Unregulated stem cell therapy A Frankenstein monster in the absence of effective laws

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The claims pertaining to stem cell therapy that it is very effective and affordable without any high costs, risks, side effects, hassles are very prominent and have regularly started appearing not only on various sites of the Internet but also being published in newspapers. One of the Internet sites has even claimed anti-ageing, health and beauty benefits from stem cell therapy.

In the past few months some of the reports published in daily newspapers states:

- Babies diagnosed with brittle bone disease can now be treated before they are born, thanks to a new stem cell treatment
- A Pune-based stem cell centre has treated patients with various diseases, such as diabetes mellitus, multiple sclerosis, Parkinson's disease, duchenne muscular dystrophy, and many others, including rare genetic and hereditary diseases. Among patients there are also people willing to undergo anti-ageing treatment.
- A Bangalore-based hospital had started treatment in regenerative medicine and stem cell therapy three years ago and have achieved significant success. Patients who entered the hospital paralysed below the neck have walked out using a crutch or walker.
- Improvement seen in just five day after stem cell therapy treatment for stroke by a doctor based in Mumbai.

- A private hospital in Delhi had claimed that stem cell therapy has been found useful in over 60 per cent of the patients due for liver transplant and the treatment is not only less cumbersome and risky but costs are also comparatively very reasonable, even less than Rs 50,000. The report further claimed that all patients responded well to the treatment without any side effects.

Reporting of such medical achievements in the Internet or newspapers by way of advertisements/ publications by the doctors involved in stem cell therapy research are in gross violation of the guidelines laid by Government of India. Such publications in newspaper definitely raises expectations in the minds of general public that stem cell therapy is very economical, well tolerated and without any side effects. The researchers in this medical field very well know that safety aspect of the stem cell therapy is yet to be established before putting its use on commercial therapeutic applications.

The Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) in 2012 had issued guidelines (The Guidelines) to ensure the safety and rights of participants receiving stem cells transplants and patients at large from receiving unproven stem cells therapies. All such research needs to be guided by the principles laid down in the Ethical Guidelines for Biomedical Research on Human Subjects by ICMR.

The Art. 5.7 of The Guidelines states under the subject, "Responsibility for Conduct of Stem Cell Research: Investigators, Institutions and Sponsors" that the physician/scientist engaged in stem cell research and therapy shall ensure that no hype or unrealistic expectations are created in the minds of subjects or public at large regarding stem cell therapy.

Even the preamble of the aforesaid Guidelines clearly states that stem cell research raises several scientific, ethical and social issues in the development of such applications. Furthermore, there are also potential dangers of tumorigenicity with use of these cells keeping in view their potential for unlimited proliferation and possible introduction of genomic changes and also has limitations of immunological tissue incompatibility between individuals.

The Guidelines issued by the ICMR and DBT are restricted mainly to stem cell research and does not address the major issues of therapeutic applications. The effectiveness of the Medical Council of India to regulate clinicians involved in unethical acts is already in controversy.

International Society for Stem Cell Research advocates dissemination of best practices to promote uniform practices worldwide following the guiding principles of responsible science, protection of citizens, intellectual freedom, transparency and integrity towards the welfare of human beings.

The era of using commercially stem cells for therapeutic use for a variety of diseases have set in worldwide and India is emerging as one of the leading centres for stem cell-based research and therapy. The private banking of cord blood is also growing at a fast pace in India.

Clinics have started mushrooming in India which are offering largely unproven stem cell therapy. Such therapy puts desperate patients at health and financial risks. There are reports that unproven injections being sold for around ` 80,000 and several companies are advertising their therapies and clinical trials as ICMR approved. Others are providing unapproved stem cell therapy underhand providing two to three doses of stem cells for cost ranging between ` 5 to 10 lakhs. The companies are taking advantage of the lack of effective laws governing the stem cell therapies.

Questionable safety of stem cell therapy

Developments in the field of regenerative medicine and stem cell research are relatively new and are associated with complicated ethical, social and legal issues. Doctors have started treating a wide range of diseases by believing that the use of adult stem cells is safe. On the other hand, various studies have shown that adult stem cells can cause severe complications and side effects in the form of cancer or tumour.

It is an admitted fact that very little pre-clinical data on animal models is available and most of the treatment modalities have not gone through rigorous clinical trials to ensure the safety of the treatments. There is a strong apprehension that the unethical medical practices may grow tremendously in the absence of any effective legal control.

In India there is an urgent need to place legal laws and enforcement agencies in order by the Government before such medical practice goes out of control of any regulatory/legal bodies or otherwise.

At present there is nothing in The Guidelines to outlaw, prohibit or punish those carrying out stem cell therapies. Stem cell treatment in humans must be governed under effective laws which should take care of all the aspects pertaining to its source, storage, research, uses in treatments, as well as punishments and compensations in the event of violation or indulgence in unethical practices in humans.

The advancement of medical treatment is unregulated and taking advantage of this, a large number of hospitals and industry involved in cellular therapies have started providing treatment for which stringent safety aspects are yet to be established. The immediate need of the hour is to put in place effective regulatory bodies and suitable amendment in the laws to include stem cells before situation goes out of control to check the expansion of unethical services.

It has been recently reported that one of the world's largest research funder, the National Institutes of Health (NIH), which is a part of the US department of health and human services, has cancelled almost 40 ongoing trials in India. Another 157 trials have been put on hold. The main reason behind this move is unstable regulatory environment in the country.

Guiding Indian policies

- Policy statement on ethical guidelines- ICMR 1980 Ethical Guidelines for Biomedical Research in Human Subjects- ICMR 2000
- GoI Guidelines for Exchange of Human Biological Material for Biomedical Research Purpose – ICMR 1997
- Guidelines for Accreditation, Supervision and Registration of Infertility Clinics – ICMR 2004
- DBT Guidelines for Genetics and Stem Cell Research- DBT 2002
- Preconception and Prenatal Diagnostic Techniques Act, 2003
- Drugs and Cosmetics (3rd Amendment) Rules 2011 for Cord Blood Stem Cells
- Guidelines for Stem CellResearch and Therapy, ICMR DBT 2007 are now the Guidelines for Stem Cell Research 2012

Under the Guidelines 2012, even though the stem cell research is promoted for therapeutic purposes, all stem cell therapy in India is considered to be experimental, with the exception of bone marrow transplants. Stem cell therapy is legalised but the use is limited to stem cells from adults, bone marrows or foetal cord blood. Embryonic stem cell therapy and research is restricted.

Generation of embryos for sole purpose of stem cells is prohibited and requires consent of National Bioethics Committee. However, use of surplus or supernumerary embryos from registered ART clinics is permitted. Implementing and monitoring is through Institutional Committee (IC-SCRT), Institutional Ethics Committee (IEC) and National Apex Committee (NAC-SCRT).

To regulate the use of stem cells, emphasis is given on basic research involving preclinical, clinical trials and clinical research to prove the efficacy, safety and utility of the cell types used before it is put to therapeutic applications. Strict procedures are prescribed for sourcing and use of stem cells by research institutions, however, the guideline is silent on legal measures on unethical use.

National Apex Committee for Stem Cell Research and Therapy was set up to govern the stem cell-related research and therapy. But the main apprehension is that how in the absence of legal measures this committee will be able to curb unethical stem cell medical practices. At present, if a consumer has a complaint against a stem cell research, the government has no power to act on the complaint. The Guidelines are totally silent on how to prohibit or punish those carrying out unethical stem cell treatments.

STEPS initiated by the Government of India to tighten regulatory laws on stem cell therapy

Government of India and the state authorities have prime responsibilities and jurisdiction to ensure the safety of patients seeking cellular therapy. The laws and regulations must differentiate clearly between standard therapies and other cellular therapies approved for marketing and clinical trials.

Government of India has initiated some steps towards regulating stem cell therapies. The Ministry of Health has issued Drugs and Cosmetics (3rd Amendment) Rules 2011 for manufacture of blood products and collection, processing, testing, storage, banking and release of umbilical cord blood stem cells under the Drugs and Cosmetics Act, 1940 which will govern cord blood stem cells. The Ministry of Health and Family Welfare also constituted a high powered committee in June 2013 for the regulation of stem cell and other cell-based therapies being practiced in India and to make specific recommendation for effective regulation of stem cell products and stem cell therapy / research.

The Supreme Court of India in an writ petition filed in 2012 by Swasthya Adhikar Manch had directed the Director General, Health Services or the Secretary Ministry of Health to file an affidavit on different aspects concerning the clinical trials of new chemical entities in particular the deaths and adverse impacts that have taken place from 2005 till June 2012.

The apex court had also observed in the aforesaid writ petition that the clinical trials should be conducted in ethical manner in compliance to regulatory provisions and there should be a robust system for regulating such trials in the country. Furthermore, the amount of money paid by the companies to investigators for conducting clinical trials should be in the knowledge of the regulatory authorities and regulatory provisions may be made to this affect.

Taken note of these observations of the Supreme Court, the Ministry of Health and Family Welfare, Government of India introduced a Bill before the Rajya Sabha in August 2013 for further amending the Drugs and Cosmetics Act 1940, which will be called as the Drugs and Cosmetics (Amendment) Act, 2013.

The Central Government withdrew its earlier Bill of 2007 and introduced the aforesaid Bill 2013 by adding more comprehensive provisions inter alia to regulate clinical trials and exports. The new Bill has included stem cells in the definition of the 'new drug' and also specified it at serial no.12 of the proposed Third Schedule of the Act. This will remove ambiguity, if any, in defining and treating stem cells as drugs if used in patients for treatment or research.

The salient features of Drugs and Cosmetic (Amendment) Bill 2013

Emphasis is mainly given around regulation, ethical supervision of trials, compensation of trial subjects etc. The first paragraph of the preamble itself has been substituted which highlights the objective of the Act ie to regulate the import, export, manufacture, distribution and sale of drugs to ensure their safety, efficacy, quality and conduct of clinical trials and for matters connected therewith or incidental thereto.

The definition of 'New Drug' will now include all vaccines, recombinant deoxyribonucleic acid derived products, living modified organisms, monoclonal anti-bodies, stem cells, gene therapeutic products and xenografts which are intended to be used as drugs.

The word 'manufacture' will also include in relation to human blood and its components any process or part of a process of collection, processing, storage, packing, labelling and testing for its use, sale, export or distribution for transfusion in human beings.

The aforesaid Bill shall make mandatory for the manufacture of any new drug to obtain prior permission from the central licensing authority. The state licensing authority before issuing any license for manufacture of a new drug shall ensure that the permission from the central licensing authority has been obtained by the manufacturer of new drug prior to applying to the state authority.

As per the aforesaid Bill, the Central Government shall constitute an authority to be known as the 'Central Drugs Authority', which will consist of seven Secretaries of Government of India from different health-related departments including Director General Health Services, Additional Secretary or Joint Secretary in the Ministry of Law and Justice and Additional Secretary or Joint Secretary in charge of the Drugs Quality Control Division in the Ministry of Health and Family Welfare. In addition to this, there will be four experts in health-related subjects and four state licensing authorities to be nominated by the Central Government including Drugs Controller General of India.

The Central Drugs Authority shall be empowered to specify regulations, guidelines, norms, structures and requirements for effective functioning of the central licensing authority and the state licensing authorities. In addition to this, it shall have power to review, suspend or cancel any permission, license or certificate issued by the central licensing authority or the state licensing authorities.

The subject of the clinical trials now has been dealt in the proposed aforesaid Bill. No person will be able to initiate or conduct any clinical trial in respect of a new drug or investigational new drug in human subjects except with, the permission granted by the central licensing authority. Furthermore, registration with the Central Drugs Authority will be mandatory prior to initiate or conduct any clinical trial.

Penalties and punishments

In the 2013 Bill, a separate chapter has been incorporated which contains penal actions against the person conducting clinical trial for violation and non-compliance of the provisions relating to the conduct of such clinical trials.

In the said Bill the provisions have been incorporated wherein if an injury or death of a person occurs due to the clinical trial, the person conducting such clinical trials shall give him, or as the case may be, his legal heir, such compensation as may be decided by the Drugs Controller General (India) or any other authority appointed for this purpose.

Penalties have been imposed in the new amendments Bill. In case where clinical trials are being conducted with new drugs without permission, then the person can be imprisoned for up to three to five years along with a fine up to Rs 10 lakhs and in the event of grave injury or death of a participant in clinical trial then the term of the imprisonment can be extended for up to 10 years with a fine which shall not be less than Rs 20 lakhs.

International scenario on implementation of laws

National regulatory authorities regulate the human cells, tissues, and cellular and tissue-based products intended for implantation, transplantation, infusion or transfer into a human recipient. Each country has its own local, regional and national regulations on the collection, manufacture and distribution of cellular therapy products for which a license is required. Implementation of laws pertaining to stem cell therapy especially the embryonic stem cell therapy is controversial in many countries including the US and these laws vary from country to country.

In the European Union i.e. in Sweden, Finland, Belgium, Greece, Britain, Denmark and the Netherlands, stem cell research using the human embryo is permitted. While in Germany, Austria, Ireland, Italy and Portugal such research is illegal. Some states in the US are enforcing a complete ban on stem cell therapy while others are giving financial support to researchers and physicians working on such therapy. Japan, India, Iran, Israel, South Korea, China, and Australia are supportive of this therapy but New Zealand, most of Africa (except South Africa), and most of South America (except Brazil) are restrictive. (Source Wikipedia).

Leigh Turner, a bioethicist at the University of Minnesota in Minneapolis, agrees. “It is much too simplistic to think that stem cells are removed from the body and then returned to the body without a ‘manufacturing process’ that includes risk of transmission of communicable diseases,” he says. “Maintaining the FDA’s role as the watchdog and regulatory authority is imperative.”

In July 2013, The US District Court in Washington DC in the matter United States of America Vs. Regenerative Sciences affirmed the right of the Food and Drug Administration (FDA) to regulate therapies made from a patient’s own processed stem cells. Stem cells separated from small sample of bone marrow were multiplied and placed back into the patient to repair an injured area. The FDA called this procedure the “manufacturing, holding for sale and distribution of an unapproved biological drug product.” The FDA further held the procedure involved the manufacture, sale, and distribution of an unapproved biologic drug product and it met the definition of the 'Drug' as it was intended to treat orthopaedic, musculoskeletal, and spinal injuries, and arthritis.

The court upheld the FDA’s conclusion that the production process of the cells was more than “minimal manipulation” and hence agreed that the drug was adulterated as Regenerative did not follow Good Manufacturing Processes. Furthermore, as the drug did not contain labelling and instructions for use, hence, rendering it misbranded. The FDA took the position that regenerative’s actions were unlawful for failure to obtain the necessary approvals for the cell production.

The Texas Medical Board in its new laws has allowed the commercial use of adult stem cells without getting formal mandatory approval from the US Food and Drug Administration (FDA). Texas doctors will have to only get approval from an Institutional Review Board (IRB) and obtain informed consent from patients about the experimental nature of the procedure before they can start the therapy.

An US federal court observed that a stem cell therapy offered by a Colorado clinic, uses stem cells extracted from a patient's own bone marrow to treat bone and joint injuries, that is a medical procedure and not subject to federal oversight.

Celltex, a stem cell bank in Sugar Land, Texas, had claimed that its treatment using autologus cells are not an investigational drug. However, FDA found problems with Celltex's manufacturing process and described its product as a biological drug. The company was told to stop treatment of patients in the US unless a number of issues were resolved.

Recently, the FDA ruled that stem cell product “Regenexx-C” is a drug and it falls under FDA regulation because the clinic is engaged in interstate commerce. A process performed at the clinic using the patient's own bodily fluids constitutes interstate commerce because, according to the administration, out-of-state patients using “Regenexx-C” would depress the market for out-of-state drugs that are approved by the FDA.

In 2003, the Ministry of Health, South Africa had passed a law which became known as the National Health Act. This law specifically spelt out the regulations which were to regulate stem cell research and utilisation in South Africa. As per the said Act, offenders face up stiff fines and a jail term of up to five years if the law is violated.

Recently, Italy has approved a law that allows limited use of stem cell-based therapy on patients of neurological diseases like spinal cord injury and motor neurone disease. However, the therapy must be carried out under regulatory oversight and using cells made according to the GMPs.

Conclusion

Like in many other countries, efforts are being made in India to regulate the stem cell therapy and applicable policies and laws are being enacted. However, the efforts made so far have not been able to curtail the mushrooming of the clinical healthcare entities providing unapproved therapies by soliciting unsuspecting patients through electronic and print media.

There is an urgent need to:

- Enact laws for banning advertising/publicity in electronic / print media or otherwise for anti-ageing, health and beauty benefits with stem cell therapy and make it punishable offence;
- Enact law by which use of cells is allowed for therapeutic purpose only after they have been thoroughly tested for purity, sterility, viability, cytogenic stability and biological potency;
- Make mandatory in the Act for any centre rendering commercial stem cell therapy to obtain license from Drug Controller Authority and this license should be given for specific treatment/indication. Any violation in this regard shall be made punishable offence;
- Enact laws to obtain regular report by officers of Drug Controller on inspection of the facilities provided in the clinic for manufacture stem cells for therapeutic use on regular basis;

- Enact laws which enforce the treating doctors/clinics/institutions to monitor patients who were treated by Stem Cell therapy for minimum five years or may be on longer period before the treatment is advertised for general public and proper data bank is prepared on its long term safety;
- A registry at the central level should maintain total information on the patients having stem cell therapy including the type of cells used, indication in which used, side effects noted etc.;
- Enact law by which government officer/department can be held liable in case gross violation of the Act if takes place by the doctor/clinic/institution situated in their jurisdiction.

The Government of India must ensure that pending Bill is passed at the earliest and notification is issued before unethical stem cell therapies attain stature of Frankenstein.

Disclaimer

A number of issues are being flagged by researchers around the globe every day on research and therapeutics aspects of stem cells. This paper contains some information available from literature in public domain.