;85: 86–94.

9. Carlson GD, Minato Y, Okada A, Gorden CD, Warden KE, Barbeau JM, Biro CL, Bahnuik E, Bohlman HH, Lamanna JC. Early time-dependent decompression for spinal cord injury: vascular mechanisms of recovery. *J Neurotrauma*. 1997;14: 951–962.

10. Carlson GD, Warden KE, Barbeau JM, Bahniuk E, Kutina-Nelson KL, Biro CL, Bohlman HH, LaManna JC. Viscoelastic relaxation and regional blood flow response to spinal cord compression and decompression. *Spine*. 1997;22:1285–1291.

11. Cengiz SL, Kalkan E, Bayir A, Ilik K, Basefer A. Timing of thoracolomber spine stabilization in trauma patients; impact on neurological outcome and clinical course. A real prospective (rct) randomized controlled study. *Arch Orthop Trauma Surg*. 2008;128:959–966.

12. Chan CC, Khodarahmi K, Liu J, Sutherland D, Oschipok LW, Steeves JD, Tetzlaff W. Dose-dependent beneficial and detrimental effects of ROCK inhibitor Y27632 on axonal sprouting and functional recovery after rat spinal cord injury. *Exp Neurol*. 2005;196:352–364.

13. Chen L, Yang H, Yang T, Xu Y, Bao Z, Tang T. Effectiveness of surgical treatment for traumatic central cord syndrome. *J Neurosurg Spine*. 2009;10:3–8.

14. Chipman JG, Deuser WE, Beilman GJ. Early surgery for thoracolumbar spine injuries decreases complications. *J Trauma*. 2004;56:52–57.

15. Clohisy JC, Akbarnia BA, Bucholz RD, Burkus JK, Backer RJ. Neurologic recovery associated with anterior decompression of

16. spine fractures at the thoracolumbar junction (T12-L1). *Spine*. 1992;17:S325–330.

16. Croce MA, Bee TK, Pritchard E, Miller PR, Fabian TC. Does optimal timing for spine fracture fixation exist? *Ann Surg*. 2001;233:851–858.

17. Croft TJ, Brodkey JS, Nulsen FE. Reversible spinal cord trauma: a model for electrical monitoring of spinal cord function. *J Neurosurg*. 1972;36:402–406.

18. Delamarter RB, Sherman J, Carr JB. Pathophysiology of spinal cord injury. Recovery after immediate and delayed decompression. *J Bone Joint Surg Am*. 1995;77:1042–1049.

19. Delamarter RB, Sherman JE, Carr JB. 1991 Volvo Award in experimental studies. Cauda equina syndrome: neurologic recovery following immediate, early, or late decompression. *Spine*. 1991;16:1022–1029.

20. Dergham P, Ellezam B, Essagian C, Avedissian H, Lubell WD, McKerracher L. Rho signaling pathway targeted to promote spinal cord repair. *J Neurosci*. 2002;22:6570–6577.

21. Dimar JR 2nd, Glassman SD, Raque GH, Zhang YP, Shields CB. The influence of spinal canal narrowing and timing of decompression on neurologic recovery after spinal cord contusion in a rat model. *Spine*. 1999;24:1623–1633.

22. Dolan EJ, Tator CH, Endrenyi L. The value of decompression for acute experimental spinal cord compression injury. *J Neurosurg*. 1980;53:749–755.

23. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52:377–384.

24. Dubreuil CI, Winton MJ, McKerracher L. Rho activation patterns after spinal cord injury and the role of activated Rho in apoptosis in the central nervous system. *J Cell Biol*. 2003;162:233–243.

25. Duh MS, Shepard MJ, Wilberger JE, Bracken MB. The effectiveness of surgery on the treatment of acute spinal cord injury and its relation to pharmacological treatment. *Neurosurgery*. 1994;35:240–248; discussion 248–249.

26. Fournier AE, Takizawa BT, Strittmatter SM. Rho kinase inhibition enhances axonal regeneration in the injured CNS. *J Neurosci*. 2003;23:1416–1423.

27. Guest J, Eleraky MA, Apostolides PJ, Dickman CA, Sonntag VK. Traumatic central cord syndrome: results of surgical management. *J Neurosurg*. 2002;97:25–32.

28. Guha A, Tator CH, Endrenyi L, Piper I. Decompression of the spinal cord improves recovery after acute experimental spinal cord compression injury. *Paraplegia*. 1987;25:324–339.

29. Harvey C, Wilson SE, Greene CG, Berkowitz M, Stripling TE. New estimates of the direct costs of traumatic spinal cord injuries: results of a nationwide survey. *Paraplegia*. 1992;30: 834–850.

30. Hejcl A, Urdzikova L, Sedy J, Lesny P, Pradny M, Michalek J, Burian M, Hajek M, Zamecnik J, Jendelova P, Sykova E. Acute and delayed implantation of positively charged 2-hydroxyethyl methacrylate scaffolds in spinal cord injury in the rat. *J Neurosurg Spine*. 2008;8:67–73.

31. Kakulas BA. Neuropathology: the foundation for new treatments in spinal cord injury. *Spinal Cord*. 2004;42:549–563.

32. Kerwin AJ, Frykberg ER, Schinco MA, Griffen MM, Murphy T, Tepas JJ. The effect of early spine fixation on non-neurologic outcome. *J Trauma*. 2005;58:15–21.

33. Kitzman PH. Effectiveness of riluzole in suppressing spasticity in the spinal cord injured rat. *Neurosci Lett*. 2009;455:150–153.

34. Kobrine AI, Evans DE, Rizzoli H. Correlation of spinal cord blood flow and function in experimental compression. *Surg Neurol*. 1978;10:54–59.

35. Kobrine AI, Evans DE, Rizzoli HV. Experimental acute balloon compression of the spinal cord. Factors affecting disappearance

and return of the spinal evoked response. *J Neurosurg*. 1979;51: 841–845.

36. Krengel WF 3rd, Anderson PA, Henley MB. Early stabilization and decompression for incomplete paraplegia due to a thoracic-level spinal cord injury. *Spine*. 1993;18:2080–2087.

37. Levi L, Wolf A, Rigamonti D, Ragheb J, Mirvis S, Robinson WL. Anterior decompression in cervical spine trauma: does the timing of surgery affect the outcome? *Neurosurgery*. 1991;29:216–222.

38. Lord-Fontaine S, Yang F, Diep Q, Dergham P, Munzer S, Tremblay P, McKerracher L. Local inhibition of Rho signaling by cell-permeable recombinant protein BA-210 prevents secondary damage and promotes functional recovery following acute spinal cord injury. *J Neurotrauma*. 2008;25:1309–1322.

39. McAdoo DJ, Hughes MG, Nie L, Shah B, Clifton C, Fullwood S, Hulsebosch CE. The effect of glutamate receptor blockers on glutamate release following spinal cord injury. Lack of evidence for an ongoing feedback cascade of damage $-$ > glutamate release $-$ > damage $-$ > glutamate release $-$ > etc. *Brain Res*. 2005;1038:92–99.

40. McKinley W, Meade MA, Kirshblum S, Barnard B. Outcomes of early surgical management versus late or no surgical intervention after acute spinal cord injury. *Arch Phys Med Rehabil*. 2004;85: 1818–1825.

41. McLain RF, Benson DR. Urgent surgical stabilization of spinal fractures in polytrauma patients. *Spine*. 1999;24:1646–1654.

42. Mirza SK, Krengel WF 3rd, Chapman JR, Anderson PA, Bailey JC, Grady MS, Yuan HA. Early versus delayed surgery for acute cervical spinal cord injury. *Clin Orthop Relat Res*. 1999;104–114.

43. Mu X, Azbill RD, Springer JE. Riluzole and methylprednisolone combined treatment improves functional recovery in traumatic spinal cord injury. *J Neurotrauma*. 2000;17:773–780.

44. Mu X, Azbill RD, Springer JE. Riluzole improves measures of oxidative stress following traumatic spinal cord injury. *Brain Res*. 2000;870:66–72.

45. Ng WP, Fehlings MG, Cuddy B, Dickman C, Fazl M, Green B, Hitchon P, Northrup B, Sonntag V, Wagner F, Tator CH. Surgical treatment for acute spinal cord injury study pilot study #2: evaluation of protocol for decompressive surgery within 8 hours of injury. *Neurosurg Focus*. 1999;6:e3.

46. Nishio Y, Koda M, Kitajo K, Seto M, Hata K, Taniguchi J, Moriya H, Fujitani M, Kubo T, Yamashita T. Delayed treatment with Rho-kinase inhibitor does not enhance axonal regeneration or functional recovery after spinal cord injury in rats. *Exp Neurol*. 2006;200:392–397.

47. Nystrom B, Berglund JE. Spinal cord restitution following compression injuries in rats. *Acta Neurol Scand*. 1988;78: 467–472.

48. Papadopoulos SM, Selden NR, Quint DJ, Patel N, Gillespie B, Grube S. Immediate spinal cord decompression for cervical spinal cord injury: feasibility and outcome. *J Trauma*. 2002;52: 323–332.

49. Pollard ME, Apple DF. Factors associated with improved neurologic outcomes in patients with incomplete tetraplegia. *Spine*. 2003;28:33–39.

50. Rabinowitz RS, Eck JC, Harper CM Jr, Larson DR, Jimenez MA, Parisi JE, Friedman JA, Yaszemski MJ, Currier BL. Urgent surgical decompression compared to methylprednisolone for the treatment of acute spinal cord injury: a randomized prospective study in beagle dogs. *Spine* (Phila Pa 1976). 2008;33:2260–2268.

51. Sapkas GS, Papadakis SA. Neurological outcome following early versus delayed lower cervical spine surgery. *J Orthop Surg* (Hong Kong). 2007;15:183–186.

52. Schinkel C, Frangen TM, Kmetic A, Andress HJ, Muhr G. Timing of thoracic spine stabilization in trauma patients: impact on clinical course and outcome. *J Trauma*. 2006;61:156–160; discussion 160.

53. Schwartz G, Fehlings MG. Evaluation of the neuroprotective effects of sodium channel blockers after spinal cord injury: improved behavioral and neuroanatomical recovery with riluzole. *J Neurosurg*. 2001;94:245–256.

54. Sekhon LH, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine* (Phila Pa 1976). 2001;26:S2–12.

55. Springer JE, Azbill RD, Kennedy SE, George J, Geddes JW. Rapid calpain I activation and cytoskeletal protein degradation following traumatic spinal cord injury: attenuation with riluzole pretreatment. *J Neurochem*. 1997;69:1592–1600.

56. Stutzmann JM, Pratt J, Boraud T, Gross C. The effect of riluzole on post-traumatic spinal cord injury in the rat. *Neuroreport*. 1996;7:387–392.

57. Sung JK, Miao L, Calvert JW, Huang L, Louis Harkey H, Zhang JH. A possible role of RhoA/Rho-kinase in experimental spinal cord injury in rat. *Brain Res*. 2003;959:29–38.

58. Tanaka H, Yamashita T, Yachi K, Fujiwara T, Yoshikawa H, Tohyama M. Cytoplasmic p21(Cip1/WAF1) enhances axonal regeneration and functional recovery after spinal cord injury in rats. *Neuroscience*. 2004;127:155–164.

59. Tator CH, Fehlings MG, Thorpe K, Taylor W. Current use and timing of spinal surgery for management of acute spinal surgery for management of acute spinal cord injury in North America: results of a retrospective multicenter study. *J Neurosurg*. 1999;91:12–18.

60. Tator CH, Koyanagi I. Vascular mechanisms in the pathophysiology of human spinal cord injury. *J Neurosurg*. 1997;86:483–492.

61. Thienprasit P, Bantli H, Bloedel JR, Chou SN. Effect of delayed local cooling on experimental spinal cord injury. *J Neurosurg*. 1975;42:150–154.

62. Vaccaro AR, Daugherty RJ, Sheehan TP, Dante SJ, Cotler JM, Balderston RA, Herbison GJ, Northrup BE. Neurologic outcome of early versus late surgery for cervical spinal cord injury. *Spine*. 1997;22:2609–2613.

63. Yamagishi S, Fujitani M, Hata K, Kitajo K, Mimura F, Abe H, Yamashita T. Wallerian degeneration involves Rho/Rho-kinase signaling. *J Biol Chem*. 2005;280:20384–20388.

64. Zhang Y, Hillered L, Olsson Y, Holtz A. Time course of energy perturbation after compression trauma to the spinal cord: an experimental study in the rat using microdialysis. *Surg Neurol*. 1993;39:297–304.