Elevated intraspinal pressure in traumatic spinal cord injury is a promising therapeutic target

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Abstract

The currently recommended management for acute traumatic spinal cord injury aims to reduce the incidence of secondary injury and promote functional recovery. Elevated intraspinal pressure (ISP) likely plays an important role in the processes involved in secondary spinal cord injury, and should not be overlooked. However, the factors and detailed time course contributing to elevated ISP and its impact on pathophysiology after traumatic spinal cord injury have not been reviewed in the literature. Here, we review the etiology and progression of elevated ISP, as well as potential therapeutic measures that target elevated ISP. Elevated ISP is a time-dependent process that is mainly caused by hemorrhage, edema, and blood-spinal cord barrier destruction and peaks at 3 days after traumatic spinal cord injury. Duraplasty and hypertonic saline may be promising treatments for reducing ISP within this time window. Other potential treatments such as decompression, spinal cord incision, hemostasis, and methylprednisolone treatment require further validation.

Key Words: blood-spinal cord barrier; decompression; duraplasty; durotomy; edema; hemorrhage; intraspinal pressure; myelotomy; spinal cord injury; therapeutic target

Introduction

In recent years, the number of patients with traumatic spinal cord injury (tSCI) has remained high due to the high incidence of traffic injuries and injuries caused by falling from a height. tSCI often causes long-lasting and irreversible changes in sensory, motor, and autonomic function, but also leads to reduced quality of life and increased paralysis and mortality rates (Hagen et al., 2010; Parra-Villamar et al., 2021; Zhang et al., 2021). An estimated 40 people per million per year are affected by tSCI in the United States alone (Cripps et al., 2011), and tSCI has become a serious social problem. However, no widely accepted therapeutic methods are available to attenuate and reverse tissue injury and enhance functional recovery after severe tSCI. The primary reasons for the poor understanding of tSCI and the failure to develop effective treatments are the complex characteristics of pathophysiological consequences of, and abundant inconsistencies in, outcomes after tSCI. A deeper understanding of the pathophysiological mechanisms that lead to the damage seen following tSCI is required.

Studies have shown that tSCI involves both the primary injury caused by immediate violence and the secondary injury process caused by amplification of a cascade of multiple cellular and molecular sequelae; the secondary injury process is considered to be reversible, and thus is frequently regarded as a potential therapeutic target. The trigger point of secondary injury is hemorrhage caused by the etiology and progression of elevated ISP, as well as potential therapeutic measures that target elevated ISP. Elevated ISP is a time-dependent process that is mainly caused by hemorrhage, edema, and blood-spinal cord barrier destruction and peaks at 3 days after traumatic spinal cord injury. Duraplasty and hypertonic saline may be promising treatments for reducing ISP within this time window. Other potential treatments such as decompression, spinal cord incision, hemostasis, and methylprednisolone treatment require further validation.

Key Words: blood-spinal cord barrier; decompression; duraplasty; durotomy; edema; hemorrhage; intraspinal pressure; myelotomy; spinal cord injury; therapeutic target

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decrease in ISP (Ghasemi and Behfar, 2016; Aarabi et al., 2019). However, this type of surgery does not sufficiently alleviate elevated ISP caused by dural compression (Wendle et al., 2014; Phang et al., 2015), which leads to persistent spinal hypoperfusion and secondary injury progression in tSCI patients. Here, we review recent developments regarding the components and pathophysiological mechanisms associated with elevated ISP and the potential contribution to the secondary damage caused by elevated ISP.

**Literature Search**

In this narrative review, an electronic search was performed using the Web of Science and PubMed databases to identify any studies published before May 2021. The Medical Subject Headings (MeSH) that were used in the search included “intraspinal pressure,” intramedullary pressure, intrathecal pressure, spinal compartment syndrome, edema, spinal cord injury, blood spinal cord barrier, hemorrhage, and hematoma”. The references in the studies obtained from this search were also manually screened to identify any other relevant studies. The identified articles were then used to conduct our review.

**Components Causing Elevated Intraspinal Pressure**

**Hemorrhage and hematoma**

Mechanical disruption of the microvasculature causes initial bleeding following primary tSCI. Subsequently, secondary petechial hemorrhage formation occurs in the spinal parenchyma surrounding the primary lesion, and these hemorrhages have been shown to be related to aggravation of the lesion (Gerzanich et al., 2009). Spinal cord hemorrhage was found in 85% of subjects with complete motor deficits and 21% of subjects with incomplete motor injuries (Flanders et al., 1996). Furthermore, blood infiltration caused by destruction of the BSCB is an important cause of hematoma in the spinal parenchyma. Petechial hemorrhage is thought to be one of the triggers of secondary tSCI (Jing et al., 2014; Sato et al., 2014; Hu et al., 2015). Spinal cord hemorrhage was shown to be persistently high for at least 28 days based on C14-protein peroxidase testing indicated that it was restricted to the first 2 weeks after injury (Noble and Wrathall, 1987, 1988). This difference may be due to variation in the BSCB permeability for molecules of different sizes.

**Edema**

Spinal cord edema includes cytotoxic (cell swelling) and vasogenic (leaky capillaries) edema characterized by excessive accumulation of water intracellularly and interstitially in tissue. Cytotoxic edema is mainly due to Na/K ionic imbalance, increased calcium influx, free radical production, excitotoxicity caused by blood cell infiltration, ischemia, and hypoxia (Alizadeh et al., 2019). Vasogenic edema is mainly related to the disruption of the BSCB, leading to leakage of water molecules, albumin, and dextran. Furthermore, accumulating evidence has shown that AQ4P, a molecular water channel that is expressed at high levels in astrocytic endfeet in the spinal cord, which is triggered by perinatal ischemic insults (Ringer et al., 1995; Nielsen et al., 1997; Nesci et al., 2010), is the main regulator of water flow into and out of the injured cord and can cause vasogenic (Kimura et al., 2010) and cytotoxic edema (Saadoun et al., 2008).

To date, several studies have reported that excessive AQ4P expression within 72 hours of tSCI is associated with increased spinal edema (Liu et al., 2015; Yu et al., 2015), and that decreased AQ4P function correlates with improved functional recovery after tSCI (Jing et al., 2014; Sato et al., 2014; Hu et al., 2015). Spinal cord edema is thought to contribute to reduced blood flow and exacerbated ischemia (Tator and Fehlings, 1991). Low blood flow perfusion will result in different levels of insult to gray and white matter, which may lead to delayed cell death. Owing to the high metabolic demands of neurons, the gray matter is particularly sensitive to ischemic injury.

**Blood-spinal cord barrier disruption**

The BSCB is formed by a significant difference in structure between the spinal cord and peripheral vasculature. Endotheliocytes, intercellular connections, pericytes, the basement membrane, and astrocytic foot process cells and structures, which form the BSCB, are responsible for regulating molecular exchanges and protecting the spinal parenchyma from toxins of the BSCB (Jin et al., 2021). Among these elements, endotheliocytes play a key barrier role because of their nonfenestrated cell membranes, high level of cytosolic mitochondria, absence of pinocytic vacuoles, and formation of tight and adherens junctions (Bartanusz et al., 2011).

Although the structures of the BSCB and blood-brain barrier (BBB) are analogous, the permeability of the BSCB is different from that of the BBB. Research based on assessing the uptake of radioactive tracers in the central nervous system (CNS) showed that the BSCB is more permeable than the BBB (Prockop, 1995). A study by Pan et al. (1997) suggested that the cervical region had the highest permeability for radiolabeled interferons (interferons α and γ) and that the permeability was highest in the peripheral region of the brain. Interestingly, any given region exhibited different levels of permeability for different cytokines, and this selective permeability may contribute to complex CNS injuries (Daniel et al., 1981). The destruction of the BSCB is accompanied by abnormal leakage of blood-borne molecules and cells, albumin dextran, and water molecules and infiltration of immune cells into the spinal cord parenchyma, which leads to vasogenic edema, reactive astrogliosis, demyelination, and scar formation (Wagner and Stewart, 1981; Ankeny and Popovich, 2009). Goodman et al. (1976) demonstrated that endothelial tight junctions in the gray matter were impaired as early as 15 minutes following primary injury. Matsushita et al. (2015) used imaging and spectrophotometric quantification of Evans blue (EvB) content to show that the permeability of the BSCB was greatly increased at 1 and 3 days post-injury in the injury epicenter of a contused SCI model and reached the peak at 1–2 weeks; however, the permeability began to increase at 2 weeks after SCI in rostral and caudal segments and peaked at 6 weeks, leading to a biphasic increase in total permeability and leakage lasting until the 12th week after SCI (Matsushita et al., 2015). This phenomenon was explained by the delayed degeneration of ascending and descending tracts after SCI, which may be related to the increased permeability of the vasculature far from the injured epicenter or the self-repair process of the vasculature (Matsushita et al., 2015). Abnormal permeability was shown to be persistently high for at least 28 days based on C14-manganese perfusion testing (Poirier et al., 1996), whereas horseradish peroxidase testing indicated that it was restricted to the first 2 weeks after injury (Noble and Wrathall, 1987, 1988). This difference may be due to variation in the BSCB permeability for molecules of different sizes.
Elevated ISP monitoring was first mentioned by Allen in 1991 and was first used in a dog model in 1995 and in human patients in 2014. Since then, 50 related articles have been published (Figure 2), including 16 animal studies, 23 clinical studies, eight reviews, and three case reports. In particular, the Saadoun and Papadopoulos teams from London University have published 46 articles pertaining to this research field, including one animal study, 18 clinical studies, and four reviews.

Elevated ISP was first mentioned by Allen (Figure 2) who described how, after a median longitudinal incision was made after the early stage of TSCI in dogs, there was “great outpouring of blood from the injured area”. Furthermore, he reported that, in a patient with TSCI who underwent surgery 4 hours after injury, “when the spinal cord was incised, the blood spurted out as if subjected to great pressure” (Allen, 1911). The first use of ISP monitoring was in a hybrid dog model, as reported by Allen et al. (1983). ISP of 30 ± 12 mmHg at C5 (Juda and Tachibana, 1995). Saadoun et al. (2008) used a Millar pressure catheter to show that the normal intramedullary pressure was 8 ± 3 mmHg at the T6 level in mice. Later, Soubeyrand et al. (2013) inserted a pressure transducer catheter into the sacral subarachnoid space of rats and found that the ISP was 5.5 ± 0.5 mmHg in normal rats vs. 8.6 ± 0.4 mmHg in rats with a contusion at T10. In addition, they demonstrated that the ISP increased when the head was elevated (Soubeyrand et al., 2013).

Subsequently, in a clinical study, Werndle et al. (2014) reported an elevated ISP of approximately 20 mmHg at 24 hours following injury compared with approximately 10 mmHg in control patients without spinal cord pathology measured by Codman probe monitoring. They suggested that ISP waveforms are similar to ICP waveforms of three components: ISP within 5 h post-injury, whereas edema became the primary cause of elevated ISP at 3–7 days in a balloon compression model in rabbits.

### Dura and pia mater

Analogous to the closed spaces that contribute to TBI and other cranial compartment syndrome, the tough and nondilated dura mater is the basis of maintaining elevated ISP. Studies have shown that ISP remains high after only anterior and posterior bony decompression (Werndle et al., 2014; Saadoun and Papadopoulos, 2020), and spinal cord herniation occurred immediately after the dura was opened in a dog model (Saadoun and Jeffery, 2021) and in a patient with traumatic thoracic SCI (Grassner et al., 2017).

In a prospective clinical trial, bony supplementary dura mater decompression significantly reduced ISP and increased spinal cord perfusion pressure (SCPP) compared with bony decompression alone (Phang et al., 2015a). These results suggest that the dura contributes to cord compression.

The role of the relatively firm pia mater in elevated ISP, however, remains controversial. In patients with severe TSCI, the swollen spinal cord was found to occlude the subarachnoid space after anterior bone compression on MRI (Aarabi et al., 2019). Furthermore, simultaneously measured pressures in the subarachnoid space and spinal parenchyma were elevated and equal (Phang and Papadopoulos, 2015b). These findings suggest that, after severe TSCI in humans, the pia mater no longer confined the swollen spinal cord. However, in a rabbit model of compressive SCI, durotomy with myelotomy significantly reduced ISP and improved histological outcomes compared with durotomy without myelotomy (Khaing et al., 2021). This result suggests that the pia mater may restrict spinal cord expansion and increase pressure within the spinal cord parenchyma.

### Epidural components

In addition to intradural factors, the contribution of epidural components, including the narrow bony spinal canal, ossified ligamentum flavum, posterior longitudinal ligament, and herniated intervertebral disc, to elevated ISP should not be ignored. These components often cause dural sac compression and cerebrospinal fluid circulation block as shown by T2-weighted MRI, especially in some elderly patients with traumatic cervical SCI. Although there is no pressure-monitoring comparison for this type of patient, some studies have shown that early epidural decompression can achieve significant radiological results and functional recovery for such patients, which may indicate that epidural decompression can partially reduce ISP (Piazza et al., 2018; Aarabi et al., 2019).

### Monitoring intraspinal pressure

Elevated ISP monitoring was first mentioned by Allen in 1991 and...
Elevated ISP impairs vascular autoregulation and decreases perfusion of the contused spinal cord (Soubeyrand et al., 2013). Analogous to brain perfusion, SCPP is computed as the mean arterial pressure (MAP) minus ISP. The effect of elevated ISP on spinal cord blood flow (SCBF) is usually attributed to a tamponade effect on the small vessels. This suggests the concept of spinal compartment syndrome, analogous to osteofascial compartment syndrome in the leg (Bourne and Rorabeck, 1989). In a clinical study, Werndle et al. (2014) found that changes in ISP were divided into three stages: stage I (steep rise) from 1 to 7 hours, stage II (steady rise) from 8 to 38 hours, and stage III (descending) from 39 to 72 hours, peaking at 38 hours. They found that ISP in conscious rabbits (sham group: 3.43 ± 1.33 mmHg; SCI group: 5.76 ± 1.80 mmHg), and that different probe insertion angles (30°, 45°, 90°) had no influence on ISP (Hogg et al., 2019). Studies have shown that elevated ISP can be accurately measured, and ISP fluctuations visualized, in rats and rabbits after TSCI using microsensor and telemetry monitoring systems (Table 2). Studies have shown that elevated ISP is mainly caused by hemorrhage, edema, and BSCB destruction in a time-dependent manner. However, most of the SCI models used in these studies involve inducing contusion injury to the spine using a weight-drop device or impactor after laminectomy, which opens the spinal canal, leaving it decompressed. Thus, these SCI models do not truly reflect patient injuries, and better animal models are needed for future studies.

**Table 2** | A summary of ISP monitoring in clinical studies

| Study | Study design | Patients recruited (n) | Description of study | Conclusion |
|-------|--------------|------------------------|----------------------|------------|
| Werndle et al., 2014 | Observational study | 18 | Developed a technique for continuously monitoring ISP at the injury site after TSCI. | ISP at the injury site can be measured safely after TSCI. |
| Phang et al., 2015 | Prospective study | 21 | Investigated the effect of laminectomy and duroplasty in patients with TSCI. | Duroplasty improved the radiological parameters and ISP in a more efficacious manner than removal of lamina alone. |
| Varsos et al., 2015 | Observational study | 18 | Analyzed ISP waveform in patients with severe TSCI. | Morphological and spectral similarities were found between ISP in TSCI and ICP. |
| Phang et al., 2016 | Observational study | 42 | Investigated the accuracy of ISP probe placement and the safety of the technique. | The pressure probe is accurate and ISP monitoring is safe for up to a week. Supine position should be avoided in patients with laminectomy to prevent rises in ISP. |
| Hogg et al., 2019 | Observational study | 64 | Investigated the clinical and MRI features for predicting ISP and optimum SCPP in TSCI patients. | Elevated ISP can be predicted by clinical factors. Reducing surgical bleeding and performing expansion duroplasty may reduce ISP. |
| Hogg et al., 2021 | Observational study | 19 | Investigated the correlations between ISP, SCPP and limb power in TSCI patients. | Motor score versus ISP and SCPP had exponential decay (ISP rise to 20 mmHg was associated with drop of 11 motor points) and linear relation (1.4 motor point rise/10 mmHg rise in SCPP), respectively. |

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**Therapies Based on Elevated ISP**

In this section, we will summarize the current state of therapeutic strategies, including surgical and nonsurgical interventions that target elevated ISP after TSCI (Figure 2). The experimental and clinical studies reviewed above showed that ISP reaches maximal levels within 3 days after injury, suggesting that there may be a substantial response to surgical bleeding and performing expansion duroplasty may reduce ISP.
### Table 2 | A summary of ISP monitoring in animal studies

| Study | Animals | Modeling method | Pressure probe | Description of study | Conclusion |
|-------|---------|----------------|---------------|----------------------|------------|
| Soubeyrand et al., 2013 | Rats | Contusion at T10 | Truwave pressure transducer Pen 600 | Investigated the change of intramedullary pressure over time after different degrees of SCI and the correlations between intramedullary pressure and serious injury. | After SCI, CSF pressure significantly increased and SCBF significantly decreased. |
| Leonardi et al., 2015 | Rabbits | Balloon compression at T10 | Codman | Investigated the temporal and spatial patterns of elevated ISP following a moderate SCI. | ISP increased threefold 30 minutes following injury and remained elevated for up to 7 days. ISP was likely to have detrimental effects on spontaneous recovery after SCI. |
| Dong et al., 2016 | Rats | Contusion at T10 | Millar | Investigated the histological and functional effects of durotomy alone and durotomy and myelotomy in combination. | The dynamic changes of ISP were divided into steep rise, steady rise and descending stages. The main cause of the elevated ISP was severe bleeding in steep rise stage, and edema and blood-spinal cord barrier destruction in steady rise and descending stages. |
| Khaing et al., 2017 | Rats | Contusion at T7 | Millar | Investigated the causal relationship between durotomy and CSBF. | Durotomy combined with myelotomy facilitated tissue sparing and recovery of locomotor function following acute SCI. |
| Zhang et al., 2019 | Rabbits | Aneurysm clip compression at T10 | Transducer PX600 | Investigated the dynamic changes of ISP in 72 hours following SCI. | The therapeutic window of opportunity for therapeutic intervention to reduce this pressure. The role of surgical and nonsurgical interventions in reducing ISP is discussed below. |
| Khaing et al., 2021 | Rats | Contusion at T8 | Millar | Investigated the histological and functional effects of durotomy alone and durotomy and myelotomy in combination. | Durotomy combined with myelotomy facilitated tissue sparing and recovery of locomotor function following acute SCI. |

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**CSF:** Cerebrospinal fluid; **ISP:** intraspinal pressure; **SCBF:** spinal cord blood flow; **SCI:** spinal cord injury.

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**Window of opportunity for therapeutic intervention to reduce this pressure. The role of surgical and nonsurgical interventions in reducing ISP is discussed below.**

**Osseous decompression**

Numerous clinical studies of tSCI have suggested that early surgical decompression may improve neurological and functional outcomes (Furlan et al., 2011; Jug et al., 2015). These beneficial effects are partially due to extensive osseous decompression of the spinal cord, which should theoretically improve SCBF. In a recent study, Piazza et al. (2018) reported that posterior laminectomy results in better radiological decompression of the posterior CSF space than anterior cervical disectomy. Ararabi et al. (2011) demonstrated that the rate of radiological decompression in patients who underwent anterior disectomy and corpectomy without laminectomy were 46.8% and 58.6%, but in those in patients who underwent laminectomy at one, two, three, four, and five levels were 58.3%, 68%, 78%, 80%, and 100%, respectively.

The effect of bone decompression alone has, however, been questioned and some researchers doubt that it can reduce ISP and improve SCBF. After sufficient decompression of the spinal cord through laminectomy, no CSF was present between the edematous brain and dura mater, causing sustained elevated ISP and low spinal perfusion. In an exploratory clinical study, SCPF after sufficient bone decompression alone was less than 60 mmHg approximately 40% of the time, which is likely to cause spinal ischemic damage (Phang et al., 2015a). RCTs and animal experiments with ISP monitoring are needed to assess whether bone decompression alone improves physiological parameters and functional outcomes.

**Durotomy, duraplasty, and myelotomy**

Recommended management of TBI involves reducing ICP by decompressive craniectomy, during which part of the skull is removed, and the dura is opened to allow outward herniation of the brain. Similarly, opening the dura to allow the spinal cord to expand is important in tSCI treatment. Perkins and Deane (1988) performed durotomy in six patients with tSCI in whom the dura appeared tense after bony decompression. Three patients had a complete recovery, and three had a partial recovery. In stretched ex vivo pig spinal cords, durotomy reduced ISP from 35 to 10 mmHg (Awwad et al., 2014). In a rat weight-drop SCI study, duraplasty resulted in more white matter sparing than laminectomy alone (Jalan et al., 2017). In a study of 21 patients with cervical or thoracic tSCI, Phang et al. (2015) found that durotomy reduced ISP by 12.7 ± 0.4 mmHg and increased SCPP to less than 60 mmHg for less than 5% of the time, compared with laminectomy alone (18.0 ± 0.5 mmHg and approximately 40% of the time). Follow-up data suggested a tendency toward greater improvement in American Spinal Cord Injury Association scores, walking, and bladder function in patients who underwent durotomy and duraplasty compared with patients who underwent laminectomy only (Phang et al., 2015a). The expansion duraplasty took 10–15 minutes to perform and had fewer complications, such as CSF leakage, pseudomeningocele, and CNS infection. The above studies suggest that opening the dura to allow the spinal cord to expand is important in tSCI treatment. Perkins and Deane (1988) performed durotomy under the assumption that opening the dura would lead to less inflammation, collagen scarring, and spinal cord cavitation. Duraplasty is beneficial after durotomy because durotomy reduces the risk of CSF leakage and wound infection. Furthermore, maintaining the continuity of the dura following durotomy maintained a pattern of CSF flow closer to physiological conditions and prevented extradural factors from inhibiting neuroregeneration and promoting inflammation (Iannotti et al., 2006). An RCT investigating the effects of duraplasty is currently underway at the University of London (ClinicalTrials.gov identifier: NCT04936620).

Owing to the possible contribution of the pial lining to elevated ISP, myelotomy as a treatment for TSCI has been the topic of several animal studies. In a rodent model of moderate contusion SCI, ptiomy contributed to 53.5% of the pressure reduction during the acute phase, whereas it contributed only 14.6% during the subacute phase of the injury (Khaing et al., 2017). This suggests that early myelotomy may be more effective in promoting functional recovery of the spinal cord. Furthermore, in a similar SCI model, the researchers found that durotomy plus myelotomy more effectively mitigated elevated ISP (3.14 ± 0.40 mmHg) than durotomy alone (4.17 ± 0.30 mmHg) at 3 days post-injury and significantly promoted recovery of hindlimb locomotor function by facilitating tissue sparing (Table 2) (Khaing et al., 2021). This study reported an interesting phenomenon in which durotomy alone led to increased recovery of bladder function compared with durotomy plus myelotomy, which may explain why surgical opening of the pia, involving additional disruption of the injury core, resulted in irritation of the spinal cord, leading to transient urinary retention in animals that underwent durotomy and myelotomy.

A review study revealed that durotomy implemented in tSCI patients resulted in improved neurological function in 92.3% of studies, while durotomy in animals preserved improved neurological function in 83.3% of studies. However, although myelotomy procedures had positive effects in 80% of animal studies, only one clinical study...
The use of high doses of methylprednisolone has been recommended to reduce inflammation and glutamate release and ameliorate edema within the first 8 hours after injury (Fehlings et al., 2017), but this approach has been limited by complications (gastrointestinal hemorrhage and respiratory tract infection) and limited time windows. Furthermore, a recent meta-analysis found no significant difference between the methylprednisolone and control groups in terms of sensory scores and pooled motor function at the last follow-up (Liu et al., 2020).

A possible explanation for this is the low permeation of drugs into the injury site when administered systemically. The disruption of the BSCB seen after acute SCI allows drug entry into the injury site, but this entry is restricted by elevated ISP and low SCPP. One study reported that an increase in SCPP of 10 mmHg resulted in a threefold increase in dexamethasone penetration into the injury site, based on microdialysis monitoring (Phang et al., 2016b). Therefore, maximizing drug delivery to the injury site requires optimization of SCPP and individualized management of MAP and ISP, rather than following the recommended guidelines by maintaining the MAP at 85 to 90 mmHg for 1 week after SCI (Phang et al., 2016b; Saadoun and Papadopoulos, 2016).

**Limitations**

This review had several limitations. First, this is a nonsystematic review. Second, articles on using stem cell engineering and materials to improve edema and BSCB were not included. In the future, combining different treatment strategies may lead to a cure for SCI.

**Conclusions**

In this article we reviewed the factors that increase ISP, as well as the impact of elevated ISP on pathophysiology after SCI. Therapeutic strategies, including both surgical and nonsurgical interventions, targeting elevated ISP after tSCI were also reviewed. Taken together, studies have shown that ISP increases to a maximal level within 3 days after SCI due to the contribution of hemorrhage and edema. Duraplasty and hypertonic saline may be promising treatments for reducing ISP within this time window. Other treatments, such as osseous decompression, myelotomy, hemostasis, and methylprednisolone, require further verification in animal studies and clinical RCTs.

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