

Introduction

Stem cells and their unique properties: Stem cells are special cells which not only have the ability of self-renewal but can also be a lifelong source of specialised functional cells of different human organs. Development of a human embryo into a healthy new-born child is possible because of the unique ability of embryonic stem cells to form different tissues and organs. Most adult human tissues and organs also have stem cells that can produce their functional specialised cells as and when required. The self-renewal ability of stem cells ensures that stem cells are not depleted and enough stem cells remain to produce sufficient number of specialized cells of that organ during the long human lifespan, until aging starts affecting stem cells.

Stem cells in Regenerative Medicine and human diseases: When a disease or injury causes severe depletion of the functional cells of a human organ or system, the function of that organ or organ system is lost. In the natural healing process, some organs such as skin, blood, liver etc. can often regenerate its form and function by producing sufficient numbers of new functional cells from the stem cells present in them. However, specialized cells of some organs like the nerve cells in the brain, spinal cord, eyes and muscles have limited or no capacity to regenerate and restore full function. In the last two decades, medical science has undertaken extensive research to explore the potential of stem cells from the same organ or tissue type (homologous use) or from a different organ or tissue type (non-homologous use) to restore some lost bodily function. These stem cells may be from the same person (autologous source) or from another person (allogeneic source). Research to regenerate the form and function of a human organ or organ system from stem cells or tissue engineering is called 'Regenerative Medicine'.

Status of Stem cells in Regenerative Medicine and human diseases: Unfortunately, the promise of Regenerative Medicine in general, and stem cells in particular, is yet to be realized due to several technical, biological, ethical and medical challenges. To produce sufficient number of specialised cells for restoring a lost body function with just a small number of stem cells or by using stem cells from one organ to restore cells and function of a different organ (such as mesenchymal stem cells in bone marrow or fat tissue to restore nerve or muscle function) has proven to be far more difficult in humans than what was thought based on animal experiments. As a result, the inherent appeal of stem cells has remained largely unfulfilled in human diseases. The exception is however the use of "Haematopoietic Stem Cells" for reconstituting or regenerating the bone marrow in order to start producing blood and immune cells. Transplantation of enough number of "Haematopoietic Stem Cell" in a procedure called Bone Marrow Transplantation or Haematopoietic Stem Cell Transplantation from the same person (autologous) or from another human donor (allogenic) is a recognized medical indication of stem cell use for benign and malignant life threatening haemato-lymphoid diseases or few immune

related diseases. Haematopoietic stem cells are also progenitors for other cells like osteoclasts and have successfully used in osteopetrosis and some inborn errors of metabolism like Gaucher disease, mucopolysaccharidosis. Use of other types of stem cells and even the bone marrow derived stem cells to restore function of other organs remains experimental and is subject of ongoing controlled clinical trials. Not only the efficacy of these experimental stem cell use is uncertain, the process of taking out stem cells, culturing or growing them, storing them and putting them back can cause changes in these cells and sometimes serious side effects, including some reported cases of cancers.

Why Stem cells continue to be used for debilitating or incurable conditions outside controlled research studies:

A large number of controlled prospective research studies (phase I, II and III clinical trials) investigating the safety and efficacy of stem cells for different diseases have been completed or are ongoing in Europe, USA, Korea and Japan. A small number of such research studies are also being conducted in other countries, including India. All developed countries have taken a very cautious and stringent regulatory approach regarding how different types of stem cells can be procured, processed, stored and used for preclinical or clinical research or as stem cell therapy outside research studies. Participants of regulated interventional research in any field, including stem cells, are made aware through a detailed written informed consent process about the experimental nature of the therapy, unproven efficacy and uncertainty regarding the benefits and risks of stem cells, the natural history of the disease, current standard therapy for that disease and any alternative treatments. It is the duty of the research sponsors to provide free of cost medical tests and treatments done as part of stem cell clinical trial and research, including the cost of procuring, storing and using stem cells. Circumventing the route of rigorous research studies to establish the safety and efficacy of a particular type of stem cells for a specific disease or aging condition, some unlicensed or even licenced and registered medical practitioners engage in unethical practices of selling unproven stem cell therapy as a magical remedy to desperate families with incurable and potentially fatal diseases with little or no hope of cure from other methods. Desperate patients from around the world including USA and Europe with stricter enforcement of regulations for stem cell use outside clinical trials get lured to stem cell clinics in South America, China, Russia and India. The US FDA and European Medical Agency has warned against this practice through several such advisories.

<https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>

<https://www.fda.gov/news-events/press-announcements/statement-stem-cell-clinic-permanent-injunction-and-fdas-ongoing-efforts-protect-patients-risks>

<https://www.fda.gov/news-events/press-announcements/federal-court-issues-decision-holding-us-stem-cell-clinics-and-owner-adulterated-and-misbranded-stem>

Is Stem cell research permitted or encouraged by the governmental agencies?

The unethical and unregulated use of stem cells as, often promoted as a magical remedy is not allowed by the government in the developed world and many Low and Middle Income Countries (LMIC) including India. However, considering the incurable nature of many diseases, and the acknowledged potential of stem cells, most countries, including India, encourage and fund scientific, ethical and regulated research in the field of stem cells. The purpose of such research is to obtain safety and efficacy data with the use of a particular type of stem cell in a particular condition. To provide guidance and to facilitate human research in stem cells, while curbing exploitation of vulnerable patients, the Indian government through the Indian Council of Medical Research (ICMR) has come out with successive National Guidelines in this field since 2007. The most recent National Guidelines for Stem Cell Research with inputs from all stakeholders including various government agencies and regulators, patients, medical and scientific experts and the industry, was released in 2017. These guidelines are revised at regular intervals to incorporate any new evidence for the safety or efficacy of stem cells.

[https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines for stem cell research 2017.pdf](https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines%20for%20stem%20cell%20research%2017.pdf)

Need for National Guidelines for evidence-based use of Stem cells as a routine or standard treatment option:

In many countries including India, there is a lack of clarity among patients, and to some extent among the medical community, whether stem cell therapy can be considered as a standard treatment option for a specific medical condition or should remain as an unproven experimental approach. There are several reports of increasing use of stem cells therapy for a wide range of diseases, often with little or no scientific evidence of efficacy or cure. Unethical promotions with false claims and misleading advertisements have been widely used to promote unscientific stem cell therapy. Several instances of public exploitation and grievances from members of the public have been received by the ICMR and other government agencies from aggrieved patients describing how they were lured into unproven stem cell therapies. Often the complainants demanded actions to be taken by the regulatory agencies and professional bodies to curb such practices. With this background, the Govt. of India has entrusted the ICMR to frame guidelines on stem cell therapy.

In order to develop a scientific and unbiased guideline for evidence based use of stem cell as a routine or standard treatment option in India, the ICMR has solicited opinion from expert clinicians, professional medical societies and through its website from any clinician or member of public to submit level I or level II scientific evidence for clinical efficacy of stem cells in any disease indications with reference for such evidence from peer reviewed Pubmed indexed medical and scientific journals.

<https://icmr.nic.in/content/icmr-inviting-level-i-or-level-ii-scientific-evidence-and-grade-or-b-recommendation-use-stem>

A critical review of the comments and evidence provided by medical experts and their professional societies or any member of the public and the scientific literature was done to draft guidelines and statements for evidence-based use of stem cell therapy.

Statements have been prepared for individual diseases or groups of diseases or conditions on the “EVIDENCE BASED STATUS FOR THE USE OF STEM CELLS IN (Disease condition)”. In these statements the first section is for the public and patients using layman terms while the second section is for doctors, scientists and allied healthcare professionals providing major research studies in the scientific literature, scientific level of evidence and a summary recommendation based on the current scientific evidence.

International Society for Stem Cell Research (ISSCR)

The International Society for Stem Cell Research (<https://www.isscr.org/>) is the leading professional organization of stem cell scientists and represents over 4,000 members in 67 countries including India. Like ICMR in India, FDA in USA, EMA in Europe, this international society also felt the urgent need to address the growing public concern regarding the unscientific or unethical use of stem cell therapy. The ISSCR has also issued a statement on reporting false marketing claims and adverse events from clinics offering unapproved stem cell therapies.

<https://www.closerlookatstemcells.org/patient-resources/how-to-report-false-marketing-claims-and-adverse-events-from-clinics-offering-unapproved-stem-cell-therapies/>.

In parallel with the ICMR initiative and public advertisement inviting comments and evidence for stem cell use from public and medical professionals, the ISSCR has also come out with factsheets on current status of stem cell use. The ISSCR document highlights that other than Hematopoietic stem cell (also called Bone Marrow) transplant for certain haematological or immune system disorder, the “list of diseases for which stem cell treatments have been proven to be beneficial and/or have obtained regulatory approval for use is still very short” and that “some bone, skin and corneal (eye) injuries and diseases can be treated by grafting or implanting tissues in which stem cells are essential for the healing process”. The ISSCR cautions that “However, clinics around the world continue to provide unproven stem cell treatments and often market them as cures for a variety of diseases and conditions without sound scientific evidence or regulatory approval. These so-called treatments have, in some cases, caused patients great harm physically, and at great expense financially”.

<https://www.isscr.org/professional-resources/scientific-professional-resources/disease-fact-sheets>

<https://www.isscr.org/scientific-clinical-resources/disease-factsheets><https://www.closerlookatstemcells.org/2020/01/14/truths-around-stem-cell-treatments/>

The ISSCR concise factsheets provide the current state of stem cell science for specific diseases, including background on the disease, rationale for using cell-based therapies, evidence for specific approaches and current status of the field with respect to clinical trials. A total of 11 conditions have been covered so far.

1. Age-related macular degeneration
2. Amyotrophic lateral sclerosis
3. Chronic obstructive pulmonary disease
4. Diabetes
5. Huntington's disease
6. Liver disease
7. Multiple sclerosis
8. Myocardial infarction / Heart failure
9. Osteoarthritis
10. Parkinson's disease
11. Paediatric leukodystrophies

Evidence Based Status of Use of Stem Cells in Spinal Cord Injury

A. Information for public and patients

What is Spinal Injury?

A **spinal cord injury** (SCI) is **damage** to the **spinal cord** resulting in temporary or permanent alteration in muscle, sensory or autonomic function in the parts of the body served by the **spinal cord** below the level of the **injury**. Spinal cord injury may be due to traumatic or non-traumatic causes. Traumatic causes include road traffic crashes (RTCs), fall from height, low falls, diving accidents, violence, sports injuries etc. Non traumatic causes include infection, degeneration, tumor, metabolic etc. If there is no residual movement or sensation below the level of the injury, especially in the perianal area, it is labelled as a complete injury. Complete injuries do not have the potential to recover neurologically. If there is any sensation or movement below the level of injury, especially in the perianal region, it is labelled as incomplete injury. Such injuries have a good potential to recover neurologically.

What is the treatment of spinal cord injury?

Treatment of SCI can be better defined as management of SCI and the associated complications. It is targeted towards minimizing the neurological damage due to the injury and maximizing recovery of the damaged nerve cells. In general, SCI management starts from the time of injury even before the patient reaches hospital (pre-hospital care) and spans from emergency room to intensive care management where applicable, management of vertebral fracture, management of complications, comprehensive rehabilitation and lifelong follow up.

In case of incomplete injuries, the chances of regaining full neurological and motor functions are high. In case of complete injuries, neurological and motor function recovery is limited but the patients can have a good quality of life with comprehensive rehabilitation which includes physical, psycho-social, sexual and vocational rehabilitation, community inclusion and lifelong follow up.

Have stem cells been used in spinal cord injury?

ICMR with inputs from medical specialists in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding any evidence-based safety and efficacy of stem cells in spinal cord injury.

In pre-clinical studies / animal experiments, use of stem cells has been shown to be effective and the cells were approved to be tested for clinical use. However, when tested at the clinical level

in validated clinical trial studies, these cells/interventions have not been proven to be very effective. Therefore, their use as a standard therapy is not recommended.

Recently completed and some ongoing clinical trials using different types of stem cells have shown some encouraging results. We need to conduct further testing of such cells in clinical trials with large population sizes to understand whether stem cells may be used as a standard therapy for repair of the injured spinal cord. However, until then use of stem cells in case of SCI is limited to conducting validated clinical trials only and their use as a “therapy” with commercial implications is unethical. Critical review of the studies reported so far do not support the use of stem cell therapy over and above the standardised and validated management as mentioned above.

Recommendations (2021): Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with spinal cord injury.

CAUTIONARY NOTE

Use of any type of stem cell in spinal cord injury should be restricted to clinical trials that have necessary approval from regulatory authorities in India. These trials should follow the National Guidelines on Stem Cell Research - 2017 and patients participating in these trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains existing standard of care, alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

There is substantial evidence at the pre-clinical level for the safety and efficacy of stem cell interventions; setting the stage to move forward with clinical translation. However, so far, this has not translated to generation of substantial evidence at the clinical trial. The factors underlying this are many, ranging from use of appropriate animal models, cell population selection, dose of the intervention, route of transplantation, time of transplantation, clinical trial design, outcome

measures and data analysis. Additionally, due to the hope generated by the idea that stem cells could be used as a 'Wonder Drug' and the ease of obtaining autologous stem cell populations, the path to identifying a scientifically validated Level 1 evidence for safety and efficacy of cellular intervention arising from an ethical and validated clinical trial has been severely hindered.

ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells in SCI. A critical review of the published human studies that are either randomized controlled trials or have been submitted as proof of level I or level II evidence supporting the use of stem cells in case of Spinal Cord Injury is outlined below:

Spinal Cord Injury	
S.No	Review of Literature Critique / Applicability of the study results
i.	<p>Source: BMMMNCs, MNC, UCMSC RoA: Intravenous, subarachnoid Fan X, Wang JZ, Lin XM, Zhang L. Stem cell transplantation for spinal cord injury: a meta-analysis of treatment effectiveness and safety. <i>Neural Regen Res.</i> 2017 May;12(5):815-825. PMID: 28616040 [Claimed Level of Evidence 1a] Total studies 10 only. All Studies from China only. Has heterogenous SCI group - AIS A-C which leads to data confounding. Hence, level of evidence not strong.</p>
ii.	<p>Source: Mesenchymal stem cell RoA: Intrathecal, subarachnoid injection, intravenous injection Xu P, Yang X. The Efficacy and Safety of Mesenchymal Stem Cell Transplantation for Spinal Cord Injury Patients: A Meta-Analysis and Systematic Review. <i>Cell Transplant.</i> 2019 Jan;28(1):36-46 PMID: 30362373. [Claimed Level of Evidence 1a] 11 studies used for meta analysis. 9 studies from China, 1 Egypt and 1 Iran. Again, has heterogenous SCI group.</p>
iii.	<p>Source: Umbilical cord mesenchymal stem cell RoA: Subarachnoid Cheng H, Liu X, Hua R, Dai G, Wang X, Gao J, An Y. Clinical observation of umbilical cord mesenchymal stem cell transplantation in treatment for sequelae of thoracolumbar spinal cord injury. <i>J Transl Med.</i> 2014 Sep 12;12:253. PMID: 25209445 [Claimed Level of Evidence 1b] RCT with 34 AIS A subjects, reports significant changes in urodynamics but no change in AIS grade. Results are encouraging, however, level of evidence not strong due to small sample size.</p>

iv.	<p>Source: Bone marrow-derived cells Route: RoA: Intravenous injection Li XC, Zhong CF, Deng GB, Liang RW, Huang CM. Efficacy and safety of bone marrow-derived cell transplantation for spinal cord injury: a systematic review and meta-analysis of clinical trials. Clin Transplant. 2015;29:786–795. PMID: 26115044 [Claimed Level of Evidence 2a] 24 studies included Only one Grade I level of evidence, six Grade II levels, three Grade III levels, and 14 Grade IV levels. prospective, randomized trials in larger cohorts are still needed</p>
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BMMNC= Bone marrow mononuclear cells; MNC= Mononuclear cells; UCMSC= Umbilical cord derived mesenchymal cells

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021):

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with spinal cord injury.

The experts observed that spinal cord injury can have a major impact on the quality of life of the individual and the family. There is therefore a need to undertake research into the prevention and more effective management of spinal cord injury. Since management does not result in neurological recovery in complete spinal cord injuries, such patients, consumers and families see a hope in some miraculous recovery with the use of stem cells without understanding the risks versus benefit ratio. It is therefore imperative that use of any type of stem cells in spinal cord injury should be restricted to clinical trials that have necessary approvals as defined in NGSCR-2017 including regulatory authorities in India. These trials should follow the national guidelines on stem cell research and patients in these trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations, and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Spinal Cord Injury.