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Timing of Surgery in the Setting of Acute Spinal Cord Injury

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Abstract The efficacy of early surgical decompression in the setting of acute spinal cord injury (SCI) has been actively discussed for decades. Primary spinal cord damage due to spinal cord contusion or compression leads to neurological tissue destruction potentiated by a post-lesion signaling cascade of downstream events, known as the secondary injury. Although there are still few therapeutic options leading to neurological recovery, preclinical animal studies have suggested that persistent spinal cord compression exacerbates secondary injury following SCI and that early surgical decompression of the spinal cord mitigates spinal cord damage, leading to improved functional outcomes. Although the heterogeneity of injuries, surgical procedures, and the definition of early decompression make it difficult to draw a definitive conclusion, clinical studies to date have provided supportive evidence for this preclinical result. Several clinical trials, including a number of prospective studies such as the STASCIS trial, showed benefits of early decompression in terms of neurological improvement, shorter hospital stay, and decreased complications, while other studies have argued that early intervention does not offer an advantage. Systematic reviews have also indicated that early decompression after SCI results in improved clinical outcomes compared to both delayed decompression and conservative treatment. In addition, from an efficacy standpoint, the 24-h cutoff for early decompression has been shown to represent the most effective time window during which surgical decompression had the potential to confer a neuroprotective effect.

Keywords Acute spinal cord injury · Timing of surgery · Decompression

Introduction

Spinal cord injury (SCI) is a devastating event resulting in severe neurological deficits, loss of function, and deterioration in quality of life. The prevalence of SCI is 15–40 cases per million in North America and approximately 750 per million in the world with an annual incidence that appears to be rising [1–3]. The annual cost of SCI exceeds seven billion dollars [1], and the impact of SCI is immense on the individual and society. Given this huge impact of SCI, it is clear that effective therapies improving neurologic outcomes after SCI are urgently needed.

The pathophysiology of acute SCI involves both primary and secondary mechanisms that lead to neurologic injury [1, 4, 5]. The primary injury is caused by acute spinal cord contusion, compression, or laceration due to displacement of bone or disk [1, 5]. This primary injury initiates a signaling cascade of downstream events, known as the secondary injury. In the secondary injury, hemorrhage, edema, and thrombosis and vasospasm in the microvasculature lead to ischemic injury with resultant (1) ionic disturbances, including increased intracellular

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calcium and sodium, and increased extracellular potassium; (2) accumulation of neurotransmitters, including serotonin, catecholamines, and extracellular glutamate; and (3) arachidonic acid release and free radical release. These pathologic changes result in apoptosis of neural tissues and amplification of the extent of tissue destruction [1, 4, 5].

Mitigating these secondary mechanisms is an opportunity for neuroprotection and neurological recovery, and the majority of therapeutic interventions investigated target this. High-dose steroid administration for acute SCI is a well-known treatment which targets the secondary mechanisms of SCI [6]. The National Acute Spinal Cord Injury Studies (NASCIS) II study reported modest improvements in recovery of patients treated with high-dose steroids within 8 h of injury, in patients with complete and incomplete SCI [6, 7]. In addition, the NASCIS III study provided evidence suggesting a better neurological outcome with high-dose steroids administered within 3 h compared to treatment initiated 3–8 h after SCI [6, 8]. These NASCIS studies emphasized the importance of early intervention after SCI to prevent or attenuate the secondary injury, although the appropriate time window after SCI is still unclear. Surgical decompression is another treatment posited to improve neurological outcome. Previous laboratory data showed the benefit of early surgical decompression of the spinal cord after SCI in attenuating secondary injury mechanisms. However, in the clinical setting, the role of this intervention remains controversial because of the lack of well-designed and executed randomized controlled trials. In this paper, we will present an overview of the basic mechanisms by which early surgical decompression after SCI is thought to have its effects. We will then review the experimental and clinical studies regarding the value of early surgical decompression in the setting of acute SCI.

Pathology of SCI and Experimental Studies of Decompression in Animal Models

Initial mechanical impact and subsequent persistent compression on the spinal cord tissue initiate secondary pathophysiological events which amplify the primary damage (Fig. 1) [4]. Within a few seconds to minutes after the injury, microvasculature in the spinal cord parenchyma is disrupted, followed by ischemic status [4]. The subsequent secondary injury lasts a few days with events including ionic dysregulation, excitotoxicity, and free radical production; these events lead to necrotic and apoptotic cell death [1, 4, 5]. In addition to these pathological conditions, permeability of the blood–brain barrier increases at the early acute stage inducing inflammatory processes which exacerbate the tissue damage. During the continuing subacute stage in SCI, the delayed secondary injury proceeds by phagocytosis, apoptosis, and demyelination followed by cyst formation.

With regard to the timing of decompression for SCI, early surgical intervention appears a reasonable and appropriate goal given that persistent compression and spinal instability are key contributors to secondary injury. To date, the timing of arresting these secondary mechanisms has been investigated in many preclinical studies (Table 1). Dimar et al. used a rat model with a range of timed extradural compression up to 72 h and demonstrated that animals with shorter compression times fared better neurologically [11]. This result indicates that the prognosis for neurologic recovery is adversely affected by a longer duration of cord compression, and early decompression had a beneficial effect for the injured spinal cord. Carlson et al. induced sustained spinal cord compression for 30 or 180 min in dog models and compared the outcomes after removing the compression [10]. They showed that the longer duration of compression was associated with reduced electrophysiological recovery, increased lesion volume, and greater functional impairment. In an attempt to reproduce the treatments currently available to humans, Rabinowitz et al. conducted a randomized prospective study in dogs comparing early surgical decompression (6 h) with or without methylprednisolone, compared with methylprednisolone alone [21]. SCI was induced by laminectomy and circumferential compression of the dura by 60 % with a nylon band. The authors demonstrated that surgical decompression with or without methylprednisolone administration offers greater neurological improvement than the use of methylprednisolone alone.

Summarizing the relevant literature on this topic, the senior author's team conducted a systematic review of the preclinical studies in which timing of spinal cord compression or decompression was examined using animal SCI models [22•]. Nineteen experimental studies fulfilled the criteria, and 11 studies indicated a time-dependent effect of spinal cord compression in behavioral recovery, spinal cord blood flow, electrophysiological recovery, and extent of histopathological lesion. Despite some discrepancies in the results of those preclinical studies, the analysis provided evidence for a biological rationale to support early decompression of the spinal cord. Recently, Batchelor et al. performed a meta-analysis to examine the preclinical literature on acute decompression of the injured spinal cord [23•]. Twenty-one articles were extracted for this analysis, and the overall effect size of the improvement in neurobehavioral outcome as a result of decompression was 35.1 %. In their univariate analysis, the effect size and compressive pressure had an inverse relationship, with higher pressures associated with smaller effects, whereas the duration of compression was not related to outcome. However, the authors observed a strong relationship of both compressive pressure and

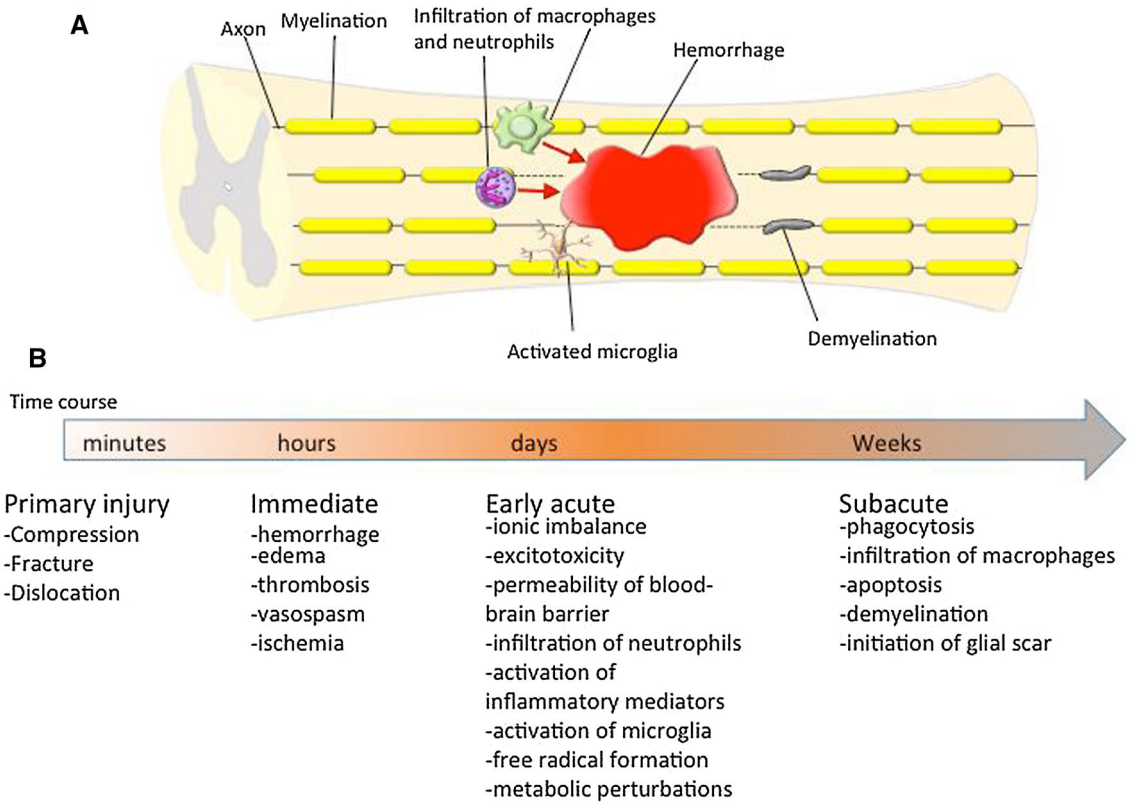

Fig. 1 Schema of spinal cord injury with time course. After the primary injury, hemorrhage occurs within a few minutes, leading to ischemic status. At acute phase, inflammatory cells infiltrate into the injured spinal cord with the increase of permeability of blood–brain barrier. At subacute phase, the severed axons are demyelinated and result in cell death

duration of compression with outcomes in multivariate analysis. These results indicate that longer duration of compression could result in a poorer outcome depending on the pressure applied to the spinal cord.

Because of the heterogeneity of the animal study models, it is difficult to define the time window where decompression is effective in the clinical field. However, the preclinical studies do support the idea that a shorter compression period can result in improvement of neurological function, and it is therefore appropriate to consider that the earlier surgical decompression is conducted, the more neuroprotective effects may be enhanced to attenuate tissue damage and promote functional recovery.

Previous Clinical Studies

Neurological Outcomes

Between 1997 and 2015, sixteen studies reported on neurological recovery after SCI in cases with early or delayed decompression (Table 2). Twelve reports were retrospective case-controlled studies, two were prospective non-randomized studies, and two were prospective randomized studies. Better neurological recovery after early decompression was found in six studies, while no significant difference was reported in the other ten studies. Eleven studies focused on cervical SCI and three focused on SCI at all levels, with the remaining studies focusing on thoracolumbar SCI. In the eleven studies regarding cervical SCI, four studies (36.4 %) showed better neurological recovery after early spinal cord decompression.

Optimal Time Cutoff for Early Decompression

Early decompression was defined as <24 h in ten studies, and as <72 h in six studies. In the ten studies with early decompression defined as <24 h, better neurological recovery was found in five studies (50 %). On the other hand, in the six studies with early decompression defined as <72 h, only one study (16.7 %) showed better neurological recovery. The 24-h cutoff for early decompression represented the optimal time window during which surgical decompression had the potential to confer a neuroprotective effect. In addition, systematic reviews of clinical studies similarly concluded that decompressive surgery performed before 24 h resulted in superior clinical outcomes as compared with decompression performed after the 24-h cutoff [40, 41]. In light of these results, we feel that the 24-h cutoff point is the most promising time window during which

Table 1 Neurological outcome after decompression in acute SCI

Investigator (year)	Animal species	Level of injury	Injury model	Timing of decompression (time after injury)	Early decompression improved NR
Jazayeri et al. [9]	Rats ($n = 12$)	T9	Clip	3 s or 10 min	Yes
Carlson et al. [10]	Dogs ($n = 16$)	T13	A device for weight-loading spinal compression with hydraulic piston was suspended	30 or 180 min	Yes
Dimar et al. [11]	Rats ($n = 42$)	T9–10	12.5 g/cm spinal cord contusion was produced using an impactor (developed at New York University [NYU]). After the contusion, spacer was placed into the canal under T9	0, 2, 6, 24, or 72 h	Yes
Carlson et al. [12]	Dogs ($n = 12$)	T13	A device for weight-loading spinal compression with hydraulic piston was suspended	Decompressed 5 min after compression, or 3 h without decompression	Yes
Carlson et al. [13]	Dogs ($n = 21$)	T13	A device for weight-loading spinal compression with hydraulic piston was suspended	30, 60, or 180 min	Yes
Delamarter et al. [14]	Dogs ($n = 30$)	L4	A nylon cable tie was placed circumferentially around the dura	0, 1 h, 6 h, 24 h, or 1 week	Yes
Delamarter et al. [15]	Dogs ($n = 30$)	L7	A nylon cable tie was placed circumferentially around the dura	0, 1 h, 6 h, 24 h, or 1 week	No Only recovery speed depended on the timing
Nystrom et al. [16]	Rats ($n = 81$)	T7–8	Injury was produced by applying weights (20, 35, or 50 g) to a plate 2.2 × 50 mm in size	1, 5, or 10 min	Yes
Guha et al. [17]	Rats ($n = 75$)	C7–T1	Clips (2.3, 16.9, or 53 g)	15, 60, 120, or 240 min	Yes The time until decompression affected recovery, but only for the lighter compression forces
Aki et al. [18]	Dogs ($n = 33$)	Thoracolumbar	Compression device was used with the weight of 6, 16, 36, or 60 g. The contact field on the spinal cord measured 3.5 mm × 5.0 mm	30 or 60 min	No No definite difference was observed in circulatory disturbance between the two compression groups
Dolan et al. [19]	Rats ($n = 91$)	T1	Clips (16, 71, or 178 g)	3, 30, 60, 300, or 900 s	Yes
Kobrine et al. [20]	Monkeys ($n = 18$)	T6	Fogarty balloon catheter was inserted into the epidural space and was inflated	1, 3, 5, 7, 15 min	Yes Only the animals in 1-min group showed return of the evoked response

NR neurological recovery

surgical decompression could provide optimal neuroprotective effects.

Prospective Studies

Superior neurological outcome after early decompression was observed in two studies [26••, 27••]. In the multicenter prospective study of a Canadian cohort by Wilson et al. in 2012 [27••], a total of 84 patients with traumatic SCI were enrolled. Of these, 35 (41.7 %) underwent surgery within 24 h after injury and were considered the early-surgery cohort, whereas 49 (58.3 %) underwent late surgery at or after 24 h post injury. The mean time to surgery was 12.7 h (±4.9) and 155.0 h (±236.7) in the early and late groups, respectively. The mean improvement in ASIA motor score (AMS) at rehabilitation discharge was 20 points among

Table 2 Neurological outcome after decompression in acute SCI

Investigator (y)	Study design (class of evidence)	Timing of Intervention	No. of patients (level)	No. of early decompression	Early decompression improved NR
Liu et al. [24]	RCS (III)	<72 h	595 (cervical)	212	No
Rahimi et al. [25]	Prospective, randomized (II)	<24 h	35 (thoracolumbar)	16	No
Fehlings et al. [26••]	Prospective, non-randomized (II)	<24 h	313 (cervical)	182	Yes
Wilson et al. [27••]	Prospective, non-randomized (II)	<24 h	84 (all)	35	Yes
Anderson et al. [28]	RCS (III)	<24 h	69 (cervical)	14	No
		<48 h		30	
Newton et al. [29]	RCS (III)	<4 h	57 (cervical)	8	Yes
Stevens et al. [30]	RCS (III)	<24 h	50 (cervical)	16	Yes
Chen et al. [31]	RCS (III)	<4 days	49 (cervical)	21	No
Cengiz et al. [32]	RCT (III)	<8 h	27 (thoracolumbar)	12	Yes
Sapkas et al. [33]	RCS (III)	<72 h	67 (cervical)	31	No
McKinley et al. [34]	RCS (III)	<72 h	779 (all): 603 decompressed, 176 non-operative	307	No
Pollard et al. [35]	RCS (III)	<24 h	329 (cervical)	86	No
Guest et al. [36]	RCS (III)	<24 h	50 (cervical)	16	No
Tator et al. [37]	RCS (III)	<24 h	583 (all): 381 surgical decompression, 202 non-operative	88	No
Mirza et al. [38]	RCS (III)	<72 h	30 (cervical)	15	Yes
Vaccaro et al. [39]	Prospective, randomized (II)	<72 h	62 (cervical)	34	No

NR neurological recovery, *RCS* retrospective case-controlled study

early-surgery patients and 15 points among late-surgery patients ($P = 0.46$). In the analysis investigating AMS improvement, adjusted for preoperative status and neurological level, there was a positive effect estimate for early surgical therapy that was statistically significant ($P = 0.01$).

In a multicenter prospective cohort study (Surgical Timing in Acute Spinal Cord Injury Study: STASCIS) at six North American centers in 2012 by Fehlings et al. [26••], a total of 313 patients with acute cervical SCI were enrolled. Of these, 182 underwent early surgery, at a mean of 14.2 (±65.4) h, while the remaining 131 had late surgery, at a mean of 48.3 (±29.3) h. Of the 222 patients with follow-up available at 6 months post injury, 19.8 % of patients with early (<24 h) surgery showed a ≧2 grade improvement in ASIA Impairment Scale (AIS) grade compared to 8.8 % in the late decompression group (OR 2.57, 95 % CI 1.11, 5.97) at 6 months post injury. In addition, in the multivariate analysis adjusted by preoperative neurological status and steroid administration, the odds of at least a 2-grade AIS improvement were 2.8 times higher in patients who underwent early surgery (OR 2.83, 95 % CI 1.10, 7.28).

Of note, in the analysis of the prospective randomized controlled data in 1997 by Vaccaro et al. [39], no significant neurological improvement was seen in patients with decompression performed within 72 h as compared to patients with a longer wait prior to surgery (>5 days). Indeed, the negative result in the Vaccaro trial stimulated the design of the STASCIS study, which used a much narrower time window (<24 h) to define early decompression.

Length of Hospital Stay

In the latest meta-analysis in 2013, performed by van Midderndorp et al., patients who underwent early spinal surgery had hospital stays that were shorter by 10 days than patients with later treatment [42••]. However, this issue remains controversial.

Vaccaro et al. reported an increased cost in the late-surgery group (>72 h) due to greater length of stay in an acute care hospital setting [39]. Patients in the early-surgery group spent an average of 1.8 and 17.7 days before and after surgery, respectively, in acute hospital care and 51.1 days in rehabilitation hospital care. On the other hand, patients who underwent late surgery spent 16.8 and 18.5 days before and after surgery, respectively, in acute hospital care and 51.5 days in rehabilitation hospital care. McKinley et al. have reported that early surgery is associated with shorter acute and total hospitalization ($P < 0.05$) [34]. However, there was no difference in the length of stay in rehabilitation.

In another study, Wilson et al. reported no significant difference in the average length of acute hospital stay between the early (24.9 days)- and late (24.7 days)-surgery groups ($P = 0.97$) [27••]. This likely reflects issues with access to early rehabilitation in the Canadian system—an issue which was examined closely after publication of the STASCIS paper. The mean length of rehabilitation stay also showed no difference between groups in the average length stay between the early (102.9 days)- and late (80.2 days)-surgery groups ($P = 0.10$). Liu et al. reported that there was no statistical difference between groups with respect to ICU stay, while the length of hospital stay was significantly longer in patients in the late group (15.4 vs. 18.3 days, $P < 0.001$) [24].

Relationship of Other Complications with the Timing of Surgical Intervention

In the past, the issue of whether early surgery increases or decreases the rate of complications in patients with SCI was a topic of intense debate and controversy. The majority of patients with severe neurological deficits and/or other trauma are in danger of subsequent complications due to cardiorespiratory compromise or other organ dysfunction. Several investigators have argued against surgery, especially early intervention, in these critically ill patients due to higher risk of complications secondary to an invasive surgery [43–45] However, advocates for early surgery note that it allows early mobilization and could reduce the occurrence of complications caused by prolonged recumbence and by allowing earlier mobilization, pulmonary toilet, and physical therapy [46, 47].

Two previous papers reported no difference in complication rates [48, 49]. In a large-scale prospective study of 2204 cases by Waters et al., similar complication rates were reported for patients with non-operative treatments and those who underwent surgery [48]. Kerwin et al. similarly reported no significant difference regarding the incidence of pneumonia in early (<72 h)- and late-surgery groups (21.8 vs. 25.6 %) [49]. The mortality was higher in the early surgical intervention group (6.9 vs. 2.5 %), in this study, although this did not reach statistical significance.

However, despite the evidence from these two studies, the majority of recent papers report a lower rate of complications after early surgical intervention. Duh et al. reported a lower rate of complications in patients with early intervention (<24 h) compared with those with later intervention [50]. McKinley et al. reported lower rates of pneumonia and atelectasis, with 34.6 % of patients with early decompression experiencing such complications (<72 h) compared to 45.4 % of patients with delayed surgery [34]. Bourassa-Moreau et al. reported the risk factors for complications using a multivariate logistic regression model to examine data from the acute phase hospitalization of SCI in 431 patients [47]. Earlier surgical intervention (<24 and 72 h) was a significant predictor of the global rate of complications, the rate of pneumonias, and pressure ulcers. In another retrospective study (191 patients) by Bourassa-Moreau et al., later surgical intervention (>24 h) was a predictor of pneumonia, urinary tract infection, and total complications [46]. In the STASCIS (a prospective large-scale non-randomized study), a non-significant decrease in the global complication rate was observed in the early (<24 h) surgical intervention group (24.2 vs. 30.5 % in early and late groups, respectively) [26••]. Overall, these results indicate that the weight of the evidence suggests a reduction in complications with early surgical intervention. Moreover, early surgery is associated with improved neurological outcomes.

Systematic Review of the Current Literature on the Role of Decompression in Acute SCI

La Rosa et al. [4]

Early decompression resulted in statistically better outcomes compared with both conservative ($P < 0.001$) and late management ($P < 0.001$). However, analysis of homogeneity showed that only the evidence regarding patients with incomplete neurological deficits who had early surgery was reliable.

Fehlings et al. [41]

Early decompression (<24 h) resulted in statistically better clinical outcomes compared to both delayed decompression

and conservative treatment. Emerging evidence has shown that early surgery (<24 h) may reduce length of intensive care unit stay and post-injury medical complications.

Furlan et al. [22•]

Patients who underwent early surgical decompression were found to have similar outcomes to patients with a delayed decompression. However, several findings within this review suggested that early surgical intervention is safe and feasible and that it may improve neurological outcomes and reduce health care costs. This study recommended that early surgical intervention should be considered in all patients from 8 to 24 h following acute traumatic SCI.

van Middendorp et al. [42••]

Early spinal surgery was significantly associated with a higher total motor score improvement (weighted mean differences (WMDs): 5.94 points, 95 % confidence intervals (CIs):0.74, 11.15), neurological improvement rate (OR 2.23, 95 % CI 1.35, 3.67), and shorter length of hospital stay (WMD: −9.98 days, 95 % CI −13.10, −6.85). In addition, patients with early surgical intervention had a lower risk of developing pulmonary complications, for example, pneumonia and atelectasis. However, this evidence supporting early spinal surgery after SCI is not considered strong due to the heterogeneity both within and between the original studies reviewed.

Conclusion

Several large multicenter studies and systematic reviews have indicated the efficacy of early surgical decompression after SCI, although it is difficult to definitively conclude the superiority of early surgical intervention due to a background of heterogeneous injuries and surgical practices. Further support for early decompression comes from the results in animal studies, the majority of which have provided supportive evidence that early surgical decompression of the spinal cord improves histological and neurological outcome after SCI. Overall, the evidence indicates that early surgical decompression in the setting of SCI is a feasible treatment which facilitates neurological improvement, reduces the length of hospital stay, and results in fewer postoperative complications.

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Compliance with Ethics Guidelines

Conflict of Interest Drs. Nakashima, Nagoshi, and Fehlings declare that they have no 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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