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REVIEW ARTICLE

Stem cell/cellular interventions in human spinal cord injury: Is it time to move from guidelines to regulations and legislations? Literature review and Spinal Cord Society position statement

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Abstract

Purpose In preclinical studies, many stem cell/cellular interventions demonstrated robust regeneration and/or repair in case of SCI and were considered a promising therapeutic candidate. However, data from clinical studies are not robust. Despite lack of substantial evidence for the efficacy of these interventions in spinal cord injury (SCI), many clinics around the world offer them as "therapy." These "clinics" claim efficacy through patient testimonials and self-advertisement without any scientific evidence to validate their claims. Thus, SCS established a panel of experts to review published preclinical studies, clinical studies and current global guidelines/regulations on usage of cellular transplants and make recommendations for their clinical use.

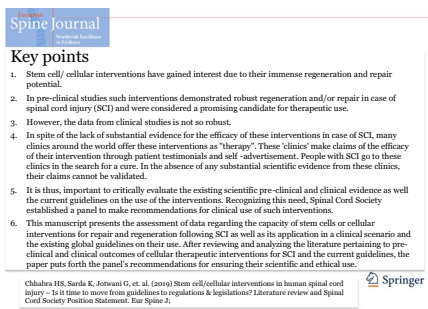
Methods The literature review and draft position statement was compiled and circulated among the panel and relevant suggestions incorporated to reach consensus. This was discussed and finalized in an open forum during the SCS Annual Meeting, ISSICON.

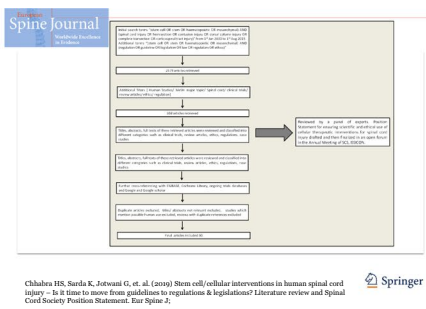
Results Preclinical evidence suggests safety and clinical potency of cellular interventions after SCI. However, evidence from clinical studies consisted of mostly case reports or uncontrolled case series/studies. Data from animal studies cannot be generalized to human SCI with regard to toxicity prediction after auto/allograft transplantation.

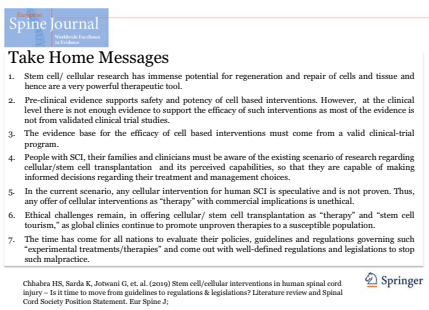
Conclusions Currently, cellular/stem cell transplantation for human SCI is experimental and needs to be tested through a valid clinical trial program. It is not ethical to provide unproven transplantation as therapy with commercial implications. To stop the malpractice of marketing such "unproven therapies" to a vulnerable population, it is crucial that all countries unite to form common, well-defined regulations/legislation on their use in SCI.

Graphical abstract

These slides can be retrieved from Electronic Supplementary Material.







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Keywords Guidelines · Spinal cord injury · Acute paraplegia · Clinical trial · Stem cell · Cellular interventions · Position statement · Regulations

Background and introduction

Recently, research on stem cells has gained the attention of researchers and clinicians in order to facilitate repair and regeneration after spinal cord injury (SCI) [1]. This is due to the huge ability of stem cells for repair and/or regeneration [2]. With the contemporary progress in stem cell research, tremendous hope for developing novel treatments for many serious diseases has been generated.

Stem cell-based/cellular transplantation has been accepted as a standard therapy only in case of leukemia, burns and corneal regeneration [3]. Other than these indications, stem cell interventions are still under trial.

As far as SCI is considered, most of the cells transplanted are not even "true stem cells," but their derivatives or similar cells or tissue which can differentiate to particular neuronal cell types or can be utilized for replacement of dead tissue to bridge a lesion [4].

Due to media attention and vested interests of few commercial enterprises, there existed several instances of misuse of such interventions where, even without the proven potency and safety, they are being offered for therapeutic reasons [5, 6].

Thus, there is a need to critically evaluate the existing literature on safety and potency of stem cell-based therapeutic interventions so as to achieve restoration and/or regeneration following SCI and also to understand the current scenario regarding the application of these cells in a clinical setting. The Spinal Cord Society India established a panel tasked with reviewing the current scenario of cellular transplantations in SCI and making recommendations for using cellular interventions in a clinical context. This panel consisted of various national and international experts from basic sciences, orthopedics, spine, neurosciences and ethics. The panel also had representatives from the major Societies in India including the Spinal Cord Society (SCS), Association of Spine Surgeons of India (ASSI), Indian Academy of Neurology (IAN), Indian Association of Physical Medicine and Rehabilitation (IAPMR), Indian Orthopedics Association (IOA) as well as representatives from the Indian Council of Medical Research, a premier body for formulating guidelines and making recommendations for conducting research in medicine in India, along with the Department of Biotechnology, Government of India. A coordinator for the panel was selected from the Indian Spinal Injuries Centre, New Delhi. The task of the coordinator was to compile existing literature on the preclinical and clinical use of cellular interventions in SCI as well as existing guidelines/regulations on their use and circulate this to the panel members for their comments via e-mail. A draft position statement was then circulated. The comments/suggestions of the panelists were collated and circulated among them. The relevant comments/suggestions were incorporated, and the draft was then re-circulated to reach consensus. The final recommendations of the panel were then discussed along with the summary of existing literature in an open forum during the annual meeting of the Spinal Cord Society, ISSICON, held in New Delhi, India.

This paper presents the assessment of data regarding the capacity of stem cells or cellular interventions for repair and regeneration following SCI and the application in a clinical scenario. It also critically evaluates the existing global guidelines/regulations on the use of these interventions. After reviewing and analyzing the literature pertaining to preclinical and clinical outcomes of cellular therapeutic interventions for SCI and the existing guidelines/regulations on their use, the paper puts forth the panel's recommendations for ensuring their scientific and ethical use.

Sources of data

We searched PubMed/MEDLINE for the terms "(stem cell OR stem OR haematopoietic OR mesenchymal) AND (spinal cord injury OR hemisection OR contusion injury OR dorsal column injury OR complete transection OR corticospinal tract injury)" from Jan 1, 2000, to Aug 1, 2017. Our initial search retrieved 2585 articles; of these 1829 were animal studies and 1208 were human studies. Additionally, a PubMed/MEDLINE search for the same time frame for the terms "(stem cell OR stem OR haematopoietic OR mesenchymal) AND (regulation OR guideline OR legislation OR law OR regulatory OR ethics)" also was undertaken. After applying additional filters, such as MeSH major topic and human species, a total of 664 articles were retrieved. The titles, abstracts and full texts (where required) of these retrieved papers were evaluated. The contents were extracted and presented/circulated from the relevant papers for further discussion. If required, recovered papers were reviewed for further relevant references. Further cross-referencing was undertaken with EMBASE, Cochrane Library, ongoing trials databases and Google and Google scholar to corroborate findings and resolve discrepancies, if any.

Stem cells and cellular interventions—an introduction

"True" stem cells are those having the ability of an indeterminate self-renewal and differentiation (development) into various cell types [1].

It is essential to recognize that in practice the term, "stem cell" has been used loosely and does not align with its accurate biological definition. In practice, cells with limited differentiation potential have been used for transplants; hence, they are not "true" stem cells. Also, many experimental interventions have been undertaken that involve transplantation of cells or tissues which have some inherent regeneration potential or have been used for replacement of the damaged tissue or cells instead of "stem cells" per se [5]. Therefore, the term "cellular or cell-based interventions" is more suitable to define such interventions and is used by us in this manuscript. The term encompasses all biological interventions that are being utilized for repair and/or regeneration after SCI.

Preclinical studies

Embryonic stem cells (ESCs), being the first true stem cells to be identified, were the first to be analyzed for their potential to transform into cells of the neuronal lineage [4, 6]. Although the cells had tremendous regeneration ability, not only in vitro and but also vivo, they were identified to be tumorigenic [4, 6].

After ESCs, the multiple lineage differentiation ability of mesenchymal stem cells (MSCs) was assessed [7]. These are chosen to study for their ability for repair because of their potency, availability and comparative safety both in autologous and allogenic uses [8–12]. However, their therapeutic role has been restricted by numerous shortcomings in their proliferation and differentiation behavior after transplant in SCI cases as well as due to differences in consequences depending on the mode of transplantation [4]. So as to prevail over the deficiencies of direct MSC transplantation, various approaches have been tried, either alone or in combination, which include transplantation of pre-differentiated cells, transducing neutrophin expression in transplanted cells, co-transplantation with glial cells and tissue engineering in SCI cases [13–16].

Other cells that have been analyzed for their therapeutic potential in SCI cases include neural stem/progenitor cells (NS/PCs) [17, 18], which did not demonstrate reproducible functional recovery, and olfactory ensheathing cells (OECs) [19, 20], where both rat [21–28] and human OECs [22] supported axonal regrowth, remyelination and conduction associated with motor recovery in a SCI replica. However, other studies suggest that the functional improvements resulting from OEC transplants might not be because of the regeneration of neurons, but because of the facilitatory microenvironment contributed by the transplanted OECs to the existing neurons, thus limiting the therapeutic potential of OECs after SCI [8].

The peripheral neural environment witnesses a morphological and electrophysiological functional recovery of the injured neurons [29]. Schwann cells (SCs) are a principal part of the PNS and are very crucial for myelinating axons of the PNS. SCs are obtained from various stem cell populations or neural progenitors such as mesenchymal stem cells [30], adipose-derived stem cells [31] and skin-derived precursors (SKPs) [32]. SC transplantation is associated with remyelination, axonal sprouting, and formation of a rostrocaudal "bridge" [29, 33]. This, however, has not been associated with any significant functional or neurological improvement, although genetic modification of SCs has been found to be associated with development of axonal regeneration and also motor activity [34].

To summarize, a considerable volume of preclinical evidence exists indicating the potency of cell-based transplantation in animal models of SCI. The published data provide good evidence for exploring the capacity of some types of cell-based interventions in human SCI.

Clinical studies

A vast spectrum of cell populations is analyzed for their potency in human SCI. These cell populations are selected based on their intrinsic properties and the results of preclinical experiments [4]. Although preclinical evidence supports the venturing of the presumptive cell populations in humans, occasionally the clinical rendition is hampered because of logistical limitations. The panel reviewed the published clinical studies using various populations and analyzed the robustness of the data for each population.

The populations tested include:

- SC, where a single study reported recovery in six cases of SCI and another reported the relatively long-term safety in chronic SCI [35, 36]. OEC feasibility, relative safety and potency were reported in 16 SCI individuals [37]. However, the results could not be replicated [38, 39]. In one case, simultaneous transplantation of OECs and fibroblasts of olfactory nerve accompanied by sural nerve graft has resulted in neurological improvement [40].
- A randomized controlled study of activated macrophages was undertaken. However, no significant improvement was seen in acute SCI [41].

- NS/PCs, though not tested due to ethical issues, are presumed to be ideal for transplantation and have yielded promising results in a few animal and human studies [42, 43]. Shin et al. conducted a phase I/IIa open-label and non-randomized controlled clinical trial transplanting human brain-derived neural stem/progenitor cells (hNSPCs) to the site of lesion in 17 individuals with American Spinal Injury Association Impairment Scale (AIS)AIS A and AIS B traumatic cervical SCI. The authors concluded that the procedure and cells were safe and exhibited some degree of neurological benefit. However, since the group was non-homogenous with respect to completeness of injury as well as the time since injury (time since injury ranged from acute to chronic), further studies are needed to confirm these findings [44].
- The feasibility of harnessing the vast regeneration capacity of ESCs has been of immense interest to researchers and clinicians alike. The media also has been fascinated by this prospect, and the field of ESC research has garnered much attention. However, various issues in regard to their safety and potency are yet to be addressed [6, 45–48]. The only trial conducted tested the safety and potency of the transplanting human ESC-derived oligodendrocyte progenitor cells, GRNOPC1, in patients with complete thoracic level paraplegia [47]. Although no safety issues were reported, the trial was suspended due to monetary constraints.
- As previously noted, MSCs are the cells of choice for assessing the safety and potency at the preclinical and clinical levels. MSCs have been co-transplanted with CD34+ cells or transplanted alone [49]. A study undertook the intrathecal application of MSCs in 45 individuals with complete chronic SCI. Monthly administrations of MSCs have also been done. MSCs were also transplanted via the intraleisonal route in 13 individuals with chronic SCI. Also, a combinational approach of administrating GM-CSF along with MSC transplantation was conducted in six individuals with SCI. Administration of MSCs via the CSF by lumbar puncture was also done in eleven individuals with SCI. One study concluded that MSC transplantation in acute and subacute SCI led to better outcomes as compared to chronic SCI. In addition to adult SCI, MSC transplantation was also attempted in pediatric SCI cases. When MSCs with chitosan–laminin scaffold and peripheral nerve grafts are simultaneously transplanted in individuals with chronic SCI, neurological recovery was observed. A study of transplantation comparing early and late SCI (less than 6 months and more than 6 months) did not yield any significant differences in radiological and electrophysiological outcomes. Similarly, transplantation of MSCs via intrathecal or intralesional route in case of acute SCI yielded comparable outcomes. Transplantation of MSCs from another source, adipose tissue, did not yield any significant improvement. Various studies have tested MSCs regarding their potency and safety. Different combinations of cell type, transplantation route, time of intervention and co-transplantations have been undertaken. With this substantial body of work, it would be expected to have a well-defined path leading toward the translation of these strategies to the clinical scenario. However, because of significant limitations of these studies, this has yet not become possible. These limitations have been discussed in other reviews and hence are not being discussed here [1, 4, 16]. Recently, several groups have conducted clinical trials or pilot studies using autologous MSCs in different doses and transplanted via different routes. Bansal et al. have reported improvement in ASIA grades, spasticity, bladder control and sexual function in patients injected with multiple doses of autologous MSCs via lumbar puncture [50]. However, since the study was not conducted as a controlled clinical trial but as a "therapy," further studies are needed to validate these findings. In a phase III clinical study, Oh et al. attempted to determine the safety and efficacy of intramedullary and intradural MSC administration in chronic SCI. Single administration was found to be safe though efficacy was not robust. They concluded that further studies with multiple administration might be more beneficial [51]. A phase I pilot study conducted by Satti et al. in nine subjects with acute and subacute SCIs established the safety of intrathecal administration of autologous MSCs [52]. In two separate studies, Vaquero et al. documented the outcome of administering autologous MSCs intralesionally followed by repeated injections into the subarachnoid space. The group concludes that this procedure was safe and led to improvement in the quality of life of patients with incomplete as well as complete SCI [53, 54]. Further studies need to be undertaken in order validate as well as establish the rationale behind empirical determination of cell dose as well as the number of injections for the "personalized therapy."

Issues in translation of preclinical data into clinical setting

In reviewing the existing literature, it becomes clear that despite encouraging preclinical evidence, cellular interventions for SCI have not yet efficiently been translated in a clinical scenario. The major reason underlying this is the deficiency of an experimental model which truly reflects human SCI. In cases where preclinical evidence is obtained from a situation close to human SCI, flaws in both clinical trial design and trial execution have led to confounding. This has severely limited the high-quality evidence arising from

the clinical studies. Sarda and Chhabra [1], in their study critically analyzed the published SCI clinical trials. To prevail over such flaws in clinical trial designs and execution, guidelines are now published and freely available to all and we can anticipate more robust data arising from ongoing and future SCI clinical trials [55–58].

To summarize, in spite of a considerable number of clinical trial studies, the strength of evidence for using cellular interventions is poor due to shortcomings in the model of those clinical trials. Better clinical trials designed to overcome these shortcomings need to be undertaken before such interventions can be brought into a clinical scenario.

Existing regulatory structure

Europe

In Europe, usage of stem cells is regulated by "The Advanced Therapy Medicinal Products" (ATMP) legislation. However, commercial clinics use the exemption for "compassionate use" and the "medical practice" exemption to deliver unproven treatments in Europe [59]. The former exemption allows doctors to utilize stem cell interventions which are under development in patients. The latter allows the usage of those "therapies" under the responsibility of the doctor, though in both cases, the cells are prepared as per the quality standards defined by EMA [60, 61].

Australia

"The Therapeutic Goods Administration (TGA)" regulates the medicines, medical devices and therapeutic goods in Australia. Similar to Europe, Australia has a medical practice exemption under which such unsubstantiated stem cell interventions are administered in a commercial setting [62]. Although a "biologicals framework" was set up by the TGA to regulate human cells and human tissues based products in 2011 [60, 63], the "stem cell therapies" do not fall under its purview and are considered for medical practice exemption. Due to this, the commercial application of unsubstantiated stem cell interventions has flourished, giving rise to concerns by the regulatory authorities, and measures are being taken to stop such malpractices.

United States of America (USA)

In USA, the FDA CFR 21 1271 provides guidelines and regulations for manufacturing human cells, tissues and cellular and tissue-based products (HCT/P's) [64, 65]. The guidelines state that cellular interventions that are "minimally manipulated, labeled or advertised for homologous use only, and not combined with a drug or device" do not need FDA approval. FDA approval is mandatory for cellular products that are more sub-maximally or maximally manipulated and/or are studied for non-homologous usage.

The maximally and sub-maximally manipulated stem cell products may be utilized for therapy in cases of "compassionate use" if the product has been tested for a clinical trial and if its use would not affect the findings of the trial per se or as "off-label prescribing" of cellular products which have approval of the FDA for different indications [65].

India

The ICMR and the Department of Biotechnology (DBT) together have laid down "Guidelines for Stem Cell Research and Therapy" in Nov 2007 which were later revised to "Guidelines for Stem Cell Research" in Dec 2013 [66]. The major difference in the two was the omission of the term "Therapy" from the title, emphasizing the truth that stem cell usage is permissible only for research and that usage of stem cells or stem cell-based interventions as a treatment option needs to undergo regulatory approval. The guideline has defined a process for reviewing and monitoring use of stem cell-dependent interventions. The process is monitored at two levels, first at the institutional level via the Institutional Committee for Stem Cell Research (IC-SCR) which reports at the national level to the National Apex Committee (the NAC-SCRT).

The IC-SCR has the power to approve all basic research studies being undertaken using the stem cell-dependant interventions. The IC-SCR reports the same to NAC-SCR. Per the guidelines, "Clinical trials using minimally manipulated or more than minimally manipulated stem cell-based interventions require approval from NAC-SCR as well as Institutional Ethics Committee (IEC)." For stem cell-dependent interventions which have commercial applications, additional approval from Drug Controller General of India (DCG(I))/Central Drugs Standards Control Organization (CDSCO) India, is also mandatory [66].

In December 2013, the Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC) set up by the CDSCO released a draft guidance document for Regulatory Approval of "Stem Cell and Cell Based Products (SCCPs)." The document recommended amending the Drugs and Cosmetics Act (DCA) 1940 to regulate all commercial applications of all SCCPs [67] in order to create regulations catered specifically for SCCPs and curb administration of unsubstantiated SCCPs interventions outside of a scientific and ethical clinical trial program. In 2017, after extensive discussions with all stakeholders and government agencies along with policy makers, the 2013 national guidelines were harmonized with the existing drug control and medical practice regulations in India. In the 2017 National Guidelines for Stem Cell Research, the IC-SCR needs to be approved

by CDSCO in addition to the NAC-SCRT approval. A registered IC-SCR, IEC, and Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) certified facility is necessary for conducting a clinical trial for cellular interventions. Also only medical professionals registered with the Medical Council Of India (MCI) with an MCI-approved post-graduate qualification in the domain area of the specific trial can be site investigators. These mandates strengthen the guidelines via regulation through the DCA [68].

Current scenario of the use of unproven stem cell interventions in India

Worldwide, the stem cell, with its capacity to multiply and differentiate, is an appealing option for a potential therapeutic. India recognizes its potential and actively supports stem cell research. However, legislation and regulations for stem cell use did not exist [59, 69]. This caused mushrooming of several clinics which offered stem cell "therapy" and invalidated claims of efficacy from such clinics [70–72]. The practices at these few clinics were subjected to widespread condemnation such as the use of ESC therapies by a center in New Delhi, which reported "improvement of nerve function" and by a center in Chennai [71, 73]. Most of the favorable neurological improvements acclaimed by such "therapies" are endorsements made by these centers. These endorsements generally are not substantiated by any scientific evidence to measure the "treatment" outcomes. Also, in a majority of the cases, the improvement cannot be extrapolated to the transplant and, with a lack of robust controls, may simply be because of the "placebo effect," supportive treatments and/or the disorder's natural history. Due to a lack of awareness regarding the SCI's natural evolution as well as the scientific technique, people with SCI erroneously may believe that their neurological improvement is because of the transplant. Most cell-based clinical trials are phase I or II trials, and assumptions about therapeutic benefit at times are drawn from their findings. This leads to ambiguity in data interpretation and presentation, especially in the method of informed consent documentation. The process of validating the possible safety and potency arising from phase I and II studies takes years and requires considerable financial investment before it is accepted as standard treatment [1].

Salter et al. [74] stated that due to lack of substantial evidence supporting the therapeutic use of stem cells as well as the deficiency of stem cell regulations in India, the stem cell development was maneuvered in a "governance vacuum". This has now been aptly addressed by the government; the harmonizing of the National Guidelines with CDSCO as published in 2017 is the step in the right direction for curbing malpractice.

To summarize, worldwide the regulations and legislation controlling stem cell research and practical use differ. They range from strict structured regulations and legislation such as those in Canada, USA, UK and Australia to published guidelines as in India. This difference in regulation of research in stem cells in different countries has promoted "Stem Cell Tourism" wherein individuals with SCI travel from countries with strict regulatory structure to those with little, permissive or no regulatory structure for stem cell use in a clinical scenario. Such a trend is very detrimental to those who are working on establishing scientifically valid evidence for the potency of cellular interventions for facilitating restoration, regeneration and neurological recovery after sustaining SCI. It is critical that all nations unite in order to form well-defined and structured regulations and legislation to stop such malpractice and promote validated clinical trial programs to analyze the safety and potency of cellular interventions in case of SCI.

Spinal cord society's position statement

Based on the reviewed literature, the recommendations of the expert panel and discussions in an open forum during its annual meeting, Spinal Cord Society has issued the following position statement, the full text of which is enclosed as supplemental data (also available on www.scs-isic.com). The concluding remarks of the statement are as under:

Stem cell/cellular interventions in human spinal cord injury: is it time to move from guidelines to regulations and legislations?

Advances in pharmacological interventions, medical/surgical management, rehabilitation and cellular interventions pave the way for future therapies to achieve repair and regeneration after SCI. Stem cell/cellular research has immense potential for regeneration and repair of cells and tissue and hence are a very powerful therapeutic tool. With the current development in stem cell/cellular research, tremendous hope for developing newer therapeutic options for many serious diseases has been created in researchers, clinicians and the individuals experiencing such diseases. Stem cell-based/cellular transplantation has been trusted as a standard therapy only in cases of leukemia, burns and corneal regeneration. However, all other stem cell transplantations are still experimental [3].

It is apparent that there exists sufficient preclinical evidence in support of the safety and potency of cell-based interventions [4]. However, the same is not able to be translated robustly at the clinical level. Cell

transplant-based interventions have significant safety risks conjoined with them which animal models may not mimic. Also, conventional practices for testing the safety and potency of therapeutic agents may fail for cell-based entities as they are very different from other small molecule drugs [75]. Additionally, in situations of risky experimental interventions, it is important to distinguish between conditions with relatively long life expectancy like SCI and rapidly progressing fatal disorders due to the possibility of long-term consequences [75, 76].

Undue claims by professionals and commercial enterprises and attention by the media has raised public expectations. This may have a profound psychological effect on SCI patients and may interfere in their rehabilitation.

The Spinal Cord Society, in concurrence with National Guidelines for Stem Cell Research [66] issued jointly by the Indian Council of Medical Research and Department of Biotechnology, Government of India, as well as position statements of International Spinal Cord Society, Association of Spine Surgeons India and the International Society for Stem Cell Research, believes that the evidence base for the efficacy of cell-based interventions must come from a valid clinical trial program [55, 56, 58, 66, 67, 77]. In the current scenario, any cellular intervention for human SCI is speculative and is not proven. Thus, any offer of cellular interventions as "therapy" with commercial implications is unethical.

The Spinal Cord Society reiterates that people with SCI, their families and clinicians must be aware of the existing scenario of research regarding cellular/stem cell transplantation and its perceived capabilities, so that they are capable of making informed decisions regarding their treatment and management choices.

The Spinal Cord Society feels that ethical challenges remain, in offering cellular/stem cell transplantation as "therapy" and "stem cell tourism," as global clinics continue to promote unproven therapies to a susceptible population. In India and in various other nations, there are only guidelines governing the usage of such transplantations. The time has come for India and other nations to evaluate their policies, guidelines and regulations governing such "experimental treatments" and come out with well-defined regulations and legislations to stop such malpractice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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