

Report: Stem cell applications in neurological practice, an expert group consensus appraisal

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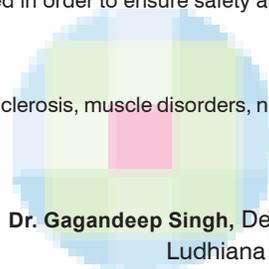
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Abstract

Introduction: Neurologists in their clinical practice are faced with inquiries about the suitability of stem cell approaches by patients with a variety of acute and chronic (namely neurodegenerative) disorders. The challenge is to provide these patients with accurate information about the scope of stem cell use as well as at the same time, empowering patients with the capacity to make an autonomous decision regarding the use of stem cells. **Methods:** The Indian Academy of Neurology commissioned an Expert Group Meeting to formulate an advisory to practicing neurologists to counsel patients seeking information and advice about stem cell approaches. **Results and Conclusions:** In the course of such counselling, it should be emphasized that the information provided by many lay websites might be unsubstantiated. Besides, standard recommendations for the stem cell research, in particular, the application of several layers of oversight should be strictly adhered in order to ensure safety and ethical use of stem cells in neurological disorders.

Key Words

Cerebellar ataxias, motor neuron disease, multiple sclerosis, muscle disorders, neurological disorders, Parkinson's disease, spinal cord injury, stem cells, stroke



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Introduction

Stem cells are clonogenic cells with an inherent capacity to self-renew and differentiate into multiple cell lineages.^[1] As biological entities with a promise of enormous therapeutic potential, stem cells have engendered considerable hope, curiosity, captivation as well as trepidation among patients, physicians, researchers, regulatory bodies, and the society at large. In a little, over a quarter of a century, two separate researchers were awarded Nobel Prizes in Physiology or Medicine (1990 and 2012) for their work on stem cells which testifies to the alluring expectancy associated with stem cell approaches.^[2]

Stem cell approaches are appealing for addressing therapeutic options in neurological disorders with unsatisfactory or unproven treatment strategies, including stroke, multiple sclerosis, Parkinson's disease (PD), Alzheimer's disease and other neurodegenerative dementias, muscular dystrophy, and spinal cord injury (SCI). The inherent lack of ability of neurons to regenerate after acutely damaging insults such as stroke,

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spinal cord injuries and multiple sclerosis, the relentlessly progressive, downhill course of many neurodegenerative disorders, and an overall dearth of curative approaches in many neurological disorders have incited experimentation using a variety of therapeutic propositions. Stem cell approaches constitute one such important therapeutic proposition.

Investigating stem cell approaches has been a major thrust area of biomedical research for the Government of India since 2001 with the Department of Biotechnology (DBT) and the Indian Council of Medical Research (ICMR) having supported several basic and translational research projects as well as early phase clinical trials using stem cell approaches. Indeed, a number of groups from basic science and medical institutes across the country have undertaken noteworthy research in this area in the past 20 years. Contemporaneously, a large number of commercial centers have emerged in different parts of the country offering hope, albeit unproven, to patients with a vast array of disorders. Not only this, many patients with a variety of incurable neurological disorders embark on overseas excursions to centers, proclaiming successful outcomes of stem cell approaches, a phenomenon known as "stem cell tourism."^[3,4] All neurologists in the course of their clinical practice are confronted by queries of patients with a variety of neurological disorders regarding the value and effectiveness of such pursuits. They are expected to be knowledgeable about such approaches and hence should have a reasonable understanding of the benefits of stem cell approaches, the short-term and long-term risks thereof and information about centers which offer such facilities as well as the costs involved.

Should neurologists counsel such patients? If so, how should they counsel them? What information should they provide such patients or their care takers? The Indian Academy of Neurology convened a meeting of experts including basic scientists and ethical and regulatory experts with experience in stem cell approaches, and neurologists with experience in early-stage clinical research in the use of stem cells. The objective of the meeting was to gather a repository of authentic information that would equip busy clinical neurologists with the ability to counsel patients seeking particulars and an opinion about stem cell approaches. Here, we report the outcome of the meeting generated by consensus among the experts. The applications of stem cell approaches in major categories of neurological disorders are then discussed.

Overview of Stem Cell Approaches

Broadly, stem cells used to ameliorate dysfunction due to injured or degenerated neuronal populations are of two types - embryonal stem cells (ESCs) and somatic stem cells (SSCs).^[5] The ESC are derived from embryos prior to implantation, but mostly after the establishment of the inner cell mass of the embryo, implying that these have the ability to differentiate into ectoderm, mesoderm, and endoderm. Hence, ESCs are pluripotent. The SSC can be found in many differentiated tissues and accordingly have a limited differentiating capacity. They are thus multipotent and not pluripotent. Stem cells have an intrinsic homing ability and there are receptors present on injured tissues,

which attract stem cells.^[6] Stem cells can thus be harvested conveniently from tissues such as the bone marrow or adipose tissue and rendered to injured, damaged, dysfunctional, or degenerating tissues. When rendered to own tissues of the individual, the stem cells are referred to as autologous and when to tissues of a different individual, they are called allogenic. Notwithstanding this simplistic but attractive theoretical premise, the actual process is complicated requiring highly precise laboratory techniques. Naturally, there are several concerns, potential risks (not only to the recipient but also to the donor) in addition to the uncertainty of their effectiveness.^[7-9] Added to the concerns is the remunerative potential of stem cell approaches in as much as stem cells are a potentially commercializable commodity.^[10,11]

Risks to recipients of stem cells include tumorigenic, uncontrolled, or misdirected proliferation of the implanted stem cells, infections originating from the donor or during the transfer process, tacit implications of intentional or unintentional enrolment of gonadal tissues, and the psychological impacts of an unsuccessful outcome.^[10,12] Issues for the donor include consenting to the use of stem cells to unknown recipients, while at the same time, maintaining traceability in contingency situations and considerations of the commercial potential arising from their participation in stem cell research (SCR).^[13,14] Methodological issues include not only ensuring quality control in the processing of stem cells but also preventing mishaps due to excessive manipulation of stem cells (e.g., alteration of the regenerative capability, tumorigenic potential, or even genomic characteristics of stem cells in a manner that has not been proven to be safe). In addition, the stem cells may not be adequately tested to rule out a latent viral infection or yet unexpressed genetic anomaly in the donor.

Current Status of Stem Cell Approaches in Human Disorders in India

At present, the only approved indications for the use of stem cells in the treatment of human diseases involves the use of hematopoietic stem cells in hematological disorders.^[15,16] An upcoming therapeutic use pending approval in India is the use of limbal stem cells in corneal scarring.^[17] Apart from these indications, there are no approved indications for stem cell treatment. Hence, stem cell approaches are purely investigational in all other disorders including neurological conditions. Any stem cell approach cannot be referred to as a "treatment," "interventional" or "transplant" and instead is at best a research undertaking in the late translational or early clinical trial stage. Hence, regulatory bodies in India, including the ICMR and the DBT advocate the use of the qualification, "SCR" instead of "Stem Cell Treatment."^[12]

Regulatory Issues in Stem Cell Research

The ICMR and DBT jointly formulated the first guidelines for the use of stem cells in human disorders in 2007.^[18] A revised version of the guideline was published in 2013.^[12] The revised guideline was formulated on the basis of principles governing SCR instead of using stem cells as a treatment modality. In keeping with this tenet, any use of stem cells in humans is subject to regulatory approval and oversight in ways

appropriate for a research undertaking only. Failure to comply with the regulatory process amounts to malpractice.

Considering the sensitive nature of SCR, the National Guidelines for SCR recommend an extra layer of oversight over and above the Human Ethics Committee in all institutions when stem cells are being used.^[12] Hence, SCR is required to be approved and monitored not only by the Institutional Ethics Committee but also by an Institutional Stem Cell Research Committee (ISCRC). Each ISCRC is to be registered with the National Apex Committee-SCR (NAC-SCR).

The 2013 Joint ICMR-DBT Guideline classifies human SCR into three categories: Permitted, restricted, and prohibited.^[12] Clinical trials with minimal or more than minimal (but not amounting to major manipulation, which refers to genetic or epigenetic manipulation of stem cells) of SSCs is designated as a permitted area of research provided, it is done with prior approval of the IEC and ISCRC, follows the National Good Laboratory Practice Guidelines and the trial is registered with the Clinical Trials Registry - India. Furthermore, if the trial eventually leads to commercialization of the biological entity, express approval from the NAC-SCR and the Drug Controller General of India should be sought. Human research involving SSCs with major manipulation and animal research using human ESCs and international trials and trials undertaken by multinational agencies requires prior approval of the NAC-SCR in addition to the two institutional committees. Cloning human preimplantation embryos and xenogeneic transplants (animal to human) are strictly prohibited.

Q. 1. Should neurologists be involved in discussions on the merits and demerits of stem cell approaches with their patients in clinics?

Answer

Many patients with chronic, incurable, nonremitting, or degenerative disorders follow-up with the neurologist for long periods of time. This leads to the development of a compelling doctor-patient relationship. Armed with the ability to grasp the patient's perspective and effective communication, the neurologist is the best resource to counsel patients with neurological disorders who wish to consider the use of stem cells. Neurologists should not hesitate to participate in discussions with their patients on the feasibility, prospects, and potential ill-effects of the use of stem cells.

Q. 2. How should the neurologist counsel patients seeking to use stem cells in the hope of ameliorating their neurological condition?

Answer

In keeping with the principles of autonomy, the neurologist should not under any circumstances dismiss the patient's intention to explore or undertake a stem cell procedure in the country or abroad as futile. While neurologists should not try to influence the patient's decision to use stem cells or vice-versa nor attempt to make a decision on the patient's behalf, they are obligated to educate the patient about the feasibility, prospects, and adverse effects of SCR in such a way that the patient is empowered to make an informed decision. This is in keeping with the principle of maintaining patient autonomy.

Q.3. What information should the neurologist provide to patients considering the use of stem cells?

Answer

During discussions in the clinic, the neurologist should focus on the following:

- i. The potential options within the scope of established standard of care of the neurological condition of the patient
- ii. Whether stem cell approaches are an established method of treatment for the particular condition (It might be useful to inform the patient if the approach is approved by the NAC-SCR or DCGI (Drug Controller General of India))? If not, the patient should be apprised of the experimental nature of the approach
- iii. Brief description of the procedure, including mention of the source, manipulation approaches, short- and long-term risks, and time, cost, and other logistic requirements of stem cell use
- iv. The possible benefits or lack thereof, and potential risks when no Phase 1 safety trials are available, and the time frame within which these are expected to occur
- v. Irreversibility of the procedure.

Often the patient requests to be directed towards additional sources of information. Here, the neurologist must emphasize that lay sources of information, e.g., websites of stem cell facility establishment's often project information extolling the benefits of the use of stem cell and patient testimonials that are heavily biased toward an improved outcome.^[3,4,10] Claims on these websites are mostly unsubstantiated. Therefore, patients should not rely exclusively on reports on websites of individual clinicians, clinics or hospitals, or testimonials of individual patients. However, certain internet sites do provide balanced, authentic, and scientifically-updated information on the use of stem cells. Reliable sites belong to professional bodies and government health regulatory agencies.^[12,19] A list of such selected sites is provided in Box 1. The National Guidelines for SCR are available at http://www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf.^[12]

Q.4. Where can the patient considering the use of stem cells be referred to?

Answer

A list of institutes and establishments in India, at which specific types of human SCR is being undertaken is provided in Box 2.

Box 1: Useful internet resources for information on stem cell research for patients

www.closerlookatstemcells.org
www.isscr.org Stem cell information for the public from the International Society for Stem Cell Research
www.explorestemcells.co.uk United Kingdom web resource for general public on various potential applications of stem cells
www.stemcells.nih.gov/info A NIH resource of reports on the use of stem cells
www.icmr.nic.in/guidelines/NGSCR%202013.pdf National Guidelines for Stem cell Research 2013
www.nap.edu
www.cihir-irsc.gc.ca/e/42071.html
www.closerlookatstemcells.org/Patient/ISSCRPatientHandbook.pdf

Box 2: List of Institutes in India, at which various forms of stem cell research is being undertaken

Basic research

National Brain Research Centre, Manesar
 Institute of Stem Cell Science and Regenerative Medicine, Bengaluru
 All India Institute of Medical Sciences, New Delhi
 National Institute of Immunology, New Delhi
 Institute of Genomics and Integrative Biology, New Delhi
 Indian Institute of Chemical Biology, Kolkata
 Manipal University, Manipal
 National Institute for Research in Reproductive Health, Mumbai
 Indian Institute of Science, Bengaluru
 National Centre for Biological Sciences, Bengaluru
 Jawaharlal Nehru Centre for Advanced Scientific Research, Bengaluru

Translational research

National Centre for Cell research, Pune
 SCCR Christian Medical College, Vellore
 Central Leather Research Institute, Chennai
 Postgraduate Institute of Medical Education and Research, Chandigarh
 Sankar Netralya, Chennai
 LV Prasad Eye Institute, Hyderabad
 Centre for Stem Cell Research, Bengaluru
 All India Institute of Medical Sciences, New Delhi
 Rajiv Gandhi Cancer Institute and Research Centre, New Delhi
 R and R Hospital, New Delhi
 Armed Force Medical College, Pune
 Sanjay Gandhi Postgraduate Institute, Lucknow

Q.5. What approach should be adopted if a single patient insists on using stem cell for an incurable neurological disorder after exhausting all approved treatments and interventions?

Answer

This is a gray area. In the event that a single patient desires to use stem cells in the hope of amelioration of an otherwise incurable or degenerative neurological disorder, the request should be forwarded to the institute head. The institute head might then obtain a report on the patient's condition from the treating neurologist and then form a committee to examine the veracity of scientific data available on the applicability of SCR in the particular neurological condition. The neurologist's and the committee's report is then put up before the ISCRC and if approved therein, the patient might be put on the list for stem cell use. The ISCRC is also obligated to constitute a Data Safety and Monitoring Committee of two or more independent physicians who monitor the procedure and report to the ISCRC. The expert group holds the view that following the above protocol will ensure that appropriate safeguards are in place while keeping the best interests of the patient in mind.

Stem Cells use in Specific Neurological Disorder

Stroke

The use of stem cells after disabling stroke with nonrecoverable neurological deficits might require approaches differing from neurodegenerative disorders. While in the latter condition, only selective neuronal populations are affected and hence require restoration, the sudden interruption of blood supply

to a certain area in stroke leads to dysfunction of diverse neuronal populations in that area. The mechanisms by which the use of stem cells could potentially mitigate the effects of stroke are several.^[20] The transplanted cells might replace and take over the function of cells damaged by ischemia. The cells might secrete trophic factors to help maintain marginally surviving cells or otherwise enhance local milieu to improve function. Finally, transplantation might produce a host reaction comprising sprouting of new axons and synapses.

In preliminary trials of using stem cells in stroke, a number of different approaches to access infarct-damaged neuronal tissue might be undertaken. Access via the intravenous route has been most commonly used. A Phase I trial (ReNeuron, UK) of stereotactically injected NSC lines was initiated recently. A Phase I controlled trial used autologous mononuclear stem cells in 11 subjects with ischemic stroke within 7–30 days of onset.^[21,22] Outcomes measured for safety included immediate reactions after cell infusion and evidence of tumor formation at 1 year with whole body positron emission tomography scan. Follow-up at 1, 4–6, 24, and 52 weeks demonstrated favorable outcomes using the National Institute of Health Stroke Scale (NIHSS) (50%), Barthel index (BI) (64%), modified Rankin scale (55%) with no serious adverse events. A Phase II, randomized-controlled trial in 120 subjects however found no benefit using the NIHSS and BI at 90 and 180 days.^[23,24] Preliminary benefits of stems cells in a heterogenous population with chronic stroke (3–24 months) that received either autologous mononuclear or culture-expanded stem cells using the BI scale were also noted leading to another randomized trial intended to study the paracrine effects of autologous, marrow-derived mononuclear stem cells in currently underway by the same investigator group.^[24,25]

Parkinson's disease

It is a chronic progressive illness resulting from the loss of dopaminergic neurons in the substantia nigra, thereby compromising the secretion of dopamine. Although, in the initial few years, oral dopaminergic drugs improve motor symptoms, patients eventually develop motor fluctuations. At this stage, while some selected patients benefit from deep brain stimulation, the long-term management is still dismal. Thus, there is a need for dopamine cell replacement therapy.

Initial studies used a wide range of tissue, viz., autografts of adrenal medulla, sympathetic ganglion, and carotid body-derived cells, as well as xenografts of fetal porcine ventral mesencephalon. Subsequently, based on the success with the tissue from human fetal ventral mesencephalon in rodents and several patients in open-label trials, two double-blind, placebo-controlled trials funded by the NIH were carried out in nearly 60 patients. However, the results raised significant doubts about the merit of this whole approach.^[26-28] The trials did not meet their primary endpoints, and patients had graft-induced dyskinesias.^[29,30]

The focus now is on producing dopaminergic neuroblasts for the transplantation from SSCs. Recently, dopaminergic neurons were produced from induced pluripotent stem cells (iPSCs) derived from fibroblasts in adult humans. Such neurons survived transplantation into the striatum of PD rodents and

produced some degree of functional recovery. The potential advantages with the use of iPSCs are that PD patient-specific DA neuroblasts could minimize the immune reactions and eliminate the ethical issues associated with the use of human ESCs.

Currently, several studies have been completed or going on using stem cells in PD. The sources of stem cells destined to produce dopamine include autologous mesenchymal stem cells, ESCs, and iPSCs. However, still the crucial questions include: (i) how to fix the optimal cell dose to be administered, (ii) which is the best administration route, considering safety and efficacy, (iii) how to obtain clinical-grade materials free of biological and chemical contaminations, (iv) ethical and regulatory hurdles. The final challenge is to show whether stem cell-derived dopaminergic neurons efficiently reinnervate the striatum and provide functional recovery.

Spinal cord injury

The limited scope for repair after, and often discouraging clinical outcome following SCI has prompted experimental and translational studies of amelioration using stem cells. Supported by a vast preclinical evidence, cell-based approaches involving transplantation of neural and nonneural tissue elements have been applied in human SCI.^[31] The majority of reports however comprise of patient testimonials or isolated case studies. A plethora of patient testimonials and case studies has reported the clinical safety and efficacy of cell transplantation after SCI. Few Phase I and II studies are available but apart from these, there are no rigorous controlled trials and hence the strength of evidence for the effectiveness of stem cell approaches is low. No firm conclusion can be made regarding the efficacy of stem cell approaches, though it might be concluded that the approach is safe. Stringent trial design with appropriate outcome measures critical in order to clarify the potential of cellular therapy in SCI.^[32-34]

Muscle disorders

All muscular dystrophies are potential candidates for this form of therapy, as no effective therapy exists. Other muscle disorders, e.g., congenital myopathies, myotonic disorders, channelopathies, storage diseases, and mitochondrial diseases also fall in the same broad category, with some differences in availability of therapeutic measures which need to be utilized before considering the use of stem cells.

Duchenne muscular dystrophy (DMD) can be considered to be the most suitable candidate for the use of stem cells in India, as it is the commonest muscular dystrophy. Moreover, it starts at young age and progresses rapidly, shortening life span and is a devastating disease. Mesenchymal stem cells have shown promise in DMD.^[35] They have been shown to produce dystrophin in grafted muscles *in vivo* and *in vitro*. Thus, although animal and human experiments are available, a number of points need to be clarified, e.g., the route of stem cell delivery, frequency of injections, dose schedules, and outcome measures in as much as repeated muscle biopsies are difficult to undertake.^[35] Based on the available experimental premise, preliminary trials using stem cells are warranted in India, only committed strategies have yet to be realized.^[36-38]

Cerebellar ataxias

The cerebellar ataxias are a diverse group of disorders characterized by motor incoordination. Both acquired (e.g., multiple system atrophy) and hereditary (e.g., spinocerebellar ataxias and young-onset autosomal-recessive cerebellar ataxias) degenerative cerebellar ataxias are contenders for SCR from both therapeutic and experimental standpoints. In animal models of polyglutamine mutation associated spinocerebellar ataxias, intravenously- or intracranially-administered human mesenchymal stem cells lead to the improvement of motor function. The results of animal studies underscore the need to investigate the safety and efficacy of mesenchymal stem cells approaches in humans. An unrelated albeit attractive approach is the use of iPSCs to create disease-specific cell models for understanding pathogenesis as well as screening new therapeutic agents. Neuronal cell populations involved in degenerative cerebellar ataxias are not readily accessible for developing disease-specific cell models. Induced pluripotent cells are somatic cells that are capable of transforming to cells of any of three primitive germ layers (endoderm, mesoderm or ectoderm) using epigenetic programming, nuclear transplantation or cell fusion.^[39,40] Using these technologies, somatic cells have the potential to transform to Purkinje cells, for instance. The transformed cells can be used to create models of disease to study the steps in and factors associated with polyglutamine inclusion-associated neuronal degeneration as well as to test a range of novel therapeutic agents in the cell-based models. The application of iPSC technology to study cerebellar ataxias hold promise but as yet there are concerns about the safety of the approach.

Multiple sclerosis

Eventually a disabling disease affecting young adults, multiple sclerosis commonly begins as a relapsing-remitting disease, which almost always advances to a secondary progressive stage. A primary progressive variety from the beginning is uncommon. SCR propositions potentially address all stages and varieties of multiple sclerosis largely due to the absence of effective treatments. Two approaches have been followed so far. One is the use of autologous hematopoietic stem cell transplantation based on the principle of reassembly of a new immune system following complete ablation of the aberrant immune system in the disease. Several anecdotal and small uncontrolled and controlled trials have affirmed efficacy and safety of this approach, and from these, it may be gathered that the approach benefits young people in an early stage of disease but with high levels of inflammatory activity.^[41] The other approach is to use mesenchymal stem cells in the hope of promoting remyelination and improving the aberrant immune status.^[42,43] SCR using both approaches is growing in momentum and results of some of the larger controlled trials are keenly awaited.

Motor neurone disease

To achieve the effective cell-mediated therapy suitable for clinical application in motor neurone disease (MND), several issues must be addressed, including the identification of most performing cell source, a possible administration protocol, and the definition of therapeutic mechanism. Methods of cell delivery represent a major issue in developing cell mediated approaches, since the cells to be effective, need to be spread across the central nervous system, targeting both lower and

upper motor neurons. It should be noninvasive; and there should be no side effect.

The first US Food and Drug Administration approved Phase I trial of neural stem cell has shown intraspinal injection of neural stem cells to be feasible and safe. Phase II clinical trials are in progress.^[44,45]

The role of autologous bone marrow-derived stem cell replacement in the management of patients with MND was studied in ten patients in a pilot trial in India.^[46] This study was extended and two shots were given after 6 months interval. Patients were recruited according to revised El Escorial criteria. The MND functional rating scale at baseline, 3 months, 6 months, 9 months, and 1 year, after the injection of mononuclear cells derived from patient's bone marrow, in the sub-arachnoid space were recorded. The study revealed that there was definite decrease in rate of progression of disease, after stem cell transplantation, but patients worsened after 6–7 months, when only one injection was given. In the extended study of two injections of stem cells, 6 months apart, follow-up after 1 year revealed 18 of 30 patients were alive without percutaneous endoscopic gastrostomy/ventilator support. There were 11 deaths. Estimated cumulative survival was 22 ± 2 months from first injection.

Clearly more work needs to be desirable and the most efficacious cell type and appropriate approaches to safely achieve positive outcome in MND are still to be determined.^[47]

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Conflicts of interest

There are no conflicts of interest.

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