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## Review Article

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# Pharmacologic and Regenerative Cell Therapy for Spinal Cord Injury: WFNS Spine Committee Recommendations

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This is a review article examining the pharmacologic and regenerative cell therapy for spinal cord injury. A literature search during last 10 years were conducted using key words. Case reports, experimental (nonhuman) studies, papers other than English language were excluded. Up-to-date information on the pharmacologic and regenerative cell therapy for spinal cord injury was reviewed and statements were produced to reach a consensus in 2 separate consensus meeting of WFNS Spine Committee. The statements were voted and reached a consensus using Delphi method. Pharmacologic and regenerative cell therapy for spinal cord injury have long been an interest of many experimental and clinical researches. Clinical studies with methylpredinisolone have not shown clear cut benefit. Other drugs such as Rho inhibitor, minocycline, riluzole, granulocyte colony-stimulating factor have also been tried without significant benefits. Regenerative cell therapy using different types of stem cells, different inoculation techniques, and scaffolds have undergone many trials highlighting the efficacies of cells and their limitations. This review article summarizes the current knowledge on pharmacologic and regenerative cell therapy for spinal cord injury. Unfortunately, there is a need for further experimental and human trials to recommend effective pharmacologic and regenerative cell therapy.

**Keywords:** Acute spinal cord injury, Methylprednisolone, Riluzole, Spinal cord regeneration, Stem cell

## INTRODUCTION

Traumatic spinal cord injury (SCI) is still considered as an uncurable disease. SCI results in a high rate of morbidity and may also carry a high risk of mortality. Incidence of acute SCI may vary by country and it is still difficult to see the accurate statics.[1-3] Acute SCI is one of the most important issues in the field of neuro-spine surgery. Although clinical management of patients with SCI has arguably significantly advanced with medical development, the establishment of neural regeneration therapy has yet to be adequately realized. Recovery from significant neurological dysfunction after SCI is a difficult problem that remains unresolved. Clinical trials on the effectiveness pharmacological therapy for SCI show limited and controversial clinical data. Research on regenerative cell therapy could not achieve promising results in spite of many trials that have been undertaken. Intense research still continues to find the best cell source, best cell type, best method of transplantation, and finally efforts are being taken to know exactly what could be the future for the regenerative therapy in SCI.

This manuscript aims to perform a thorough review of the data on the topics of pharmacologic and regenerative cell thera-

py for SCI based on the current clinical evidence and results of WFNS consensus meeting.

## METHODS

The authors performed a systematic literature search in Pub-Med, ScienceDirect, and Cochrane Library databases to find clear answers to the following questions: Question 1: Is there good evidence that high doses of methylprednisolone sodium succinate (MPSS) administration for acute SCI is beneficial?; Question 2: Is there any pharmacologic agent with high evidence level that actually can be administered for acute SCI?; Question 3: How is the current understanding of regenerative cell therapy for acute SCI? Search terms comprised relevant key words on pharmacologic therapy for acute SCI. Databases were searched between 2009 and 2019. All related clinical studies/original articles, review articles, and meta-analyses were included. We excluded case reports, experimental (nonhuman) studies, nonrelevant studies, and papers other than English language. Then, the relevant studies were identified based on the title and abstract.

The search for the "Acute Spinal Cord Injury" revealed a total of 3,786 papers that were eligible for this study. A total of 93 papers were finally selected based on the title and abstract as valid papers by combining keyword of "methylprednisolone sodium succinate," "Rho inhibitor or cethrin," "minocycline," "riluzole," or "granulocyte colony-stimulating factor." The search results of pharmacologic therapy for acute SCI are on Fig. 1.

First consensus meeting was done in June 1, 2019 in Moscow. A re-evaluation meeting was done in November 13, 2019 in Peshawar, Pakistan. Based on the literature review the authors prepared statements covering different aspects of the SCI and cervical spine trauma. A presentation based on the literature review and the prepared statements were subjected to discussions, followed by voting process by the members of the World Federation of Neurosurgical Societies (WFNS) Spine Committee using Delphi method. Answering to the questionnaire each expert voted for all of the statements grading every item on a 5-point scale according to Delphi method. 1 = total disagreement, 2 = disagreement, 3 = agreement, 4 = more than agreement, 5 = total agreement. Consensus is reached when the sum of items "1"+"2" or "3"+"4"+"5" exceeds 66%. We called a negative consensus if 1-2 > 66%, positive consensus = 3-4-5 > 66%, nonconsensus = 1-2 or 3-4-5 < 66%. The recommendations were prepared from those statements after consensus meeting.

## REVIEW

### 1. Pharmacologic Therapy for Acute SCI

Acute SCI is a serious problem that remains unresolved. It leads to severe deterioration of not only activities of daily living, but also quality of life. Research on the mechanisms of secondary injury with acute SCI has gradually progressed, and the possibility of pharmacological therapy has been recognized in recent years. However, clinical evidence resulting from clinical trials for acute SCI remains limited and controversial. This sec-

Search for key words "Acute Spinal Cord Injury" and "Methylprednisolone Sodium Succinate", "Rho Inhibitor or Cethrin", "Minocycline", "Riluzole" or "Granulocyte Colony-Stimulating Factor during the years of 2009 - 2019

Case reports, experimental (nonhuman) studies, nonrelevant studies and papers other than English language were excluded.

3786 papers

Abstract review based on the title and content.

93 papers final selection

26 paper for "Methylprednisolone Sodium Succinate"
9 papers for "Rho Inhibitor"
10 papers for "Minocycline"
33 papers for "Riluzole"
15 papers for "Granulocyte Colony-Stimulating Factor"

**Fig. 1.** A flowchart of search for the pharmacological therapy for acute spinal cord injury.

tion focused on clinical studies of the major pharmacologic therapy for acute SCI.

### 1) Methylprednisolone sodium succinate

MPSS is a synthetic corticosteroid with potential anti-inflammatory and neuroprotective effects in acute traumatic SCI.[4,5] While considerable concerns have been expressed regarding the increased risk of infections following administration of high-dose MPSS for acute SCI, this regimen remains the only pharmaco-therapeutic option for acute SCI. The optimal dose, timing of administration, efficacy, and adverse effects remain as issues in need of discussion. The results of experimental animal studies have suggested that MPSS may be effective in acute SCI, but little evidence of positive effects of MPSS has been accumulated from clinical studies. The National Acute Spinal Cord Injury Study I (NASCIS I) was a multicenter, prospective, randomized, double-blinded trial of 330 patients with acute SCI.[6] Two treatment groups were compared. Treatment 1 was a 100-mg bolus of MPSS, followed by 25 mg every 6 hours for 10 days, whereas treatment 2 was a 1,000-mg bolus of MPSS, followed by 250 mg every 6 hours for 10 days. No significant differences in neurologic outcome were identified between the 2 groups. A significant increase in wound infections was noted in the high-dose group (9.3%) compared to the low-dose group (2.6%, p = 0.01). NASCIS II was a multicenter, prospective, randomized, double-blinded trial of 487 patients with acute SCI.[7] Three treatment groups were compared: treatment 1, MPSS as a 30-mg/kg bolus followed by 5.4 mg/kg/hr for 23 hours; treatment 2, naloxone as a 5.4-mg/kg bolus, then 4.5 mg/kg/hr for 23 hours; and treatment 3, placebo (control). Patients were examined on admission, and at 6 weeks, 6 months, and 1 year after injury. Motor strength was measured using the American Spinal Injury Association (ASIA) scale, and pin prick and touch sensation were assessed. No differences in motor score were seen between treatment groups at any time point. Significant improvements in pinprick (3.4/58) and light touch (3.8/58) scores were identified at 6 months, but were lost 1 year after injury. Frequencies of wound infection and pulmonary embolus were doubled in the MPSS group, but were still not statistically significant. When patients were stratified by time to treatment, patients receiving MPSS within 8 hours displayed a statistically significant improvement of 5 points on the motor score at 6 months and 1 year (p = 0.03). Patients treated with MPSS longer than 8 hours after injury tended to show worse neurological outcome, but this difference did not reach the level of statistical significance. All reported positive results from the NASCIS 2 trial were from

post hoc comparisons. NASCIS III was a multicenter, prospective, randomized, double-blinded trial without any placebo arm, and included 499 patients with acute SCI.[8] Three treatment groups were compared: treatment 1 was MPSS at 5.4 mg/kg/hr for 24 hours. Treatment 2 was MPSS at 5.4 mg/kg/hr for 48 hours. Treatment 3 was tirilizad at 2.5 mg/kg every 6 hours for 48 hours. Patients were examined on admission and at 6 weeks, 6 months, and 1 year after injury. Motor strength was measured using the ASIA scale, and both pin prick and touch sensation were assessed. Disability was scored using the Functional Independence Measure (FIM) to interpret the functional significance of any improvement in motor score. No significant difference in motor score was evident between treatment groups at any time point. The rate of mortality due to respiratory complications was higher in the MPSS 48-hour group. The incidence of severe pneumonia was doubled and the incidence of severe sepsis was 4 times greater in the MPSS 48-hour group compared to the MPSS 24-hour group. However, these differences were not statistically significant, as the study was underpowered for this analysis. Patients were stratified by time to treatment into those treated less than 3 hours after injury and those treated 3–8 hours after injury. No differences in outcome were identified for those patients receiving MPSS within 3 hours of injury. A 5-point improvement in motor scores at 1 year was seen only for those patients treated between 3 and 8 hours of injury. No differences in sensory outcome were identified. Disability as measured by FIM was also unchanged at 1 year. All positive results reported from the NASCIS III trial were from post hoc comparisons. Opponents of the standard use of high-dose MPSS for acute SCI have highlighted these issues as serious concerns.[9-11] Hurlbert[9] carefully reviewed the published results from NASCIS II and III in the context of the original study design, including primary outcomes compared with post hoc comparisons. He demonstrated that both NASCIS II and III failed to demonstrate improvements in primary outcome measures as a result of high-dose MPSS. Post hoc comparisons did not provide compelling data for establishment of a standard high-dose MPSS for acute SCI. Administration of high-dose MPSS for 24 hours was considered experimental in clinical use for acute SCI, and 48-hour use of high-dose MPSS was not recommended. Fehlings et al.[12] conducted a systemic review of the literature to address the key questions related to the use of MPSS for acute SCI. That careful review concluded that: (1) no differences exist in motor score change at any time point in patients treated with high-dose MPSS compared to those not treated; (2) when high-dose MPSS was administered within 8 hours after injury, outcome measures at

6- and 12-month indicated modest improvements in mean motor scores in the high-dose MPSS group compared with the control group; and (3) no statistical difference was evident between treatment groups in terms of the risk of complications. They suggested 24-hour infusion of high-dose MPSS for adult patients with acute SCI within 8 hours after injury as a treatment option, and not 48-hour infusion of high-dose MPSS.

## 2) Rho Inhibitor (Cethrin, VX-210)

Cethrin (VX-210) is a recombinant inhibitor of Rho that is mainly involved in the control of the cytoskeleton, and has been shown to promote axonal outgrowth on inhibitory substrates both *in vitro* and *in vivo*.[13,14] In a rodent thoracic spinal cord contusion model, local delivery of Cethrin to the injury site has been found to reduce the extent of the lesion and improve locomotor function. Fehlings et al.[15] conducted a phase I/IIa clinical study to examine the safety and tolerability of Cethrin for acute SCI. Patients with acute cervical or thoracic SCI with complete injury of ASIA A were sequentially recruited for the multicenter study. ASIA assessment was performed in the prestudy period and in follow-up periods up to 1 year after treatment. No serious adverse events were attributed to Cethrin. The largest change in motor score was observed among cervical patients treated with Cethrin. Approximately 6% of patients with acute thoracic cord injury converted from ASIA A to ASIA C or D, compared to 31% of patients with acute cervical cord injury. Fehlings et al.[16] further designed a multicenter, randomized, double-blinded, placebo-controlled clinical trial, the SPRING (SPinal cord injury Rho INhibition investiGation) trial. A subset of patients with acute traumatic cervical SCI is currently being enrolled in the United States and Canada. Medical, neurological, and functional changes are evaluated at 6 weeks and at 3, 6, and 12 months after Cethrin administration. Ongoing clinical trials evaluating the efficacy of Cethrin for acute SCI appear interesting, but the results have yet to be published.

## 3) Minocycline

Minocycline is a tetracycline antibiotic with neuroprotective and anti-inflammatory properties, and represents another candidate for pharmacotherapy of acute SCI.[17,18] Casha et al.[19] conducted a single-center, placebo-controlled, double-blinded clinical trial to evaluate the efficacy and safety of intravenous (IV) minocycline within 12 hours after acute SCI. A total of 27 patients received minocycline and 25 patients received placebo. Patients treated with minocycline showed motor recovery 6 points greater than that of control. Although no difference in

recovery was observed for thoracic SCI, significance was recognized among patients with cervical injury (p = 0.05). Patients with cervical motor-incomplete injury may have shown a larger, but still not statistically significant difference. The study analysis showed a trend toward improvement of motor scores in incomplete cervical SCI in the absence of any serious adverse effects. A phase III randomized control trial, Minocycline in Acute Spinal Cord Injury, has been initiated as a multicenter, placebo-controlled, double-blinded randomized controlled trial.[20,21] Adult patients with cervical SCI presenting within 12 hours of injury are being randomly assigned to receive IV administration of minocycline or placebo. Ongoing clinical trials evaluating the efficacy of minocycline for acute SCI appear interesting, but the results have yet to be published.

## 4) Riluzole

Riluzole is a benzothiazole that inhibits voltage-gated sodium channels and glutamate release, thereby mitigating excitotoxicity, and can be used for the treatment of amyotrophic lateral sclerosis.[22,23] Grossman et al.[24] conducted a prospective, multicenter, phase I matched-comparison trial of the safety, pharmacokinetics, and preliminary trial of riluzole for acute SCI. The study included a total of 36 patients with acute SCI categorized as ASIA impairment scale A–C. Riluzole was administered every 12 hours either orally or by nasogastric tube, starting within 12 hours after injury. A control group comprised 36 patients with SCI—matched for neurological impairment, sex, and age—received the standard of care, but no riluzole. Mean motor score for cervical injury patients treated with riluzole increased by 31.2 points from admission to 90 days, compared to 15.7 points for 26 control patients, representing a 15.5-point difference (p = 0.021). In particular, patients with ASIA impairment scale B showed the highest improvement. Riluzole blocks the sodium channels in neurons and may prevent increases in the intracellular concentration of sodium, finally leading to the inhibition of cellular death in the process of secondary mechanisms of injury in acute SCI. Fehlings et al. further designed a randomized, double-blinded, placebo-controlled parallel multi-center trial (Phase IIB/III trial) named "Riluzole In acute Spinal Cord Injury Study."[25] The primary objective of that trial was to evaluate the superiority of riluzole. Riluzole was administered orally at a dose of 100 mg twice-daily to adult patients within 12 hours after injury, followed by two 50-mg doses daily for 14 days, and compared with placebo in terms of improving neurological motor outcomes in patients with C4–8 level, International Standards for Neurological Classification of Spinal Cord Injury Ex-

amination (ISNCSCI) grade A, B, or C acute SCI. The primary end point for that study is the change in ISNCSCI motor score between 180 days and baseline. The study is estimated to be completed by 2021.

### 5) Granulocyte Colony-Stimulating Factor

Granulocyte Colony-Stimulating Factor (G-CSF) is a major growth factor for the activation and differentiation of granulocyte colonies in bone marrow.[26,27] The effects of G-CSF on acute SCI have been investigated with experimental acute SCI. Several clinical trials have been conducted. Inada et al.[28] conducted an open-labeled multicenter prospective, nonrandomized, controlled clinical trial to examine the neuroprotective effects of G-CSF for acute SCI. Patients were divided into 2 groups. In the G-CSF group, G-CSF was intravenously started for 5 consecutive days within 48 hours after injury. In the control group, patients were treated similarly except for the G-CSF administration. A significant improvement in ASIA motor score was detected in the G-CSF group from 1 week after administration compared with the control group ($p < 0.01$). Some spontaneous increases in motor score were detected in the control group, but the significant increase in the G-CSF group was maintained until 1 year of follow-up ($p < 0.05$). Kamiya et al.[29] conducted a clinical trial and confirmed the safety and feasibility of G-CSF as a neuroprotective pharmacological therapy in patients with acute SCI. They retrospectively analyzed clinical outcomes in SCI patients treated with G-CSF and compared the results with a historical cohort of SCI patients treated with high-dose MPSS in the NASCIS II protocol. They suggested that G-CSF is safe and superior to MPSS in terms of the clinical outcomes of acute SCI. Koda et al.[30] designed a prospective, multicenter, randomized, double-blinded, placebo-controlled comparative phase III trial of G-CSF-mediated neuroprotection for acute SCI. This clinical trial is ongoing and the results have yet to be published.

A summary of published clinical trials of major pharmacological therapies for acute SCI is given in Table 1.

### 6) Statements

Statement 1: There is not good evidence that high doses of MPSS administration for acute SCI is beneficial, in correlation with its high rate of complications. This statement had a positive consensus (90% yes).

Statement 2: In selected young patients with acute SCI 24-hour infusion of high-dose MPSS administered within 8 hours of injury can be suggested. This statement had a positive consensus (73% yes).

Statement 3: Against acute spinal cord injuries, there is no pharmacologic agent with high evidence level that actually can be administered. This statement had a positive consensus (90% yes).

### 2. Cardiopulmonary Management

Maintenance of acceptable blood pressure (BP) have been

**Table 1.** Summary of published clinical trials of major pharmacological therapies for acute SCI

| Clinical trial | Publication year | Study design | Interval from injury to study entry | Outcome |
|---|---|---|---|---|
| MPSS (NASCIS I) | 1984 | Multicenter, randomized, blinded MPSS, 2 dose regimens | 48 hr | Negative |
| MPSS (NASCIS II) | 1990 | Multicenter, randomized, blinded, placebo-controlled High-dose MPSS, naloxone, placebo | 12 hr | Negative |
| MPSS (NASCIS III) | 1997 | Multicenter, randomized, blinded 24-hr MPSS, 48-hr MPSS, tirilazad mesylate | 6 hr | Negative |
| Rho inhibitor (Cethrin, VX-210) | 2011 | Multicenter, phase I/IIa | 7 days | Positive for complete cervical SCI compared to complete thoracic SCI |
| Minocycline | 2012 | Phase II, randomized, placebo-controlled | 12 hr | Partly positive for incomplete cervical SCI |
| Riluzole | 2014 | Multicenter, prospective, phase I | 12 hr | Partly positive for incomplete cervical SCI |
| G-CSF | 2014 | Multicenter, prospective, non-randomized | 48 hr | Motor score improvement from 1 wk to 1 yr after treatment |
| G-CSF | 2015 | Retrospective, phase I/IIa G-CSF vs. MPSS as a historical control | 48 hr | Motor score improvement at 3 mo after treatment |

SCI, spinal cord injury; MPSS, methylprednisolone sodium succinate; NASCIS, National Acute Spinal Cord Injury Study; G-CSF, granulocyte colony-stimulating factor.

found to improve the neurologic outcomes of spinal cord injured patients for many years.[31] Subsequent studies have found that BP augmentation to maintain mean arterial blood pressure (MAP) more than 85 mmHg for 7 days and a good oxygenation are necessary for better outcomes.[32] Almost half of the cervical SCI patients required pressors to maintain MAP above 85 mmHg.[32]

In another study, 82% of the patients had volume-resistant hypotension requiring pressors within the first 7 days. This resistant was more common in complete injury patients.[33]

Early correction of hypotension in SCI (systolic BP < 90 mmHg) when possible is encouraged. MAP should be maintained between 85–90 mmHg for the first 7 days following an acute SCI.[34] MAP correlates with neurological recovery after human SCI.[35]

Some researchers have postulated that American Spinal Injury Association Impairment Scale (AIS) grade A patients may have greater benefit from MAP augmentation than AIS grade D patients.[36]

The risks of vasopressor therapy must also be considered. Since dobutamine can cause vasodilation with the possible risk of reflex bradycardia, it should not be used in SCI, instead dopamine, norepinephrine, or epinephrine should be chosen.[37,38]

Dopamine has greater complication rate than phenylephrine, and older patients experienced more complications than younger patients.[39]

Another concern is the level of the injury. In high cervical and thoracic injuries (above T6), with both hypotension and bradycardia Dopamine or Norepinephrine is recommended because of bradyarrhythmias due to unopposed vagal tone. In lower thoracic injuries, where hypotension can result in vasodilation, pure α-adrenergic agents such as phenylephrine are recommended.[38] Phenylephrine avoids reflex bradycardia and is also preferred in older patients.

Recommendations on cardiopulmonary management will be done in another paper of this special issue.

## 3. Hypothermia

There are many experimental animal studies that demonstrated hypothermia is useful to prevent secondary damage of SCI.[40-43] Hypothermia historically has been tried for brain and SCI patients.[41,42,44] Hypothermia was tried especially in thoracoabdominal aortic aneurysm repair.[43] However, its usage in traumatic SCI as a neuroprotectant still remains experimental. There are some case reports and some small human studies reporting that localized and systemic hypothermia can be beneficial in clinical setting. It was used as a sole treatment or com-

bined with surgical decompression and steroids.

There are some case reports[45] and some case-controlled studies.[46-48]

Levi et al.[46] have applied systemic cooling (32°C–34°C) by intravascular cooling catheter to 14 patients with complete AIS grade A, after decompression, stabilization. No steroids were used. Six of 14 patients (42.8%) in hypothermia group and 3 of 14 patients in the uncooled control group exhibited improvement from AIS grade A to another grade at 12 months.

In a study by Dididze et al.[47] 43% of AIS grade A patients (15 of 35) improved from AIS A to another grade after systemic hypothermia. In 2013, Hansebout and Hansebout[48] have reported a prospective case-series including 20 patients with neurologically complete SCI (AIS grade A) who underwent a combination of surgical decompression, dexamethasone, and local extradural cord hypothermia. Regional hypothermia (6°C) achieved by placing a suspended epidural cooling saddle onto the dura of the exposed, injured spinal cord. Sixteen of 20 patients (80%) with AIS grade A (12 cervical and 4 thoracic) attained some degree of sensory and motor recovery.

The results of those clinical trials are encouraging. There is a need to organize multicenter higher-level clinical trials involving larger patient groups.

## 4. Role of Regenerative Cell Therapy in SCI

Regenerative cell therapy is being looked forward to provide some solution and hence significant effort is put on research in finding the best cells to improve functional status in patients. There are many articles published on this subject. Search is continuously on to find the best cell source, best cell type, best method of transplantation, and finally the future for the regenerative therapy in SCI. Neuro regenerative trials have been attempted to enhance endogenous regeneration process, exogenous supplement, and alterations of intrinsic barriers. From basic bone marrow stem cells to the recent pluri-potent cells large number of clinical trials have gone through.

### 1) Cell types and salient features:

Bone marrow mononuclear cells (BMMNC) consisting of hematopoietic stem cell (HSC) and mesenchymal stem cell (MSC) are autologous stem cells with less immune rejection.

### (1) Bone marrow mononuclear cells

They comprise of cells obtained from bone marrow of a heterogenous population pool consisting of both HSCs and MSC. The main advantage is that autologous stem cells produce less

immune rejection. Presence of MSCs and HSCs in these unfractioned cell population may offer synergistic results in angiogenesis and matrix rebuilding. However, plasticity is less, *in vitro* culture is difficult, and differentiation potential is limited.

In a study done by Sharma et al.[49] in 2012, among 71 children suffering from neurological disorders such as muscle dystrophy, cerebral palsy, and injury to the brain and spinal cord, 100% of SCI patients showed an improvement. While most studies have reported improvement in motor and sensory function, Park et al.[50] evaluated the therapeutic effects of autologous BMMNC in adjunction with granulocyte macrophage colony-stimulating factor (GM-CSF) at the injury site and subcutaneously. The study showed sensory improvements almost immediately within a time frame of 3 weeks to 7 months, with no morbidity or mortality. Three hundred twenty-eight ASIA A and B score patients were assessed in a large metanalysis by Aghayan et al.,[51] encouraging autologous mononuclear cell transplantation for SCI. However, the regeneration of the neural tracts has not been reported.

### (2) Hematopoietic stem cells

Like BMMNC, HSCs also produce less immune rejection. However, not only is their purification difficult, but the differentiation potential is very limited.

Thakkar et al.[52] studied the infusion of autologous adipose tissue from neuronal differentiated MSCs and HSCs in posttraumatic paraplegics in 2016. Variable yet sustained motor and sensory improvements were noted by routinely used scoring systems. Al Zoubi et al.[53] have reported a study of 19 patients with ASIA A SCI using transplanted purified autologous leukapheresis derived CD34+ and CD133+ stems cells. Among those chronic patients, 53% demonstrated no improvement, but the rest of the patients showed segmental sensory improvement to ASIA B.

The status remains the same as for HSCs too, while most of them have reported improvement in motor and sensory function, but per se regeneration of the neural tracts has not been reported

### (3) Mesenchymal stem cells

MSCs have high neuronal differentiation potential. They also cause less immune rejection with impressive immunomodulation potential. MSCs can easily be harvested from bone marrow, fat, and skeletal muscle. Difficulty is with it's purification, and the genomic instability during long term *in vitro* manipulation. Deda et al.[54] used pre- and postoperative somato-sensory evaluation and magnetic resonance imaging guidance in 9 pa-

tients with complete SCI (ASIA A). It proved to be safe and effective with promising results. As suggested by Khan et al.,[55] MSCS in conjunction with scaffolds were reported to have better results. Variable trends in sensory, motor, neuropathic pain, and bowel-bladder dysfunction were observed in a study by Vaquero et al.[56] in 10 complete SCI patients. They also saw a profound improvement in the degree of spasticity in the study group. In another study by him, comprising of 12 complete SCI patients, all patients experienced an improvement especially in clinical and neurophysiological outcomes.

On the contrary, in a phase III clinical trial, Oh et al.[57] showed a limited efficacy in chronic patients with ASIA B status for over 12 months duration and another group of SCIs within 3 months. There was hardly any improvement in motor function with power improving from grade 1 to 3 in only 2 out of 16 patients. The immunomodulatory characteristics make them attractive for clinical therapy and several studies are still ongoing.

Hur et al.[58] suggested the use of intrathecal (IT) MSCs. While a few showed some improvement in motor scores, sensory nerve involvement was not very significant in the population. A fraction of the population also suffered adverse effects.

Other trials are still uncertain showing minimal to moderate improvement in motor and sensory scores, hence questioning the overall efficacy of MSCs.

### (4) Neural stem cells (NSCs), neural progenitor cells (NPCs)

These multipotent progenitor cells can differentiate to neural cells, oligodendrocytes, and astrocytes. In a normal adult, they locate around the central canal of the spinal cord. Like other stem cells, their isolation and differentiation are tedious too.

In a phase I/IIa open label nonrandomized controlled clinical trial by Shin et al.,[59] transplanted progenitor cells into the injured spinal cords showed at least a 2-point score improvement on ASIA score and in electrophysiological studies.

Kucher et al.[60] carried out the first human study in 2018, to assess the feasibility, safety, pharmacokinetic and preliminary efficacy of human anti-Nogo A antibody ATI3555 following IT administration in acute complete traumatic paraplegic and quadriplegic patients. Motor scores showed an elusive but considerable improvement.

Though they are native to the tissue being repaired, their inaccessibility in regard to source and inability to provide a wholesome environment for regeneration are still hurdles for further progress.

## (5) Olfactory ensheathing cells

Olfactory ensheathing cells (OECs) are harvested from the olfactory bulb and the nasal mucosa. They express neurotrophins and have the ability to support neurogenesis, reduce the risk of hypertrophy of the central nervous system astrocytes. The autologous transplantation is considerably conceivable, as it shows no graft rejection or need for immunosuppression, besides the added benefit of easy accessibility. However, differentiation potential is limited when compared with embryonic stem cells (ESCs) and MSCs, and the inadequate cell source particularly in autologous transplants is noted. The cell purification and distillation are also challenging. The major hurdle is, the limited cell quantity for autologous transplants.

While prospective randomized double-blind study of Chen et al.[61] showed good improvements, another study by Rao et al.[62] showed no significant motor or sensory improvement. Another trial by Tabakow et al.[63] showed a restitution of the continuity of some of the white matter tracts, hence showing improvement in motor and sensory function below the level of injury. Although safety studies have shown no adverse effect, they have not found efficiency in SCI.

## (6) Embryonic stem cells

ESCs have the remarkable ability to differentiate into various cell lineages, along with the ability to proliferate over several passages.[64] Due to immuno-rejection of ESC, immunosuppressive therapy is also co administered.

Many ethical issues, and the risk of teratoma with ESC are some important concerns. The Geron Corporation is a publicly traded company that launched a phase I clinical trial of a human ESC-based therapy for SCI.[20] The company enrolled the first patient in October 2010 and stopped the trial 1 year later. The fifth patient had been enrolled but not transplanted when the company announced the trial's end.

## (7) Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) have the advantage of personalized cell therapy, and their differentiation potential is similar to that of ESCs.[65] However, the immunogenicity and high level of genomic instability are the main handicaps. In February 2019, the Japanese Government's Health Ministry had given permission for a trial of human induced pluripotent stem cells to treat SCI. Researchers at Keio University plan to recruit 4 adults who had sustained recent nerve damage in sports or traffic related accidents.

## 2) Inference on the cell types

Several clinical trials using different kinds of cells and stem cells have reported realistic outcomes mainly establishing safety rather than efficacy. The actual need of the hour is a multicentric large randomized clinical trial comparing all these cell sources to arrive at a consensus. Cells like ESCs and iPSCs which have pluripotency remain as probable ideal sources for future clinical trials, but several hurdles like teratogenicity, mutagenicity, ethical issues, etc. remain unsolved.

## 3) Route of injection

IT, IV, and direct intralesional (IL) transplantations are the common routes employed. Though IL transplantation is the most efficacious, the complexity of the procedure combined with a risk of damage to the already compromised tissue in case of IL makes the minimally invasive IT and IV routes a better choice. If IT and IV routes compared, cell engraftment and tissue sparing were better in IT compared to IV route according to a study. The host immune response was also reduced in IT route. In Takahashi's tracking of neural stem/progenitor cells by bioluminescence imaging after they were transplanted by IL, IV, and IT routes, the study concluded that in terms of cell engraftment and safety, IL route was the most effective and feasible method.[66] Geffner et al.[67] suggested that multiple routes offered more efficacious results in cell transplantation for SCI.

## 4) Scaffolds or biomaterials

Retention of the transplanted cells to the site of injury still remains a problem, for which various biomaterials offer a potential solution. Scaffolds promote regeneration, help survival of transplanted cells, and can act as an environment to deliver drugs. Tissue engineering employing scaffolds is an attractive option for optimal *in vivo* repair in SCI. Scaffolds such as collagen, poly-lactic-co-glycolic acid (PLGA), PEG, etc. have been employed for cell transplantation in SCI.

QL6a biomaterial peptide has been found useful for graft survival of NSCs.[68] Hyaluronan/Methylcellulose (HAMC) is a biodegradable polymer and helps to support the grafts of neural stem cells and oligodendrocyte progenitor cells (OPCs). Neuro-Spinal Scaffold is another bioresorbable polymer scaffold called INSPIRE and has been used in humans.[69] Fibrin glue containing acidic fibroblast growth factor (aFGF) is another scaffold. It has been used for sural nerve grafts to bridge the spinal cord gap and placing fibrin glue mixed with aFGF to the grafted area is the technique used.[70] Currently, a phase III multicenter, double-blinded, placebo-controlled, randomized trial continue. The

name of the trial is ES135/rhFGF1 and it is based on Taiwan.

There are some other novel therapies in the pipeline such as "Neurite Growth-Promoting Anti-Nogo-A Antibodies" and activating endogenous NSCs to promote regeneration *in situ*.

### 5) Final thoughts on cell source, cell type, and transplantation conditions

The blood-brain barrier is an important aspect to be considered while identifying ideal cell source for regenerative therapies for spinal cord. Though there are different autologous adult cell sources such as bone marrow stem cells, MSCs, OECs, an ideal cell source would be one which has both hematopoietic component for providing nutrition and matrix building component for optimal regeneration. Autologous cells are safe and non-immunogenic. Even if the blood-brain barrier is breached, they will not be rejected. Allogenic cells have teratogenic character. Hence autologous adult cells are the best bet for regenerative therapies of SCI. Comprehensive mononuclear cells from the bone marrow–BMMNC–will be one such ideal source which has both HSCs and MSCs. BMMNCs can be derived autologous and from adults too.

Once an ideal cell source is chosen, then next step to focus on will be to retain the cells in the lesion area and an interface should be present between the transplanted cells and the host environment. Scaffolds offer a potential solution.

Natural scaffolds such as Chitosan, Collagen, Alginate have been employed for SCI repair. Though they possess excellent biocompatibility, they have risk of biological contamination and immunogenicity. Synthetic scaffolds have better mechanical properties and lesser risk of biological contamination and immunogenicity. Synthetic scaffolds such as PVC, PTFE, PHEMA, PLA, PLGA, PLCL, TGP have been employed for spinal cord repair.[71,72]

In general, there are different types of stem cells currently being searched in SCI trials: MSCs, OECs, Schwann cells, NSCs, OPCs. ESCs can have ethical problems. But iPSCs can proliferate and generate cells of all 3 germ layers, and avoid the ethical issues. Besides, it is possible to program somatic cells into NSCs and MSCs without changing their pluripotent potentials.[73,74]

### 6) Statements

Statement 4: We are not able to make any recommendation regarding efficacy of stem cell therapy in SCI treatment. This statement had a positive consensus (100% yes).

## CONCLUSION

Administration of methylprednisolone has been discussed for many years. There is no good evidence that high-dose MPSS administration is beneficial for acute SCI. In selected young patients with acute SCI and no comorbidity, infusion of high-dose MPSS administered within 8 hours of injury can be suggested. No pharmacological therapy with high-level evidence can actually be administered for acute SCI. The results of ongoing clinical trials need to be carefully evaluated and applied in actual clinical practice for acute SCI.

Although clinical management of patients with SCI has arguably significantly advanced with medical development, the establishment of neural regeneration therapy has yet to be adequately realized. Stem-cells research and clinical trials will continue. However, it is premature to recommend stem cells as a treatment modality in SCI at present.

## WFNS SPINE COMMITTEE RECOMMENDATIONS

Recommendations for Pharmacologic Therapy of Acute SCI
- There is not good evidence that high doses of MPSS administration for acute SCI is beneficial, in correlation with its high rate of complications.
- In selected young patients with acute SCI 24-hour infusion of high-dose MPSS administered within 8 hours of injury can be suggested.
- Against acute spinal cord injuries, there is no pharmacological agent with high evidence level that actually can be administered.

Recommendations for Regenerative Cell Therapy in SCI
- We are not able to make any recommendation regarding efficacy of stem cell therapy in SCI treatment.

## CONFLICT OF INTEREST

The authors have nothing to disclose.

## REFERENCES

1. O'Connor PJ. Survival after spinal cord injury in Australia. Arch Phys Med Rehabil 2005;86:37-47.
2. Martins F, Freitas F, Martins L, et al. Spinal cord injuries--epidemiology in Portugal's central region. Spinal Cord 1998;

36:574-8.

3. Ackery A, Tator C, Krassioukov A. A global perspective on spinal cord injury epidemiology. J Neurotrauma 2004;21: 1355-70.

4. Hsu CY, Dimitrijevic MR. Methylprednisolone in spinal cord injury: the possible mechanism of action. J Neurotrauma 1990;7:115-9.

5. Takami T, Oudega M, Bethea JR, et al. Methylprednisolone and interleukin-10 reduce gray matter damage in the contused Fischer rat thoracic spinal cord but do not improve functional outcome. J Neurotrauma 2002;19:653-66.

6. Bracken MB, Collins WF, Freeman DF, et al. Efficacy of methylprednisolone in acute spinal cord injury. JAMA 1984;251: 45-52.

7. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med 1990; 322:1405-11.

8. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. JAMA 1997;277:1597-604.

9. Hurlbert RJ. Methylprednisolone for acute spinal cord injury: an inappropriate standard of care. J Neurosurg 2000;93(1 Suppl):1-7.

10. Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. Neurosurgery. 2013 Mar;72 Suppl 2:93-105.

11. Nesathurai S. Steroids and spinal cord injury: revisiting the NASCIS 2 and NASCIS 3 trials. J Trauma 1998;45:1088-93.

12. Fehlings MG, Wilson JR, Tetreault LA, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the use of methylprednisolone sodium succinate. Global Spine J 2017;7(3 Suppl): 203S-211S.

13. Baptiste DC, Fehlings MG. Pharmacological approaches to repair the injured spinal cord. J Neurotrauma 2006;23:318-34.

14. Dergham P, Ellezam B, Essagian C, et al. Rho signaling pathway targeted to promote spinal cord repair. J Neurosci 2002; 22:6570-7.

15. Fehlings MG, Theodore N, Harrop J, et al. A phase I/IIa clinical trial of a recombinant Rho protein antagonist in acute spinal cord injury. J Neurotrauma 2011;28:787-96.

16. Fehlings MG, Kim KD, Aarabi B, et al. Rho inhibitor VX-210 in acute traumatic subaxial cervical spinal cord injury: design of the spinal cord injury Rho INhibition InvestiGation (SPRING) clinical trial. J Neurotrauma 2018;35:1049-56.

17. Teng YD, Choi H, Onario RC, et al. Minocycline inhibits contusion-triggered mitochondrial cytochrome c release and mitigates functional deficits after spinal cord injury. Proc Natl Acad Sci U S A 2004;101:3071-6.

18. Wells JE, Hurlbert RJ, Fehlings MG, et al. Neuroprotection by minocycline facilitates significant recovery from spinal cord injury in mice. Brain 2003;126(Pt 7):1628-37.

19. Casha S, Zygun D, McGowan MD, et al. Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. Brain 2012;135(Pt 4):1224-36.

20. Badhiwala JH, Ahuja CS, Fehlings MG. Time is spine: a review of translational advances in spinal cord injury. J Neurosurg Spine 2018;30:1-18.

21. Ulndreaj A, Badner A, Fehlings MG. Promising neuroprotective strategies for traumatic spinal cord injury with a focus on the differential effects among anatomical levels of injury. F1000Res 2017;6:1907.

22. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev 2012;2012:CD001447.

23. Mu X, Azbill RD, Springer JE. Riluzole and methylprednisolone combined treatment improves functional recovery in traumatic spinal cord injury. J Neurotrauma 2000;17:773-80.

24. Grossman RG, Fehlings MG, Frankowski RF, et al. A prospective, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma 2014;31:239-55.

25. Fehlings MG, Nakashima H, Nagoshi N, et al. Rationale, design and critical end points for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): a randomized, double-blinded, placebo-controlled parallel multi-center trial. Spinal Cord 2016;54:8-15.

26. Nishio Y, Koda M, Kamada T, et al. Granulocyte colony-stimulating factor attenuates neuronal death and promotes functional recovery after spinal cord injury in mice. J Neuropathol Exp Neurol 2007;66:724-31.

27. Pitzer C, Klussmann S, Krüger C, et al. The hematopoietic factor granulocyte-colony stimulating factor improves out-

come in experimental spinal cord injury. J Neurochem 2010; 113:930-42.

28. Inada T, Takahashi H, Yamazaki M, et al. Multicenter prospective nonrandomized controlled clinical trial to prove neurotherapeutic effects of granulocyte colony-stimulating factor for acute spinal cord injury: analyses of follow-up cases after at least 1 year. Spine (Phila Pa 1976) 2014;39:213-9.

29. Kamiya K, Koda M, Furuya T, et al. Neuroprotective therapy with granulocyte colony-stimulating factor in acute spinal cord injury: a comparison with high-dose methylprednisolone as a historical control. Eur Spine J 2015;24:963-7.

30. Koda M, Hanaoka H, Sato T, et al. Study protocol for the G-SPIRIT trial: a randomised, placebo-controlled, double-blinded phase III trial of granulocyte colony-stimulating factor-mediated neuroprotection for acute spinal cord injury. BMJ Open 2018;8:e019083.

31. Zäch GA, Seiler W, Dollfus P. Treatment results of spinal cord injuries in the Swiss Parplegic Centre of Basle. Paraplegia 1976;14:58-65.

32. Vale FL, Burns J, Jackson AB, et al. Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. J Neurosurg 1997;87:239-46.

33. Levi L, Wolf A, Belzberg H. Hemodynamic parameters in patients with acute cervical cord trauma: description, intervention, and prediction of outcome. Neurosurgery 1993;33:1007-16.

34. Ryken TC, Hurlbert RJ, Hadley MN, et al. The acute cardiopulmonary management of patients with cervical spinal cord injuries. Neurosurgery 2013;72 Suppl 2:84-92.

35. Hawryluk G, Whetstone W, Saigal R, et al. Mean arterial blood pressure correlates with neurological recovery after human spinal cord injury: analysis of high frequency physiologic data. J Neurotrauma 2015;32:1958-67.

36. Catapano JS, John Hawryluk GW, Whetstone W, et al. Higher mean arterial pressure values correlate with neurologic improvement in patients with initially complete spinal cord injuries. World Neurosurg 2016;96:72-9.

37. Bao FP, Zhang HG, Zhu SM. Anesthetic considerations for patients with acute cervical spinal cord injury. Neural Regen Res 2017;12:499-504.

38. Consortium for Spinal Cord Medicine. Early acute management in adults with spinal cord injury: a clinical practice guideline for health-care professionals. J Spinal Cord Med 2008;31:403-79.

39. Readdy WJ, Whetstone WD, Ferguson AR, et al. Complications and outcomes of vasopressor usage in acute traumatic central cord syndrome. J Neurosurg Spine 2015;23:574-80.

40. Jorge A, Fish EJ, Dixon CE, et al. The effect of prophylactic hypothermia on neurophysiological and functional measures in the setting of iatrogenic spinal cord impact injury. World Neurosurg 2019;129:e607-13.

41. Alkabie S, Boileau AJ. The role of therapeutic hypothermia after traumatic spinal cord injury--a systematic review. World Neurosurg 2016;86:432-49.

42. Tracy B, Armola R, Micham J. The "cold cord": a review of therapeutic hypothermia for traumatic spinal cord injuries. Am J Crit Care 2015;24:540-3.

43. Martirosyan NL, Patel AA, Carotenuto A, et al. The role of therapeutic hypothermia in the management of acute spinal cord injury. Clin Neurol Neurosurg 2017;154:79-88.

44. Zhu L. Hypothermia used in medical applications for brain and spinal cord injury patients. Adv Exp Med Biol 2018;1097:295-319.

45. Cappuccino A, Bisson LJ, Carpenter B, et al. The use of systemic hypothermia for the treatment of an acute cervical spinal cord injury in a professional football player. Spine (Phila Pa 1976) 2010;35:E57-62.

46. Levi AD, Casella G, Green BA, et al. Clinical outcomes using modest intravascular hypothermia after acute cervical spinal cord injury. Neurosurgery 2010;66:670-7.

47. Dididze M, Green BA, Dietrich WD, et al. Systemic hypothermia in acute cervical spinal cord injury: a case-controlled study. Spinal Cord 2013;51:395-400.

48. Hansebout RR, Hansebout CR. Local cooling for traumatic spinal cord injury: outcomes in 20 patients and review of the literature. J Neurosurg Spine 2014;20:550-61.

49. Sharma A, Gokulchandran N, Chopra G, et al. Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life. Cell Transplant 2012;21 Suppl 1:S79-90.

50. Park HC, Shim YS, Ha Y, et al. Treatment of complete spinal cord injury patients by autologous bone marrow cell transplantation and administration of granulocyte-macrophage colony stimulating factor. Tissue Eng 2005;11:913-22.

51. Aghayan HR, Arjmand B, Yaghoubi M, et al. Clinical outcome of autologous mononuclear cells transplantation for spinal cord injury: a systematic review and meta-analysis. Med J Islam Repub Iran 2014;28:112.

52. Thakkar UG, Vanikar AV, Trivedi HL, et al. Infusion of au-

tologous adipose tissue derived neuronal differentiated mesenchymal stem cells and hematopoietic stem cells in post-traumatic paraplegia offers a viable therapeutic approach. Adv Biomed Res 2016;5:51.

53. Al-Zoubi A, Jafar E, Jamous M, et al. Transplantation of purified autologous leukapheresis-derived CD34+ and CD133+ stem cells for patients with chronic spinal cord injuries: long-term evaluation of safety and efficacy. Cell Transplant 2014; 23 Suppl 1:S25-34.

54. Deda H, Inci MC, Kürekçi AE, et al. Treatment of chronic spinal cord injured patients with autologous bone marrow-derived hematopoietic stem cell transplantation: 1-year follow-up. Cytotherapy 2008;10:565-74.

55. Khan S, Mafi P, Mafi R, et al. A systematic review of mesenchymal stem cells in spinal cord injury, intervertebral disc repair and spinal fusion. Curr Stem Cell Res Ther 2018;13: 316-23.

56. Vaquero J, Zurita M, Rico MA, et al. Repeated subarachnoid administrations of autologous mesenchymal stromal cells supported in autologous plasma improve quality of life in patients suffering incomplete spinal cord injury. Cytotherapy 2017;19:349-59.

57. Oh SK, Choi KH, Yoo JY, et al. A phase III clinical trial showing limited efficacy of autologous mesenchymal stem cell therapy for spinal cord injury. Neurosurgery 2016;78:436-47.

58. Hur JW, Cho TH, Park DH, et al. Intrathecal transplantation of autologous adipose-derived mesenchymal stem cells for treating spinal cord injury: a human trial. J Spinal Cord Med 2016;39:655-64.

59. Shin JC, Kim KN, Yoo J, et al. Clinical trial of human fetal brain-derived neural stem/progenitor cell transplantation in patients with traumatic cervical spinal cord injury. Neural Plast 2015;2015:630932.

60. Kucher K, Johns D, Maier D, et al. First-in-man intrathecal application of neurite growth-promoting anti-Nogo-A antibodies in acute spinal cord injury. Neurorehabil Neural Repair 2018;32:578-89.

61. Chen L, Huang H, Xi H, et al. A prospective randomized double-blind clinical trial using a combination of olfactory ensheathing cells and Schwann cells for the treatment of chronic complete spinal cord injuries. Cell Transplant 2014;23 Suppl 1:S35-44.

62. Rao Y, Zhu W, Liu H, et al. Clinical application of olfactory ensheathing cells in the treatment of spinal cord injury. J Int Med Res 2013;41:473-81.

63. Tabakow P, Jarmundowicz W, Czapiga B, et al. Transplantation of autologous olfactory ensheathing cells in complete human spinal cord injury. Cell Transplant 2013;22:1591-612.

64. Gazdic M, Volarevic V, Harrell CR, et al. Stem cells therapy for spinal cord injury. Int J Mol Sci 2018;19:1039.

65. Nagoshi N, Okano H. Applications of induced pluripotent stem cell technologies in spinal cord injury. J Neurochem 2017;141:848-60.

66. Takahashi Y, Tsuji O, Kumagai G, et al. Comparative study of methods for administering neural stem/progenitor cells to treat spinal cord injury in mice. Cell Transplant 2011;20: 727-39.

67. Geffner LF, Santacruz P, Izurieta M, et al. Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: comprehensive case studies. Cell Transplant 2008;17: 1277-93.

68. Liu Y, Ye H, Satkunendrarajah K, et al. A self-assembling peptide reduces glial scarring, attenuates post-traumatic inflammation and promotes neurological recovery following spinal cord injury. Acta Biomater 2013;9:8075-88.

69. Theodore N, Hlubek R, Danielson J, et al. First human implantation of a bioresorbable polymer scaffold for acute traumatic spinal cord injury: a clinical pilot study for safety and feasibility. Neurosurgery 2016;79:E305-12.

70. Wu JC, Huang WC, Chen YC, et al. Acidic fibroblast growth factor for repair of human spinal cord injury: a clinical trial. J Neurosurg Spine 2011;15:216-27.

71. Dedeepiya VD, Williams JB, Parthiban JKBC, et al. Scaffolds for cells transplantation in neurology- the suitability of thermo-reversible gelatin polymer: our perspectives. J Spinal Surg 2014;1:16-24.

72. Dedeepiya VD, William JB, Parthiban JK, et al. The known-unknowns in spinal cord injury, with emphasis on cell-based therapies - a review with suggestive arenas for research. Expert Opin Biol Ther 2014;14:617-34.

73. Chen W, Baylink DJ, Lau KH, et al. Generation of mesenchymal stem cells by blood cell reprogramming. Curr Stem Cell Res Ther 2016;11:114-21.

74. Nagoshi N, Khazaei M, Ahlfors JE, et al. Human Spinal Oligodendrogenic neural progenitor cells promote functional recovery after spinal cord injury by axonal remyelination and tissue sparing. Stem Cells Transl Med 2018;7:806-18.