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SPECIAL REPORTS

Clinical guidelines for neurorestorative therapies in spinal cord injury (2021 China version)

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ABSTRACT

Treatment of spinal cord injury (SCI) remains challenging. Considering the rapid developments in neurorestorative therapies for SCI, we have revised and updated the *Clinical Therapeutic Guidelines for Neurorestoration in Spinal Cord Injury (2016 Chinese version)* of the Chinese Association of Neurorestoratology (Preparatory) and China Committee of International Association of Neurorestoratology. Treatment of SCI is a systematic multimodal process that aims to improve survival and restore neurological function. These guidelines cover real-world comprehensive neurorestorative management of acute, subacute, and chronic SCI and include assessment and diagnosis, pre-hospital first aid, treatment, rehabilitation, and complication management.

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1 Introduction

Spinal cord injury (SCI) can result in acute edema or hemorrhagic contusion and cause motor, sensory, and autonomic neurological dysfunction below the level of injury [1]. SCI imposes a heavy public health burden [2–4]. According to incomplete statistics, there are more than one million patients with SCI in China and the number is growing by 120,000 per year [5–8]. Disability and mortality related to SCI have been significantly decreased because of effective pre-hospital emergency care, progress in clinical treatment, and improved nursing techniques. Furthermore, various effective neurorestorative treatment strategies are now being widely used [9–13]. In view of the rapid developments in neurorestorative therapy for SCI, the Chinese Association of Neurorestoratology (Preparatory) and China Committee of International Association of Neurorestoratology revised and updated the *Clinical Therapeutic Guidelines for Neurorestoration in SCI* in 2016 [14]. SCI can be divided into four stages according to time: acute (< 48 h), subacute (48 h –14 d), intermediate (14 d–6 months), and chronic (> 6 months) [15]. The guidelines presented here are based on evidence published before 31 December, 2020. Although the methods in the guidelines can restore neurologic function in SCI patients to a certain extent, complete recovery from severe SCI remains difficult.

2 Acute and subacute stages of SCI

2.1 Assessment

SCI patients should undergo a thorough neurological examination as early as possible to assess severity and prognosis as well as a comprehensive physical examination to rule out associated injuries [16, 17]. The International Standards for Neurologic Classification of SCI (ISNCSCI) is the most widely accepted classification system for sensorimotor impairment [18–20]. The American Spinal Injury Association (ASIA) neurological score is the most widely used quantitative neurological assessment. Quality of life is evaluated using the International Association of Neurorestoratology SCI Functional Rating Scale [14, 15].

2.2 Imaging examination

Radiography may miss spinal fracture and is not recommended as the modality of choice for cervical spine injury [21]**.** However, anterior–posterior and lateral views should be obtained when used, which can demonstrate vertebral alignment and type of fracture or dislocation. Computed tomography (CT) is the most commonly used imaging modality to diagnose spinal fracture or dislocation [22]. Axial and three- dimensional views can show the shape of the spinal canal and facet joints and can detect small and hidden lesions missed by plain radiography [21, 22].

Magnetic resonance imaging (MRI) is the modality of choice to evaluate the integrity, injury site, severity, and involvement of the intervertebral disc, ligaments, spinal cord, cauda equina, and nerve roots [23]. MRI can show displaced disk fragments and ligamentous injury as well as spinal cord edema and hemorrhage on T2-weighted sequences [24]. Range of hemorrhage and edema and degree of spinal cord compression on MRI are associated with neurological prognosis [25, 26]. Evaluation of both preoperative and postoperative MRI is more helpful in predicting neurological outcome [27]. In addition to conventional sequences, new quantitative MRI techniques such as diffusion tensor imaging can reflect microscopic pathological changes in spinal white matter by detecting diffusion direction and dispersion of water molecules. MRI accurately evaluates SCI

to guide classification and surgical treatment [23, 28–30].

2.3 Diagnosis

The diagnosis of SCI should include the injured level, severity of injury, type of vertebral fracture and/or dislocation, and stability of the spine. Severity of SCI is currently classified according to the ASIA Impairment Scale (AIS) [18, 20]. Grade A is a complete injury, with no sensory or motor function preservation in S4 and S5. Grade B is an incomplete injury with preservation of sensory but not motor function below the level of injury, including S4 and S5; no motor function is preserved more than three levels below on either side of the body. Grade C is also an incomplete injury but motor function is preserved below the level of injury with more than half of the key muscles below graded less than 3 on manual muscle testing. In grade D, at least half of the key muscles below are graded 3 or more. Grade E indicates normal neurological function or function unchanged compared to before the injury.

2.4 Treatments

In addition to treatment of the primary injury, secondary SCI requires attention [9, 14–16]. The main purpose of SCI treatment is to reduce secondary injury in the acute and subacute stages. Treatments include early reduction and fixation, complete decompression, cell therapy, early rehabilitation, and prevention of complications [5, 16, 31–33].

2.4.1 Pre-hospital aid

Appropriate pre-hospital emergency treatment is important to reduce mortality and improve outcomes. Neurorestorative treatments require close cooperation between treating specialists. Regional spinal cord injury centers with a specialized multidisciplinary SCI team comprising representatives from emergency medicine, orthopedics, neurosurgery, general surgery, intensive care medicine, radiology, neurology, anesthesiology, and others should be established [34–38].

After trauma, emergency personnel should evaluate the patient quickly and stabilize the head and entire spine to prevent secondary injury. Three or more people should be utilized to lift and move the patient to a flat plate or special stretcher and transport them to a qualified hospital by ambulance or helicopter [5, 37]. Life support (airway, breathing and circulation) should be provided when necessary [39]. Telehealth communications can be used to inform hospital personnel of impending arrival and receive medical direction in transport. After admission, a multidisciplinary team should evaluate the patient, determine injuries and their severity, and initiate immediate treatment. Use of multidisciplinary teams reduces mortality and length of hospital stay [40].

2.4.2 Drug therapy

Early high-dose methylprednisolone (MP) has been considered to improve SCI prognosis [41]. However, the National Acute SCI Studies I and II in the United States showed only moderate efficacy with possibly serious complications. MP has not been recommended in the guidelines of the American Association of Neurosurgeons (AANS) and the Congress of Neurological Surgeons (CNS) since 2013. The current consensus is that evidence for use of high-dose MP in SCI is insufficient [42] and it is no longer routinely recommended because of complications such as respiratory system infection, gastrointestinal bleeding, arrhythmia, and even death. However, it remains an option in selected cases [11, 42–45]. In 2017, AOSpine recommended MP as a treatment option for patients within 8 h of acute SCI [46].

When MP is elected, attention should be paid to the following points:

a) The time window for use is < 8 h from injury. Administration should proceed as follows: 30 mg/kg initial intravenous bolus within 15 min, a pause of 45 min, followed by maintenance continuous infusion at 5.4 mg/(k·h) for 23 h [41].

b) To reduce the risk of side effects, MP should be stopped as soon as possible in patients whose neurological symptoms have resolved.

c) Contraindications to high-dose MP are as follows: spinal injury without neurological dysfunction, discontinuity of the spinal cord, > 8 h after injury, gastrointestinal bleeding, gunshot SCI, elderly patients with high risk of pneumonia, and diabetic patients.

Although the combination of ganglioside (100 mg/d) and MP can improve outcome in early acute SCI [47], Guillain–Barre syndrome has been reported after ganglioside use. The development of antibodies secondary to exogenous gangliosides significantly increases the probability of Guillain–Barre syndrome [48, 49]. Therefore, ganglioside is not currently recommended for routine use in SCI. Large clinical trials are needed fully determine ganglioside efficacy [45, 46, 50].

Other drugs, including erythropoietin, riluzole, minocycline, sex hormone, neurotrophic factor, sodium aescinate, axonal growth promoting agent, granulocyte colony stimulating factor, magnesium agent, and fibroblast growth factor [2] are in clinical trials or have been in clinical use, but high-level evidence to support their routine use is lacking [15, 45, 51–53]. Although intravenous vasopressor agents such as norepinephrine can improve local spinal cord perfusion pressure and hemodynamics after SCI [54–56], their effect on neurological recovery is uncertain. Furthermore, they may be associated with increased risk of adverse events, predominantly cardiac [56, 57].

2.4.3 Hypothermia therapy

The purpose of hypothermia treatment is to reduce the basic metabolic rate of the central nervous system, reduce energy consumption of the spinal cord, and alleviate the energy supply disorder caused by spinal cord ischemia and hypoxia [58]. Induction of systemic hypothermia to a temperature between 32 ℃ and 34 ℃ seems to be most effective [58–66]. Local hypothermia is also effective [64–66], which can be achieved using epidural or subdural coolant (6 ℃) [62] infused via an open or closed system. So, far, there is no recognized indication or contraindication for hypothermia treatment in acute SCI. If medical and patient conditions permit, systemic and local hypothermia treatment should be carried out at the same time [62–64].

2.4.4 Surgery

Early decompression and stabilization

Early spinal cord decompression and spinal stabilization are the basic treatment principles of SCI [67]. It is safe to perform emergency spinal reduction and stabilization during the acute phase, which can improve neurological outcome, shorten hospitalization time, and reduce complications. Emergency spinal cord decompression can reduce secondary injury, preserve neurological function of surviving axons, and prevent further spinal cord damage. Spinal cord compartment syndrome (SCCS) after severe acute SCI, similar to osteofascial compartment syndrome, has been proposed as a mechanism of secondary injury [37, 38, 68–72]. This theory hypothesizes that spinal cord ischemia, edema, contusion, and laceration along with bony compression of the spinal canal increases intradural spinal pressure, aggravating secondary injury via ischemia, edema and

degeneration necrosis in a vicious cycle [69–71, 73]. An alternative term for SCCS is spinal cord intramedullary hypertension (SCImH).

Surgical window

Decompression and internal fixation should be performed as early as possible (< 24 h) in patients with obvious neurological dysfunction, whether the injury is complete (AIS A) or incomplete (AIS B–D) [37, 73–75]. The idea that "time is spine" has been widely recognized [38, 68, 74–87]. In 2017, AOSpine guidelines recommended that when the acute SCI patient is stable, surgery should be performed within 24 h of injury, whether complete or incomplete [77]. However, due to the problems of patient transport and need for preoperative examination and preparation, this cannot be achieved in many patients. Nonetheless, other studies have shown that surgical intervention within 3 days for SCI can provide benefit, with greater benefit associated with earlier surgical treatment [78–80, 85, 87]. Therefore, surgery should be performed as early as possible and within 3 days of injury in patients who cannot undergo surgery within 24 h [67]. In particular, patients with cervical SCI need to be thoroughly assessed, especially for lung injury and smoking history. Postoperative risk of infection and respiratory failure is increased in patients with unstable vital signs before surgery, which can result in a difficult postoperative clinical course.

Operative methods

Surgical treatment is mainly determined using the Sub-axial Injury Classification and Severity Scale, and Thoracolumbar Injury Classification and Severity Score (TLICS) developed by the Spine Trauma Study Group [88, 89]. Conservative treatment is recommended for scores ≤ 3. For a score of 4, either surgery or conservative treatment can be selected. For scores ≥ 5, surgical treatment is recommended. Surgery is crucial in SCI patients, particularly bony decompression because of its remarkable curative effect. Commonly used methods include the anterior approach (ACDF/ACCF), posterior approach (laminectomy/laminoplasty), and combined anterior and posterior approaches [90, 91]. The goal of surgery is to remove spinal canal compression directly or indirectly. The approach is selected based on preoperative CT and MRI [33, 92]. These imaging modalities demonstrate fracture characteristics, position of the injured disc compressing the spinal cord, and spinal stability and structure [33, 88, 89, 93]. The role of the dura mater in SCI should not be ignored [94, 95]. Numerous studies have shown that surgical durotomy can significantly reduce intraspinal pressure [68–72, 96, 97]. In patients with elevated intraspinal pressure, anterior decompression alone is not sufficient and extensive posterior laminectomy combined with durotomy or even myelotomy is required for decompression [68–72, 94–100]. Therefore, in the presence of spinal cord compression and only local edema, anterior or posterior local decompression is feasible. Extensive laminectomy plus durotomy for decompression is required in cases with extensive spinal cord edema. In the presence of spinal cord hematoma or necrotic foci, additional myelotomy can be considered.

Durotomy and duroplasty

Indications for durotomy mainly include the presence of extensive spinal edema (more than two segments) or disrupted local cerebrospinal fluid (CSF) circulation on MRI in AIS grades A–C. Intraoperative absence of CSF pulsations after laminectomy suggests the need for surgical durotomy. However, it is not recommended in patients with AIS grade of D or E, or those with

localized edema on MRI [68, 69, 97]. Durotomy is associated with risk of CSF leakage and meningitis, so surgeons should weigh the potential benefits with the risks of longer operation time and other complications when selecting treatment [98]. Durotomy with preservation of the integrity of the arachnoid membrane can theoretically reduce most of the intraspinal pressure without causing CSF leakage and entrance of inflammatory factors into the CSF and spinal cord [69]. This method can be used in patients with spinal cord edema without significant subarachnoid hemorrhage after intraoperative durotomy.

Myelotomy

For patients with severe spinal cord contusion or extensive hematoma in the spinal cord, myelotomy can be selected. In theory, myelotomy can prevent further expansion of secondary injury and relieve the state of high intraspinal pressure [94, 97, 100]. Although several clinical studies have reported neurological improvement in acute SCI patients who underwent myelotomy [5, 99], prospective randomized controlled clinical trials to fully evaluate it have not been conducted. A meta-analysis of data derived from four independent prospective multicenter data sources showed that surgical decompression within 24 h of acute SCI was associated with improved sensorimotor recovery [100].

The operative method of intramedullary decompression should be considered according to injury severity, imaging results, and intraoperative findings. For patients with limited compression, anterior discectomy or laminoplasty can be performed. In patients with severe spinal cord contusion and/or hemorrhage, myelotomy to clear the hematoma can be considered if hematoma is found after durotomy [68–72, 94–101].

Since complete transection of the spinal cord is rare in clinical setting and in order to avoid iatrogenic injury, microscope assisted surgery combined with the findings of CT and MRI is necessary for intramedullary decompression in order to preserve the living axons of patients with neurological impairment [101]. The 4 types of SCI and their corresponding surgical interventions are presented below:

a) In type I, arachnoid adhesions, disappearance of spinal cord pulsations, obstruction of CSF, and pale swelling of the spinal cord are present. Interventions include release of adhesions and restoration of CSF flow and spinal cord pulsations.

b) In type II, intramedullary hematoma and bone fragments are present. Interventions include removal of hematoma and bone fragments and spinal cord exploration.

c) In type III, the SCI is partial. Once the dura mater is opened, liquefied tissue may emerge. Interventions include exploring the injured area, removing necrotic tissue, and gently washing the area with normal saline.

d) In type IV, intramedullary softening is present. Interventions include a 0.3–0.5 cm longitudinal myelotomy in the softened area, removal of softened tissue, and gently washing the cavity with normal saline.

The boundary between the contused spinal cord and normal spinal cord is not clear in the early stage, so the scope of intramedullary decompression should be limited [101].

Pediatric SCI without radiographic abnormality (usually caused by backbends during dancing in China), acute hyperextension myelopathy, and surfer's myelopathy are often characterized by spinal venous hypertension and SCCS or SCImH [25, 73]. Early decompression is recommended in these patients. However, the time threshold and method of early decompression remain controversial and need to be

examined in large randomized controlled trials [72, 74–87].

2.4.5 Cell therapy

Neurorestorative mechanisms targeted in SCI cell therapy include axon regeneration and remyelination, neuroplasticity, neuroprotection, neural regulation, neural structure repair, regulation of inflammation and immune responses, neurogenesis, angiogenesis, reduction of scar and cavity formation, and cell substitution [101, 102]. The few clinical trials of cell therapy for acute or subacute SCI have shown both positive [103] and negative outcomes [104]. Acute SCI results in obvious edema and inflammation in the damaged area and early cell injection may exacerbate injury; therefore, direct cell transplantation cell is not recommended in the acute phase. Intrathecal or intravenous injection of mesenchymal stromal cells can be considered to improve systemic or local inflammation [105].

2.4.6 Electrical stimulation therapy

The nervous system relies on electrical signals for information transmission and local electrical stimulation can improve and induce axon regrowth [101, 106–108]. Four categories of electrical stimulation can be used [101]. First, neuromuscular electrical stimulation is generally used initially, which can delay loss of muscle mass. The second is the regulation of electrical stimulation in paralyzed patients. The third is functional electrical stimulation of peripheral neural structures and the spinal cord. This method appears promising but it is still being studied. The fourth is comprehensive physical, medical, and neuroelectrophysiological interventions combined with various neurobiological stimulations to promote SCI motor control. These methods can effectively adjust neurological function through stimulation and inhibition and are currently being studied [101, 109, 110].

2.4.7 Rehabilitation

Rehabilitation training can reduce the incidence of pressure sores, deep vein thrombosis, and other complications, and can restore neurological function [111]. If the patient's condition allows, rehabilitation can be started with head, neck, and lumbar back supports after surgery. The main principle of rehabilitation is active movement to target strengthening, which helps patients to maximize recovery of neurological function [112]. Use of an exoskeleton robot in rehabilitation can maintain and extend motor function in the recovery period after SCI [113].

Early occupational and physical therapy is important after SCI. Reintegration of patients with SCI through work [114]. Early rehabilitation training should include physical and occupational therapy as well as neuroelectric stimulation [115].

2.4.8 Complications and comorbidity management

Hypotension

After SCI, the sympathetic nerves below the injured level are inhibited, which results in reduced heart rate and dilation of peripheral blood vessels, causing susceptibility to hypotension and shock [116]. The blood supply of the spinal cord is segmentally distributed and has little collateral flow; therefore, its ability to compensate for ischemia is poor [117]. Hypotension after SCI can lead to insufficient spinal cord perfusion. Several studies have shown that the maintenance of mean arterial pressure (MAP) > 85–90 mmHg is beneficial in SCI patients [118–120]. The 2013 AANS/CNS guidelines recommend that the MAP be maintained at 85–90 mmHg for 5 to 7 days [50]. Appropriate fluid supplementation and volume

expansion or administration of noradrenaline can improve local spinal cord perfusion pressure after SCI and relieve spinal cord ischemia [121, 122].

Hyponatremia

Hyponatremia is a common complication of cervical SCI. For mild hyponatremia, fluid intake should be limited and a high salt diet administered while closely monitoring blood sodium concentration. For moderate to severe dilutional hyponatremia, additional sodium supplementation may be needed. For hypovolemic hyponatremia, both volume expansion and sodium supplementation should be administered at the same time [67, 123, 124].

Deep vein thrombosis

The reported incidence of deep vein thrombosis after SCI ranges between 16.3% and 79% [67, 101] but large-scale epidemiological data is lacking. Low molecular weight heparin combined with physical methods is recommended for prevention. Routine use of inferior vena cava filters is not [67, 71, 125].

Respiratory complications

Respiratory complications such as respiratory failure, repeated pneumonia, atelectasis, and pleural effusion are the main causes of death in SCI patients [1–4, 39, 126]. SCI above C4 may cause respiratory muscle paralysis and weakened or absent cough reflex, which can result in breathing and sputum discharge difficulties and aggravate lung infection. Tracheotomy is occasionally needed to facilitate mechanical ventilation and sputum suctioning. Proper posture can help prevent or reduce respiratory tract infection: patients should be encouraged to sit or raise the head of the bed as early as possible. After raising the head of the bed, the patient should be closely monitored for postural hypotension [127, 128].

3 Intermediate and chronic SCI stages

3.1 Chronic evaluation

Fourteen days to 6 months after SCI is considered the intermediate stage, and after 6 months is considered chronic [14, 15, 101]. Neurological status, spinal alignment and stability, and spinal cord lesions should be evaluated in these stages. Comprehensive assessment of local and systemic conditions is necessary to develop the optimal treatment plan.

3.2 Examination

Neurological function can be assessed by the ASIA neurological score [18, 20]. Quality of daily life should be evaluated by the International Association of Neurorestoratology SCI Functional Rating Scale [14, 101]. MRI can show spinal cord status and evaluate spinal cord compression, atrophy, softening, and development of cysts, syringomyelia, and scar. Electrophysiological examination using somatosensory evoked potentials and electromyography can evaluate sensory and motor function, respectively [14, 101].

3.3 Diagnosis

The clinical diagnosis of intermediate and chronic SCI includes determining the level and severity of injury, quality of life, and any remaining spinal cord compression [21–25, 28]. Neurophysiological examination and MRI may assist in understanding structural abnormalities and assessing motor and sensory function [23–25, 28].

3.4 Treatments

3.4.1 Decompressive surgery

For patients with intermediate and chronic SCI and severe spinal cord compression, surgical decompression may promote neurological

recovery.

3.4.2 Nerve bridging

Nerve bridging may also restore some neurologic function in patients with complete chronic SCI [129, 130]. There are three main methods:

a) A peripheral nerve (such as the accessory or an intercostal nerve) above the injury is used to bridge to a nerve root or peripheral nerve innervating a paralyzed muscle below the injured level [131, 132].

b) Ventral roots are removed from L5 or S1 above the injured level and connected below the injured level to the S2 or S3 ventral roots that innervate the bladder [133–137].

c) A peripheral nerve is resected and inserted into the ventral tract of the thoracic spinal cord (corticospinal tract) for 4–5 mm and the distal end of the nerve is connected to a neuromuscular junction in a lower limb muscle [138].

Recent clinical reports have described the role of these methods in neurological function recovery in patients with SCI [139–141].

3.4.3 Electrical stimulation

Epidural stimulation training can activate nerve circuits and promote nerve remodeling and functional recovery in patients with complete SCI [142]. Transcranial electrical stimulation can effectively treat neuropathic pain after chronic SCI [143]. Functional electrical stimulation of permanently denervated muscle is also effective and can preserve muscle quality and function [144]. In addition, electrical stimulation can improve neuroplasticity and reduce systemic complications [145, 146] and improve pain relief, trunk stability, and motor function [147–149]. Use of a brain–computer interface and artificial nerve prostheses can help paralyzed patients carry out activities of daily living and promote neural remodeling [150–152]. Rehabilitation therapy using an exoskeleton robot has been shown effective in gait rehabilitation, injury plane decline, and improving spasms [152–154].

3.4.4 Cell therapy

Cell transplantation is an important treatment for patients with intermediate and chronic SCI. Several cell types have been found suitable for transplantation, including olfactory ensheathing cells, mesenchymal stromal cells, peripheral blood mononuclear cells, bone marrow and umbilical cord blood cells, bone marrow hematopoietic stem cells, Schwann cells, and embryonic stem cells [100, 101, 155–174]. Transplantation of cells into the spinal cord parenchyma through intravascular infusion, intrathecal or intralesional injection, or multichannel administration can improve both neurological function and quality of life, with most subjects experiencing both sensory and motor function recovery [155–174]. However, a few patients experience no effect [175, 176].

Recent studies have reported spinal cord resection after acute and chronic complete SCI and replacing the area with a neural regeneration scaffold and umbilical cord blood stromal cells [177, 178]. However, this remains experimental and is not recommended, as patients with complete SCI still have the potential to recover some function using the strategies mentioned above. Complete removal of the spinal cord precludes the chance for patients to spontaneously restore neurological function in the acute and subacute stages of SCI. Furthermore, it precludes the use of neurorestorative treatments in the chronic stage [179].

3.4.5 Comprehensive treatment

The clinical effect of a single neurorestorative treatment is limited. However, comprehensive application of several treatments is expected to

achieve greater neurological function recovery. Options include cell transplantation, nerve bridging, electrical stimulation, and neurorehabilitation [112, 179–183], as well as brain–computer interface gait training programs, which can partially restore walking ability [184]. Implanted electrode stimulation can strengthen neural rehabilitation and result in partial recovery of standing and walking ability in patients with chronic complete SCI [185, 186].

The neural and skeletal systems form a neuro–osteogenic network, which is important to maintain skeletal health [187]. In SCI, there is interruption of the ascending and descending neural tracts that connect the brain to the sensory and autonomic innervation of bone. Neurogenic osteoporosis after SCI is strikingly severe [188]. Immobilization, bone denervation, and hormonal and metabolic changes contribute to SCI-induced bone loss [189]. Approximately one-half of SCI patients sustain a long bone fracture after injury [188]. Furthermore, neurogenic osteoporosis after SCI causes difficulty in bone healing after fracture [187]. However, at present, there are no evidence-based recommendations regarding prevention and treatment of osteoporosis after SCI [188–190]. Nonetheless, comprehensive neurorestorative strategies may provide some benefit in treating neurogenic osteoporosis, maintaining skeletal health, and promoting fracture healing.

4 Summary

In the last four years, new developments have arisen in clinical neurorestoration treatments for SCI patients. These guidelines aim to provide clinicians with knowledge of these developments to assist in treating SCI patients. Future large-scale multicenter randomized trials are needed to further examine the efficacy of neurorestorative therapies. Future guideline revisions and updates will be provided as new evidence develops.

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Conflict of interests

The authors report no conflict of interests in this work.

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