Journal of Clinical Orthopaedics and Trauma 35 (2022) 102043

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

Time is spine: What's over the horizon

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A R T I C L E I N F O

Article history:
Received 10 August 2022
Received in revised form
13 September 2022
Accepted 18 October 2022
Available online 22 October 2022

Keywords:
Early decompressive surgery
Outcomes
Surgical timing
Traumatic spinal cord injury

A B S T R A C T

The overarching theme in the early treatment of acute spinal cord injury (SCI) is to reduce the extent of secondary damage to facilitate early neurological and functional recovery. Although multiple studies have brought us innovative and potential new therapies to treat SCI, ameliorating neural damage remains a formidable challenge. Knowledge translation of clinical and basic research studies has shown that surgical intervention is a valuable treatment modality; however, the role, timing and optimal technique in surgery remains a topic of great controversy. While evidence to support the concept of ultra-early surgery for acute SCI continues to emerge, current protocols and international guidelines that encourage reducing time from trauma to surgery support the concept of “Time is Spine”. The present article provides a critical narrative review of the current best practice, with a particular focus on the timing of surgical intervention, which shapes our understanding of how time is of the essence in the management of acute SCI.

1. Minding the gap: The burden of SCI and rationale for early surgical decompression

The collective effort to understand the ideal treatment for spinal cord injury (SCI) has spanned many centuries of controversies. Since its first recording from the Egyptian Edwin Smith papyrus until the modern times, acute SCI has remained a catastrophic event with profound impact on an individual, their family, and society. Data from the global burden of the disease study reports a prevalence of 0.93 million cases of SCI in 2016 with an age-standardized incidence rate of 13 per 100,000 population.[1] SCI is a significant contributor to long term disability and dependency on caregivers.[2] An estimated 20–30% of people with a SCI show clinical signs of depression, which may in turn negatively impact the prospect of recovery and overall health.[3] Finally, the combined motor and sensory deficits, in addition to neurogenic sphincter dysfunction, exert an enormous cost to one's quality of life and ability to function independently and productively. Such figures serve to highlight the tremendous physical, functional and financial toll of this disease condition.

Our current understanding of the pathophysiology of SCI highlights the existence of both primary and secondary injury leading to a cascade of neuronal, axonal and endothelial dysfunction in the spinal cord.[4] Primary mechanisms refer to the initial rapid cord compression as a result of fracture, which initiates a cascade of pathobiological changes that contribute to secondary injury. Secondary mechanisms, on the other hand, refer to reversible changes that may induce further insults to the spinal cord such as hemorrhage, edema, vasospasm, ischemia, excitotoxicity and apoptosis.[5] In cases of SCI, further neural tissue destruction is perpetuated by persistent compression against an unyielding spinal canal. In this situation, expeditious decompression to relieve the spinal cord has been shown to improve long-term neurological and functional outcomes in animal and clinical studies.[6]

2. The genesis of the management principle: “Time is Spine”

The landmark STASCIS (Surgical Timing in Acute Spinal Cord Injury) trial published in 2012 was pivotal in ushering in a new era in spine surgery with emphasis on early intervention for SCI. This was a multicenter, nonrandomized, prospective cohort study that enrolled a total of 222 adult patients with cervical SCI from six North American centers. The authors demonstrated a significantly greater proportion of patients (19.8%) who underwent early surgery (<24 h) attaining a 2-or-more grade improvement in ASIA score at 6 months compared to patients receiving late surgery (8.8%).[7] This treatment effect persisted even after adjustment for

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https://doi.org/10.1016/j.jcot.2022.102043
0976-5662/

preoperative neurological status and steroid administration (OR 2.83, 95% CI 1.10–7.28). These findings fostered a new worldview aptly encapsulated in the aphorism *"Time is Spine"*, which emphasizes the crucial time element in managing these patients.[8] Since then, the attitude towards SCI treatment, which historically has been nihilistic, has changed dramatically in favor of early and timely surgery. The public's view was likewise transformed with heightened awareness of SCI and its available therapy, as well as demand for specialist urgent care. In an effort to amalgamate the current body of knowledge and standardize spine trauma care, the joint commission of AO Spine North America and AO Spine International issued its recommendation regarding timing of surgery in 2017.[9] This was based on a comprehensive evaluation using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process with a multidisciplinary supervising team. Based on the best evidence assessment, a recommendation that adult patients with SCI be offered early surgery (<24 h post SCI) regardless of level and severity of injury was suggested.

3. Emerging evidence for early surgical decompression in SCI

Contemporary methods in data mining have worked to further strengthen the evidence of early surgery in SCI. For example, a pooled analysis of individual patient data was recently published using 4 large SCI databases from North American spine centers.[10] Using data harmonization and meta-analysis tools, this study of 1548 patients with SCI further substantiated a strong argument in favor of early surgical intervention after injury. Patients with early decompressive surgery within 24 h had improvements in ASIA motor scores by 23.7 (95% confidence [CI]: 19.2–28.2) and better AIS grades (crude odds ratio [cOR] 1.48; 95% CI: 1.16–1.89; $p = 0.0019$), signifying less severe impairment, as compared to patients undergoing late surgery (>24 h).[10] Additionally, the study provided deeper insight into surgical timing in SCI by demonstrating an interesting time-dependent relationship of motor change with the greatest prospect of recovery if surgery is performed within the 24–36-h period. To date, the statistics accrued in this study represent the largest and highest quality of evidence supporting the practice of early surgery for acute SCI. Additional benefits of early surgery, in terms of reducing complications after SCI, were described by Balas et al.[11] Using data from 4108 patients from the American College of Surgeon Trauma Quality Improvement Program (TQIP), the odds of major complications and immobility-related hospital events were observed to be significantly lower in the early surgery group (<12 h). The same significant pattern emerged for total hospital and ICU length of stay, with lower values in the early surgery group as compared to those in the delayed surgery cohort.

As more emphasis is given to evidence-based medicine, it is highly likely that the future of SCI research will continue to harness new ways of obtaining data while maintaining the highest degree of precision and accuracy using unbiased study designs. To this end, randomized controlled trials (RCTs) on the timing of surgery will play a key role despite having their own set of logistical and financial challenges. Recently, progress has been made on this aspect with the publication of results of an SCI trial from Iran involving patients with traumatic thoracolumbar injuries.[12] This RCT enrolled a total of 73 patients with T1-L2 traumatic SCI over the span of 8 years and randomized patients into either an early (<24 h) or late (24–72 h) surgery group. At 12 months follow-up, the authors reported a significantly higher number of patients in the early group (24.3%) reaching a $\geq$2-grade improvement in AIS than in the late surgery group (5.6%) (OR 5.46, 95% CI: 1.09–27.38, $p = 0.025$). Modern methods of knowledge synthesis will also be important in reinforcing the concept of time is spine with the end goal of helping to establish best practices in the field while reducing variations in healthcare delivery. The AO Spine Foundation, in partnership with the Praxis Spinal Cord Institute, is currently in the process of re-examining the evidence that has accumulated since 2017, which favours early intervention for SCI. The result of this joint effort is expected to provide the most up to date guideline on this topic using a exhaustive systematic review process to critically appraise the current body of spine literature.

4. Barriers to early surgery

Despite the burgeoning evidence on the safety and efficacy of early surgery for SCI, hospital reviews show that less than 50% of patients with a SCI in North America receive the recommended early treatment after traumatic SCI.[13–15] Moreover, survey results reveal a higher probability of being operated within 24 h when admitted to academic teaching hospitals.[16] Unfortunately, this represents a discord in knowledge translation, as the majority of surgeons were shown to be knowledgeable of the advantage of early surgery as shown in a survey done in 2017.[17] This fact brings to surface several administrative factors that need to be addressed to increase the proportion of patients receiving early surgery. The study of Thompson and associates highlighted this issue by enumerating various barriers to early surgery, which include transfer delay to SCI centers, delay before surgical plan completion and waiting time for the operating room.[18] Currently, efforts are underway to understand the worldwide diversity of spine practice, including the timing of surgery and barriers to SCI, with the goal of forging an inclusive policy recommendation across a global organization.[19] There is a growing need for high quality spine trauma studies with global perspective to help bring forward some efforts towards capacity building in low- and middle-income countries (LMICs), where a disproportionately higher number of trauma patients abound.

5. A closer look into central cord syndrome

The positive impact of early surgery in SCI is especially demonstrated in a subset of patients with central cord syndrome. In fact, the advancement in our understanding of the role of early surgery in SCI parallels the remarkable evolution in the way we manage patients with this condition. Dubbed as the most common type of incomplete SCI type, the rate of CCS is predicted to continuously rise with the aging population and in this specific subgroup, early surgery is shown to result in better outcomes and recovery.[20] A recent position paper supports and recommends surgery within 24 h in this specific subgroup of trauma patients.[21]

The traditional concept that central cord syndrome is largely a non-surgical case in favor of its excellent outcome, even with non-operative treatment, has failed to withstand the test of time. While the current body of knowledge is limited due to a lack of good quality randomized studies, two recent syntheses of the literature regarding surgery for CCS were published by The Spine Trauma Study Group and AO Spine Knowledge Forum Trauma in favor of surgery, as it is associated with earlier improvement in neurologic status, shorter hospital stay, and shorter intensive care unit stay.[22,23] Additionally, a contemporary distillation of evidence using three large multi-center datasets of patients with CCS challenges the status quo by revealing a favorable outcome in upper limb function after early surgical intervention (<24 h) in patients with CCS.[24] Moreover, the trajectory of recovery in these patients generally follows the same patterns observed in other forms of incomplete cord syndrome, showing a trend towards good functional outcome after early decompressive surgery.[25]

6. Establishing the ideal time cut-off

A significant number of research studies related to early surgery in SCI have been directed towards discovering the most optimum time cut-off of urgent decompression in order to promote maximal neural repair and functional recovery (Table 1). These clinical studies have published heterogenous time limits, and their results have stirred issues on real-world pragmatic application and uncovered potential barriers to early specialty care. In reality, there likely is no arbitrary time cut-off. It is recognized that the secondary injury events after acute traumatic SCI are time dependent. Early decompression of the injured spinal cord can mitigate these secondary injury cascades. However, the logistics of achieving safe, effective early surgical intervention must be balanced with the need to personalize the management for each individual patient. With an aging demographic, many of whom have significant medical comorbidities, in the neurotrauma population, the ideal goal of early surgery needs to be balanced against the medical realities of managing the individual patient.[26]

Against the traditional target limit of 24 h, the benefits of an "ultra-early" surgery, defined as surgery within 8–12 h after trauma, has been explored in several observational studies. Two of the most recent publications on this topic described neurologic recovery between two groups of patients receiving ultra-early (<8hrs) versus early intervention (8–24 h). Lee et al. compared functional outcomes in 56 patients who sustained a SCI and underwent surgery in a single center in Korea.[27] At a minimum of 6 months follow-up, patients who received early surgery showed a statistically significant improvement in AIS grade compared to patients in the late surgery group ($p = 0.018$). Additionally, a disproportionately higher rate of improvement was observed among patients with incomplete SCI. With regards to functional outcome, Wutte et al. evaluated the impact of surgery within 8 h of injury using the Spinal Cord Independence Measure (SCIM) in 43 patients who sustained a thoracic SCI.[28] Despite a stronger trend towards more clinically complete SCI syndrome and more severe AIS grade ($p < 0.057$), patients receiving surgery within 8 h displayed higher SCIM scores in bladder and mobility function ($p < 0.045$ and $p < 0.019$, respectively) compared to patients undergoing late intervention.[28]

Alternatively, using the 12-hr surgery cut-off, two recent studies showed benefits of early aggressive intervention in SCI patients. In a retrospective cohort of 48 patients with cervical SCI, investigators from the University of California-San Francisco compared the neurological outcome between patients assigned to ultra-early (<12 h, n = 18), early (12–24 h, n = 17) or late (>24 h, n = 13) surgery subgroups.[29] After adjusting for preoperative confounders such as age, sex, injury severity score and length of stay, the authors showed that patients who received surgery within 12 h after presentation improved 1.3 AIS grades on average as compared to 0.5 in the 12–24 h group at hospital discharge ($p = 0.02$). Additionally, 88.8% of patients with AIS grade A converted to a higher grade in those who received surgery within 8 h compared to 38.4% in the 12–24 or >24 h surgery groups ($p = 0.054$). Lastly, a single center prospective cohort from Italy evaluated 81 patients with cervical SCI and compared the neurologic outcome in two subgroups of patients undergoing ultra-early (<12 h) and early surgery (12–48 h).[30] A higher rate of postoperative neurological recovery was observed in patients within the ultra-early surgery group, as evidenced by a greater degree of AIS score improvement ($p = 0.009$) compared to the early subgroup. It is interesting to note that the SCI-POEM, a large European multicenter study involving adult patients with SCI has completed enrollment and the results are highly anticipated to give guidance on the efficacy of early surgical decompression with a <12 h threshold.[31]

At the opposite end of the spectrum are studies that advocate for a longer allowable time period for decompression and stabilization after SCI. Thresholds of up to 48 h (late) or 72 h (delayed) are described in the literature. In a study by Kim and colleagues, for example, patients receiving surgery up to 48 h were shown to achieve statistically significant AIS improvement at 6 months compared to those treated at a longer time duration.[32] Aarabi et al., on the other hand, showed no significant difference in neurologic recovery in patients who were operated up to 72 h from injury.[33] While these views offer a more relaxed perspective against the traditional concept of "early" surgery, it nevertheless provides an

Table 1
Overview of selected key studies on early surgery after spinal cord injury.

First Author	Publication year	Region	Number of patients	Study design	Timing of decompression	
					Early (hr)	Late (hr)
Studies with <24 h cut-off						
Fehlings[7]	2012	North America	222	Prospective Observational	<24	>24
Wilson[38]	2012	Canada	55	Prospective Observational	<24	>24
Rahimi-Movaghar[39]	2014	Iran	35	Randomized controlled trial	<24	24–72
Umerani[40]	2014	Pakistan	98	Prospective Observational	<24	>24
Bourassa-Moreau[41]	2016	Canada	53	Prospective Observational	<24	24–72
Du[42]	2018	China	711	Prospective Observational	<24	24–72
Sewell[43]	2018	UK	95	Retrospective observational	<24	>24
Mayol[44]	2019	Puerto Rico	45	Retrospective observational	<24	>24
Qadir[45]	2020	Pakistan	317	Retrospective observational	<24	>24
Studies with <12 h cut-off						
Dobran[46]	2015	Italy	57	Retrospective observational	<12	12–72
Aarabi[47]	2017	USA	100	Retrospective observational	<12	>12
Burke[29]	2019	USA	48	Retrospective observational	<12	12–72
Nasi[30]	2020	Italy	81	Retrospective observational	<12	12–48
Aarabi[35]	2020	USA	72	Retrospective observational	<12	12–138.5
Studies with <8 h cut-off						
Cengiz[48]	2008	Turkey	27	Quasi-randomized controlled trial	<8	72–360
Jug[49]	2015	Slovenia	42	Prospective Observational	<8	8–24
Grassner[50]	2016	Germany	70	Retrospective observational	<8	>8
Lee[27]	2018	Korea	56	Retrospective observational	<8	8–24
Wutte[28]	2019	Germany	43	Retrospective observational	<8	>8

appealing bailout option suitable in resource-challenged settings or in situations where other medical and surgical reasons preclude early spine intervention. Until stronger evidence from large clinical trials is available, however, the implication of these studies remains limited and at best offers further proof of the existing widespread practice variation in this aspect of spine care.

Indeed, all the studies described thus far on ultra-early and early surgery provide promising and encouraging results. However, it must be acknowledged that this body of evidence is highly limited by the small number of patients and observational single-center study designs. A recent meta-analysis of all studies on timing of surgery for SCI over the last decade echoes this concern. The authors warned that despite their meta-regression analysis showing that the cut-off of 8 or 12 h is associated with the greatest benefit across all 26 studies included in the review, there is an overwhelming paucity of high-quality data that precludes extraction of meaningful recommendations.[34] Therefore, it is clear that this topic remains understudied in the spine literature and will remain an attractive research focus over the horizon. It demonstrates that the ideal timing in SCI surgery remains a moving target requiring more detailed dissection and in-depth investigation. It is imperative that each proposed time cut-off is enriched by high quality data to support sound clinical decision-making among spine surgeons. Recommendations geared towards resolving this issue must strike a balance between biologic plausibility and clinical feasibility in the face of worldwide challenges known to cause pre-hospital and in-hospital delays for spine care.

7. Timing of surgery in SCI: Quo Vadis?

The precise appraisal of a surgical therapeutic window for neurologic and functional improvement after SCI is fundamental in establishing an optimal treatment recommendation and clinical guideline. Unfortunately, the accurate definition of “early” surgical decompression has been challenging to establish because of the different cut-off points recommended and the low level of evidence that supports these studies. Despite these varied findings, the application of early decompressive surgery remains a valid and effective treatment to reduce secondary injury mechanisms after SCI.

The timing of surgery is only one aspect in the multi-faceted complex care of patients with SCI. For the field to continue to advance and mature towards a personalized platform, a few unsolved issues need to be addressed including a greater understanding of ways to integrate surgical timing within the emerging paradigm of advanced imaging biomarkers and innovative surgical strategies. A growing body of evidence, for example, suggests that the extent of decompression also plays a crucial role in functional and neurologic recovery in patients receiving early decompressive surgery. In a study of 72 patients with cervical SCI, researchers from Maryland evaluated the outcomes in three groups of patients receiving ultra-early (<12 h), early (12–24hrs) and late (>24 h) surgery.[35] Interestingly, the results showed that AIS improvement did not differ significantly between groups and only the length of the spinal cord intramedullary lesion (IMLL) was predictive of neurologic improvement in a multiple regression analysis. Consequently, the findings of this study underscore the significant role of adequate decompression, more than timing of surgery, in attaining good functional and neurologic recovery after SCI. Additionally, future work is needed to identify the best approach in surgical decompression and whether the use of adjunct intraspinal pressure monitoring and routine postoperative MRI is necessary and cost-efficient in these patients. A new salvo of evidence suggests that bony decompression might be inadequate, advocating the use of expansile duraplasty and/or insertion of an intradural catheter analogous to neurosurgical interventions in traumatic brain injury.[36] Extensive studies led by a UK-based team have emphasized the importance of recognizing the consequences of SCI-induced spinal cord swelling and the appropriate application of therapy based on spinal cord perfusion pressures (SCPP) to optimize autoregulation ($SCPP_{opt}$).[37] These groundbreaking studies revealed that $SCPP_{opt}$ varies widely between patients, which leads to the concept of individualized and targeted perfusion management. It is within this context that spinal pressure monitoring is advocated as a guide to surgical therapy for SCI patients in order to prevent the adverse ramifications of cord malperfusion. The programmed implementation of the DISCUS (Duroplasty for Injured Cervical Spinal Cord with Uncontrolled Swelling) trial hopes to shed light further on this novel concept by exploring the role of duraplasty in improving the outcomes of SCI patients along with a preplanned mechanistic sub-study to determine the utility of multimodality monitoring in boosting spine critical care.[36]

In summary, early decompression after SCI remains fundamental in the practice of spine surgery and shows no sign of being taken over by alternative viewpoints given its strong support from pre-clinical and clinical studies. The battle to improve neurologic and functional outcomes in SCI patients will remain futile unless significant improvements are seen in reducing time from trauma to surgery after injury. Further refinement in the definition of “early” surgery with consideration of real-world scenarios and existing limitations will improve safety and efficacy of surgery in this patient population. With still numerous unsettled issues, however, the race against time to save the injured spinal cord provides a promising future research direction and should be given high priority in further studies.

Funding statement

No funding was received for this work.

Disclosure Statement

The authors have no relevant conflicts to declare.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

MGF would like to acknowledge support from the Robert Campeau Family Foundation/Dr. C.H. Tator Chair in Brain and Spinal Cord Research at UHN.

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