World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v6.i1.34

World J Orthop 2015 January 18; 6(1): 34-41
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

Kemal Nas, MD, Professor, *Series Editor*

Current and future surgery strategies for spinal cord injuries

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Received: October 24, 2013
Peer-review started: October 25, 2013
First decision: December 2, 2013
Revised: April 8, 2014
Accepted: May 13, 2014
Article in press: May 14, 2014
Published online: January 18, 2015

Abstract

Spinal cord trauma is a prominent cause of mortality and morbidity. In developed countries a spinal cord injury (SCI) occurs every 16 min. SCI occurs due to tissue destruction, primarily by mechanical and secondarily ischemic. Primary damage occurs at the time of the injury. It cannot be improved. Following the primary injury, secondary harm mechanisms gradually result in neuronal death. One of the prominent causes of secondary harm is energy deficit, emerging from ischemia, whose main cause in the early stage, is impaired perfusion. Due to the advanced techniques in spinal surgery, SCI is still challenging for surgeons. Spinal cord doesn't have a self-repair property. The main damage occurs at the time of the injury primarily by mechanical factors that cannot be improved. Secondarily mechanisms take part in the following sections. Spinal compression and neurological deficit are two major factors used to decide on surgery. According to advanced imaging techniques the classifications systems for spinal injury has been changed in time. Aim of the surgery is to decompress the spinal channel and to restore the spinal alinement and mobilize the patient as soon as possible. Use of neuroprotective agents as well as methods to achieve cell regeneration in addition to surgery would contribute to the solution.

Key words: Spinal cord injury; Surgery; Classification; Mechanism; Management

Core tip: Spinal cord trauma is a prominent cause of mortality and morbidity. In developed countries a spinal cord injury (SCI) occurs every 16 min. Due to the advanced techniques in spinal surgery, SCI is still challenging for surgeons. Spinal compression and neurological deficit are two major factors used to decide on surgery. Aim of the surgery is to decompress the spinal channel and to restore the spinal alinement and mobilize the patient as soon as possible. Use of neuroprotective agents as well as methods to achieve cell regeneration in addition to surgery would contribute to the solution.

Dalbayrak S, Yaman O, Yılmaz T. Current and future surgery strategies for spinal cord injuries. *World J Orthop* 2015; 6(1): 34-41 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i1/34.htm DOI: http://dx.doi.

org/10.5312/wjo.v6.i1.34

EPIDEMIOLOGY

Every year more than 1 million spinal cord trauma cases and more than 50000 spinal trauma related spinal cord injuries occur in the United States[1]. The incidence of spinal cord injuries amounts to 7500-10000 annually. In developed countries, 32000 new cases occur every year, which means, a spinal cord injury (SCI) occurs every 16 min. Spinal cord trauma may occur due to a number of reasons, which usually include motor vehicle accidents, falls and gunshot wounds[2]. Damage to the spinal column usually occurs at the cervicothoracic or thoracolumbar region. Studies revealed that SCI incidence is frequent at ages 16 to 30[3].

PATHOPHYSIOLOGY OF THE SCI

A lot of tissues in the human body are capable of self-repair. However, it is not the case for the central nervous system. SCI occurs due to tissue destruction, primarily by mechanical and secondarily ischemic[4,5]. Primary damage occurs at the time of the injury. It cannot be improved[6]. Following the primary injury, secondary harm mechanisms gradually result in neuronal death[7]. One of the prominent causes of secondary harm is energy deficit, emerging from ischemia, whose main cause in the early stage, is impaired perfusion[4,7]. Following the local infarction, caused by ischemia, grey matter becomes damaged, especially because of its high metabolic requirements. Ischemia leads to insufficient glucose and oxygen transfer to tissues, energy deficit and reduction in adenosine triphosphate store. As a result, the system starts to perform anaerobic respiration. Ischemia and subsequent anaerobic respiration induce many pathological processes.

Another important mechanism, in the process of secondary damage, is post-traumatic over synthesizing of nitric oxide. Nitric oxide (NO) plays a part in continuing the transmission starting with glutamate, in the central neural system. Besides its physiological function, as a result of its high production, NO becomes neurotoxic and plays an important role in the process of secondary damage as a free radical[8]. Over production of nitric oxide causes necrosis with peroxynitrite development, protein damage, increase in lipid peroxidation, cellular energy loss, mitochondrial diaphoresis and deoxyribonucleic acid replication inhibition[9].

Macrophages assume the main role for giving an immune response to the damage occurring in cells other than those of the central nervous sytem (CNS). They activate lymphocytes by releasing cytokines while trying to get rid of the toxic elements. Macrophages act as the antigen presenting cell (APC) for lymphocytes. Cytokines and growth factors are released by the activated macrophages and lymphocytes.

The microglia in the CNS are weak in their APC function. Microglia may have destructive effects in addition to their repair function. Even if the lymphocytes arrive at the location of damage, they lack the APC to activate them.

CLASSIFICATION OF SCI

SCI can be classified into two groups, notably the complete and the incomplete[10]. Complete SCI cannot be diagnosed before the spinal shock regresses. Once the bulbocavernosus reflex (BCR) is back, the injury is diagnosed as complete damage if there is no motor or sensory function. Once the BCR is back, if there is a sensation below the level of injury, it is diagnosed as sensory incomplete SCI. If there is some preserved motor and sensory function below the level of injury, the case is diagnosed as incomplete motor and sensory incomplete SCI. There are 4 types of incomplete SCI syndromes. Anterior spinal cord syndrome is observed as a result of the trauma in the anterior of spinal cord. The damage usually occurs as a result of flexion compression. Posterior spinal cord syndrome is relatively rare. The motor function is preserved below the level of injury, but there is decreased sensory function. Central cord syndrome is more common. It occurs in old patients with cervical spondylosis due to extension injury. Loss of function is more severe in the upper extremities compared to the lower extremities. Brown-Sequard Syndrome is characterized by the lateral hemisection of the spinal cord. Patients with Brown-Séquard syndrome suffer from ipsilateral motor paralysis and loss of proprioception, and as well as contralateral loss of pain and temperature sensation. It is very difficult to reverse this syndrome.

MECHANISM OF INJURY

Majority of the classifications suggested for the spinal trauma are structured along how the damage occurred[11-15]. Spinal injury occur due to flexion, extension, lateral rotation, axial loading, or the combination of these forces. Majority of SCI classifications aim at evaluating the acute phase of trauma. Holdswort explained spinal cord injuries with suggested treatment methods[16]. Denis suggested three column theory built on this classification[17]. Allen Ferguson presented another classification about lower cervical trauma[11]. AO proposed a new classification system for thoracolumbar traumas, which was found suitable by McCormack *et al*[18] according to the load-bearing theory[16-18]. The classification is intended to identify whether the fracture is stable or not. However, there are certain drawbacks in the current classification system. Damage occurs due to the impact of the majority of the abovementioned mechanisms. The results of the modern imaging methods are not taken into account in many classification systems. One can determine the posterior-ligamentous complex in thoracolumbar traumas where instability plays an important role, and the status of the disco-ligamentous complex in cervical traumas through magnetic resonance imaging (MRI) images. Many

systems are not sufficient to decide on the treatment of the existing trauma. Spine Trauma Study Group (STSG) proposed Subaxial Injury Classification (SLIC) for the subaxial cervical traumas in order to eliminate the current gaps[14,15]. The current system took into account the disco-ligamentous complex and the neurological status in addition to the mechanism of injury. The compression forces, distraction and translation forces were also taken into consideration in determining the mechanism of injury. Injury morphology of the disco-ligamentous complex is divided into intact, indeterminate (interspinous spreading, or soft tissue T2 hyperintensity) or disrupted (facet dislocation or disc space widening). Neurological status is classified as (1) intact; (2) radiculopathy; (3) incomplete SCI; and (4) complete SCI. Patients with a score equal to or higher than 4 and above as a result of the classification require surgery.

On the other hand, the classification system proposed by the STSG to address the thoracolumbar injuries is the Thoracolumbar Injury Classification and Severity Score[15]. This system is easier to use and has a high standardization.

SURGERY

Spinal compression and neurological deficit are two major principles used to decide on surgery. However, the surgical approach-either anterior, posterior or combined-varies depending on each patient. As a general principle, the main approach for the patients without the presence of any pathology causing compression in the canal is the posterior stabilization and fusion. Anterior compression and fusion as well as posterior stabilization are required for the patients with certain pathologies causing compression in the canal. In some cases, anterior or posterior surgical approach does not cause any difference. Brodke *et al*[19] operated some of 52 SCI patients with subaxial cervical traumas with anterior approach and some with posterior approach and there was no difference wound between two groups with respect to fusion rates, sagittal alignment and neurological recovery.

Anterior decompression

Anterior decompression is preferred to address the anterior compression[13,20]. Surgery alone can be preferred with posterior approach to remove the compression in the lower cervical spine whereas anterior decompression and stabilization can be achieved with anterior approach in certain cases affected by an anterior disc or bone.

Anterior surgery is usually needed after the posterior compression to treat the lumbar and thoracic injuries since it often achieves indirect decompression. In more than 50% of the compression cases, anterior surgery is required.

The benefit of decompression in thoraclumbar traumas with neurological deficit is still controversial[21-23]. Reduction and stabilization in patients with incomplete neurological injury was demonstrated to be effective in neurological recovery[24,25]. Stabilization in patients with complete neurological damage was reported to decrease the hospital stay, rehabilitation need and complications[26,27]. It was also demonstrated that the pressure removed by anterior decompression later accelerated the neurological recovery of the patients[27,28]. The pressures in the conus and cauda equine decompressed at later a phase were also reported to be beneficial[29].

Despite different views, it is stated that there is not any relation between the stenosis in the canal and the neurological deficit[21]. There is a direct association between the spinal cord contusion rates and neurological injury. Neurological deficit in stenosis of patients with burst fractures is likely to increase by 35% at T11 and T12 levels, by 45% at L1, and by 55% at L2[30].

The studies conducted to determine whether anterior or posterior surgery is more effective showed that anterior decompression was more effective than the posterior approach to treat the patients with incomplete injury. Neurological recovery was found to be better in patients operated with anterior approach according to the urine and stool examinations[25]. Difference was not found between anterior and posterior surgery in 60 SCI patients with compression in the canal by more than 20%[21]. In another study, it was observed that anterior decompression was easier to apply for patients with burst fractures whereas no difference was found between the groups in terms of sagittal alignment[30].

Surgical approaches for spinal decompression

Decompression should achieved by posterior, posterolateral and anterior approaches. Posterior laminectomy for thoracolumbar fractures should be avoided as it will further increase the instability[31,32]. Posterior laminectomy can only be performed to repair the dural tear, to decompress a posterior fracture, and in the presence of epidural hematoma[25]. Posterolateral approach should only be performed with costotransversectomy, lateral extracavitary decompression and lateral extrapleural parascapular decompression[33].

INDICATIONS AND OPERATIVE TECHNIQUES FOR THORACOLUMBAR INJURIES

Compression fractures

Injury of the posterior elements with the presence of 30 degree-kyphosis due to the compression fracture and more than 50% loss in the vertebrae height is indicated for surgery. Posterior approach would be appropriate for such patients. Reduction and stabilization should be performed in distraction mode[34]. Lateral flexion-compression fractures should be stabilized in distraction mode on the damaged side and in compression mode on the non-damaged side.

Burst fractures

Surgical treatment of thoracolumbar burst fractures is controversial. Anterior decompression and stabilization would be appropriate for the instable burst fractures in

the thoracolumbar junction with neurological deficit[35]. Anterior decompression is more effective than posterior indirect decompression approach[36]. The reconstructive technique to be applied following decompression should be determined depending on the shape of the deformity. If the posterior elements remain intact, anterior and medial middle columns should be supported[36]. Parker reported that he performed anterior decompression and fusion for 150 patients who had thoracolumbar burst fractures with neurological deficit and 72% of patients had recovery in their neurological deficits[37]. Posterior instrumentation should be supplemented to the treatment of patients with posterior injury. Short segment pedicle screws lead to high rates of insufficiency in instable thoracolumbar fractures due to the rigidity of the posterior pedicles[12]. 360 degree fusion surgery would be appropriate for the patients with serious injury in the anterior column rather than anterior approach alone[38].

Flexion-distraction injuries

Interspinous ligaments, posterior longitudinal ligament (PLL) and disc that are damaged due to the flexion-distraction injury cause instability in adults[38]. If the middle column remains intact, one level above and one level below the damaged level should be stabilized in compression mode. If the middle column is not intact, the system should be stabilized by distraction to prevent the fracture fragments from entering into the canal.

Fracture-dislocations

Fracture-dislocation fractures are instable, and postural reduction is not effective on the bilateral facet dislocations[39]. In this case, decompression and stabilization by anterior surgical approach should be performed after the posterior surgery[39].

Distraction-extension injuries

Distraction-extension injuries are instable and accompanied by neurological deficit. Posterior reduction can achieve spinal stability and sagittal alignment.

Cervical injuries: Indications and options for surgery

The basic principle of surgery is to perform decompression and restore stability in order to reverse the neurological deficit. To this end, anterior, posterior or combined surgery can be chosen. In some cases, halo and traction may be needed. The objective is to make the patient mobile again as soon as possible and provide rehabilitation to the patient.

Anterior decompression and stabilization

Decompression can be achieved between C3 and C7 with anterior approach[40-42]. Anterior approach may also be applied to the C1-2 junction, though rarely. It is possible to access upper pathologies by transoral approach. There are methods available where stabilization with transoral approach has been defined[42].

Posterior decompression and stabilization

It is also possible to access the entire cervical spine by posterior approach. It would be suitable to use the traction device for patients with fracture dislocation. As correction of the dislocation in such patients eliminates the main problem which causes stenosis in the canal, it would also exclude the need for laminectomy. Fusion should be performed after correcting the dislocated vertebrae.

Cervical fractures

Atlas (C1): SCI is less likely to occur as the canal diameter at C1 and C2 is larger than the subaxial cervical canal. Results of the direct radiographies have been used to determine whether surgery is required for the fractures of the anterior and posterior arches, which are commonly known as Jefferson fractures. The stability of the fracture depends on the lateral displacement of the fracture. If the lateral displacement is greater than 7 mm, it is good for transverse ligament damage and a sign for instability[43,44]. Since MRI is now used on a daily basis, it is possible to clearly identify any damage in the transverse ligament. Spence divided atlas fractures into two categories by assessing the MRI images, which are transverse ligament damage without fracture in the bone (Type Ⅰ) and transverse ligament damage accompanied by avulsion in the bone (Type Ⅱ). Authors suggest that the instability of C1-2 in case of Type I injuries should be stabilized surgically.

McGuire *et al*[45] reported that they fixed and fused the instable atlas burst fractures with C1-2 transarticular screws. Halo should be used for 12-16 wk by patients for whom posterior wiring was performed at C1-2 level[20].

Axis (C2) [odontoid (dens) fracture]: They occur due to the flexion or extension mechanisms. Classification is done depending on the location of the fracture. Type Ⅰ fractures are in the apex of the dens. They can be treated with rigid neck collars. Separation of 4 to 5 mm in Type Ⅱ fractures might not be probably fused[43]. C1-2 wiring can be performed for patients without posterior arch fracture. Lateral mass or transarticular screwing can be an option in the presence of a posterior fracture. Alternatively, odontoid screws may also be used[20]. The advantage of the odontoid screw is that it does not restrict rotation. Julien et al. reported 89% fusion in Type Ⅱ fractures and 100% in Type Ⅱ fractures where they used odontoid screws[46]. Moon *et al*[47] reported to have achieved fusion in all cases for whom he used odontoid screws.

Traumatic spondylolisthesis (Hangman's fracture): It is a fracture caused by C2 sliding onto C3. Type Ⅰ fractures are stable and can be treated by collars whereas Type Ⅱ fractures are displaced more than 3 mm and have an angulation more than 11 degrees. Dislocation is low in Type ⅡA but angulation is higher. Type Ⅲ fractures have a displacement greater than 3.5 mm, angulation more than 11 degrees and bilateral facet dislocation. Type ⅡA, Ⅲ fractures are instable. Fixation and surgery are required for the cases with failed fusion by rigid immobilization. Moon *et al*[47] reported to have achieved fusion in all instable patients treated with anterior C2-3 interbody fusion.

Vaccaro achieved fusion through surgical fixation in Type Ⅱ A patients with failed fusion by immobilization[38]. Xu *et al*[48] reported to have achieved fusion in all patients treated by anterior discectomy and fusion. Posterior surgery is one of the alternatives to treat the Hangman fractures. El milgui reported that they achieved fusion in all patients that stabilized by transpedicular screws[49]. Dalbayrak *et al*[50] reported successful fusions in all patients stabilized with pars screws.

Subaxial spine (C3 to C7): SCI is more likely to occur in subaxial cervical traumas with more stenotic spinal canal compared to subaxial[41-43]. Decompressive surgery is usually needed due to the compression in the anterior side. Posterior fusion might also be needed more in patients with PLL tear.

Bilateral facet dislocation occurs after high energy traumas. PLL, disc and facet capsule are ruptured. This type of trauma with double column damage is instable and requires surgery. Posterior reduction and fusion and also anterior compression might require anterior decompression. PLL might remain intact in unilateral facet dislocations, in this case the fracture is stable and fuses itself. Unilateral facet dislocations which are not reduced might cause pain and radiculopathy in later stages[40]. To prevent this, posterior reduction and fusion should be performed. In some cases, compression may be caused by the disc. In this case, anterior decompression fusion is needed before reduction. Posterior surgery would increase the likelihood of fusion in later stages[20].

Depressed fractures might occur in the vertebrae due to the compression forces. If 1/3 of the fracture is in the anterior, if the displacement is not greater than 3.5 mm den and angulation is not greater than 1 degree, the fracture is considered to be stable[32]. If the fracture also affects the middle column, the fracture is considered to be stable and requires surgery[13]. Decompression should also be performed for the disc and bone fragments pressing into the canal.

TIMING OF SURGERY

Urgent surgery is indicated in the presence of compression in the canal and progressive neurological deficit. In all other cases, timing of the surgery is still debated[13]. Some authors suggests surgery as soon as the vital functions of the patient become stable whereas some other authors claim that surgery would be appropriate in 4-5 d following the trauma. Some clinical studies reported that decompression within 24 h would be effective for neurological recovery[51]. Early decompression was demonstrated to be effective for the neurological recovery in the animal tests conducted to reverse the neurological deficit caused by SCI[4]. In the controlled study conducted by Delamarter on canines, he stated that surgery within the first hour following the trauma achieved neurological recovery[1]. He also reported that decompression surgery at hour 6 could not achieve neurological recovery. In another study, decompression within 1-3 h was reported to be effective on neurological recovery[52].

IN THE FUTURE

Many tissues in human body have a self-repair property. However, central nervous system does not have such property. Aguayo demonstrated that the CNS axonal regeneration could be achieved by grafts obtained from peripheral nerves.

The response of the immune system to the damage in the spinal cord is different from the response of the immune system to the damages in other tissues. The initial response of the nervous system except in central nervous system is mediated by the macrophages in the blood. Macrophages move to the damaged area and try to keep the toxic elements away. Macrophages activate the lymphocytes. Immune response is primarily mediated by the microglia cells to the spinal cord injuries rather than rather than the macrophages in the blood. The first reaction of the microglia cells is to increase the existing damage. The spinal cord cells cannot respond to the existing damage following the trauma. The main objectives of the strategies that are being developed is to provide the cells which can mediate the immune response to the damaged area[53].

Macrophages are known to transform into antigen-presenting cell-like cells by incubation with the peripheral nerves that have the regeneration capability [bomstein]. MHC-Ⅱ responsible in the delivery of antigens and also the auxiliary molecules (CD80, CD86 and Intercellular Adhesion Molecule 1) were observed to increase in the incubated macrophages. Macrophages release IL-1β IL-6, brain-derived neurotrophic factor.

Macrophages which are co-intubated with peripheric nerve system (PNS) cause increase in the myelin clearance and axon regeneration and continuity when transected optical nerve is injected[54]. In the mice tests, motor recovery was observed in 15 out of 22 mice in their spinal cord transaction models injected by macrophages which were co-intubated with PNS[55]. Neurological recovery was observed in the spinal transaction models of the mice injected with skin-cointubated macrophages.

Contusion model of mouse spinal cord is a frequently used method for the spinal cord damages. It mimics the spinal cord damages in humans[56]. When skin-coincubated macrophages were injected to mice on different days following contusion, motor recovery was observed to be at the highest level on the 8^{th}-9^{th} day. This period corresponds to the peat time when the number of T cells increases. Lower number of cysts was observed in the mice injected with the macrophages within a few months following contusion[57]. Motor recovery as well as much lower number of cyst formation were also reported in mice injected with dendritic cells[53].

Treatment with macrophages is indicated for the human spinal cord damages. Neurological recovery was reported in 5 of 14 patients with complete spinal cord damages in a study in which autoologous skin incubated macrophages were injected within 2 wk following the

spinal cord damage.

Lu *et al*[58] found that U0126 inhibited extracellular signal-regulated kinase (ERK) phosphorylation and the migration of astrocytes across a wound and showed to. Mitogen-activated protein kinase (MAPK)/ERK (MEK) phosphorylation activates ERK. Lin *et al*[59] showed that MEK inhibition reduces glial scar formation and promotes the recovery of sensorimotor function in rats following SCI. Walker *et al*[60] showed the neuroprotective effect of phosphatase and tensin homolog (PTEN)/phosphatidylinositol 3-kinase and mitogen-activated protein kinase signaling cascades and they improved neurological outcome after injury to the spinal cord.

Wu *et al*[61] demonstrated functional restoration of injured spinal cord by self-assembled nanoparticles composed of ferulic acid modified glycol chitosan (FA-GC). And their histological analysis revealed that FA-GC treatment significantly preserved axons and myelin and also reduced cavity volume, astrogliosis, and inflammatory response at the lesion site[61]. In another study it was shown that the selective inhibition of signal transducer and activator of transcription 1 (STAT1) reduces SCI in mice[62]. Wang *et al*[63] demonstrated that curcumin, a natural product inhibited the activation of signal transducer and activator of transcription-3 and NF-kappa B in the injured spinal cord and reduced the astrogliosis in SCI mice.

CONCLUSION

For almost 4000 years since the first introduction of SCI in the written documents of Edwin Papyruses, it is still debated. Progress could not be achieved much except the attempts to surgically eliminate the pathology causing the compression. The studies to correct SCI are ongoing. Use of neuroprotective agents as well as methods to achieve cell regeneration in addition to surgery would contribute to the solution.

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P- Reviewer: Grote S, Tokuhashi Y **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

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