I feel honored to be delivering Late Prof. Iftikhar Ali Raja Memorial Lecture. We worked together for several years during formation of Young Neurosurgeons Forum and ASEAN Conference.

STEM CELL THERAPY IN SPINAL CORD INJURY – WHERE DO WE STAND?

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TBI and SCI

• TBI and SCI has drawn the attention of researchers for several decades.
• The researchers have been relaying from one mode to another.
• Till today there is no meaningful answer for primary injury to Neuronal Tissue.
• Let us hope (at least through Genes) the researchers will evolve a clinically viable compromise in near future.
• I shall be concentrating on SCI and highlight the role of stem cells.
Acute Spinal Cord Injury

- Has estimated worldwide incidence of 180,000 new cases per year
- It is devastating
- Has high mortality and morbidity
- Usually involves young people who are full of aspirations in life
- Till today there is no satisfactory answer to primary injury of the spinal cord
- Since neurons are not able to regenerate effectively for functional improvement, complete injuries do not generally recover neurologically. The treatment goal is to rehabilitate them comprehensively so that they can lead a meaningful life in a disabled condition
- SCI is very common in India.

Assessment of Spinal Cord Injury

- Immediate assessment of neurological function and neurologic function + ADL (FIM = functional independence measure) has to be compared with findings at one year.
- Clinical examination should be accurate enough to be compared.

Dilemma

- Today in 2015 we are still in dilemma regarding correct management of primary damage to the spinal cord.

Principles of management

1. Targeting secondary SCI mechanism to prevent aggravation of primary injury
2. Remove mechanical compression on spinal cord
3. Prevent further compression in future by stabilization
4. Look at the horizon to treat primary injury.
Steroids in SCI

- The glucocorticoid steroids, mainly dexamethasone and methylprednisolone (MP), were employed in the clinical treatment of spinal cord injury beginning in the mid-1960s and throughout the 1970s.
- The rationale for their use initially centered on the expectation that they would reduce post-traumatic spinal cord edema.

NASCIS I- 1970

- In the mid-1970s, a randomized, multi-center clinical trial was organized to determine if steroid dosing was beneficial in improving neurological recovery in humans after SCI ……. NASCIS-I
- The answer was rather vague and clinicians continued using steroids.

Extensive use of Methyl Prednisolone-MP

Nascis II (92) Recommendations

- Steroids as MP to be administered within 8 hours upto 24 hrs.

Nascis III (97) Recommendations

- MP to be administered within 3 hrs. upto 24 hrs. 3 to 8 hrs. upto 48 hrs.
- MP gives 5.1% improvement in motor score in 45.9% when administered in time.

Current status of MP-2013

- Current practice of methylprednisolone administration for acute SCI in Germany - a national survey – SPINE 2013
- Specialized SCI centres differ in the use of MP and during the past several years, practice patterns have shifted away from the treatment of SCI with MP.
- Methylprednisolone treatment helps to improve neurological motor recovery to the extent of not more than 6% but it cannot return the patient to normal function.
The timing of surgical intervention in the treatment of spinal cord injury: a systematic review of recent clinical evidence

- Animal studies consistently show that neurological recovery is enhanced by early decompression.
- Several prospective series suggest that early decompression (<72 hours) can be performed safely and may improve neurological outcomes.
- A recent review showed that early decompression (<24 hours) resulted in statistically better outcomes compared to both delayed decompression and conservative treatment.
- Urgent decompression in acute cervical SCI can be performed safely.
- We in India are unable to achieve this due to late arrival of patients.

Bone marrow transplants are done since 1968.

Umbilical cord blood transplants are available since 1988. (Umbilical cord blood contains adult stem cells.)

What is stem cell?

- It is the most primitive cell in the body.
- By its multiplications, cell lines can be established.
- Before they mature, the cells can be moulded in the laboratory to produce the desired type of cells.
- The cells can then be multiplied to produce the required number of cells.
**Adult stem cells**

- Found in many organs of the body.
- Commonest source in umbilical cord blood and nasal mucosa – upper one third.

**Olfactory tissue for transplant**

- Olfactory tissue of nose has plenty of stem cells (Neuronal Progenitor Cells).
- When transplanted, they promote axonal regeneration by producing myelin around damaged axons and secrete growth factor and generate structural matrix that lays the tracks for axonal elongation.

**Umbilical cord blood**

- Umbilical cord blood is extracted, frozen and preserved.
- When need comes the blood is thawed, centrifused and the stem cells are separated, multiplied with specificity and injected into the blood of recipient in desired quantity.
- It takes at least one month before results can be seen.
### Umbilical cord blood

- Umbilical cord blood is a potential vast source of primitive hematopoietic stem and progenitor cells available for clinical application. There are several trials using UCBSC currently in progress.

### Bone marrow stem cells

- Currently, BMSC are the main source in stem cell-based therapy in many neurological diseases, including SCI, because the immune rejection is small and there is the possibility of using autografts.

### Bone marrow mesenchymal stem cells injected intrathecally

- Autologous bone marrow mesenchymal cells that include stem cells (MSCs) is a clinically attractive cellular therapy option in many centres to treat severe spinal cord injury (SCI). The practice is to give a monthly dose for 3 doses.
- However, no differences were found in baseline measures between the MSC group and control group.
- No significant improvements were found in clinical measures between the 2 groups.
- Adverse effects of cells included spasticity and, in 24 out of the 43 patients in one series developed neuropathic pain.

### Stem cell therapy in acute spinal cord injury

**Therapeutic use of stem cells for SCI is thought to be useful as it helps:**

1. Replacement of damaged neurons and glial cells,
2. Secretion of trophic factors,
3. Regulation of gliosis and scar formation,
4. Prevention of cyst formation, and enhancement of axon elongation.
Therapeutic approaches that use stem cells involve
- Implantation of these cells into the spinal cord directly after excision of scar was thought to be more specific
- Injected into the CSF intermittently over a determined period without ascertaining specificity.

Evidence on the use of stem cells in SCI
- There has been a lot of excitement about the potential of stem cell and cellular based interventions for spinal cord injuries.
- However, there is no established clinical evidence to-date that stem cell transplants are successful in the management of human spinal cord injuries.

Conflict of interest
- Spinal cord injured and their families make informed decisions regarding the plethora of so-called “effective” stem cell and cellular transplants being offered across the world, typically for monetary gains.
- They should not get influenced just by patient testimonials.
- The testimonials cannot be relied upon because of the possibility of biases by many confounding factors like placebo effect and natural history of the disease.

ICMR (Indian Council of Medical Research) Guidelines
- As per the latest National guidelines for stem cell research published by ICMR and DBT (Dept of Bio Technology) “Any stem cell use in patients must only be done within the purview of an approved and monitored clinical trial with the intent to advance the science and definitely not offered as therapy.
- In accordance with this stringent definition, every use of stem cells in patients outside an approved clinical trial shall be considered as malpractice.”
ASSI (Association of Spinal Surgeons of India) approves the guidelines

- ASSI endorses the National Guidelines on stem cell research. (http://icmr.nic.in/guidelines/NGSCR%202013.pdf)

Academic Societies

Academic Societies should endorse guidelines as above and make people aware of it by public education.

In our country, several centres are not following guidelines as dictated by the Govt of India?

It is unethical to offer experimental unproven interventions, promising it to be an effective treatment and charging a fee for the same.

Gene therapy using cord blood cells. New thoughts on the horizon

- Genes are transferred into cord blood stem cells with a genetically guided specificity and when implanted can produce beneficial results.
- Cryo preserved cord blood cells produce retroviral receptors easily.
- They are widely used for transplanting gene vectors.
Gene therapy

- SCI induces astrocyte hypertrophy to repair the blood brain barrier and induces hyperplasia to form glial scar.
- Many micro RNAs have been implicated in gliosis through various signaling pathways.
- miRNA mir-21 and mir-146a play a key role in inhibiting the astrocyte activation and the function of cell proliferation.
- Many miRNAs inhibit the expression of inflammatory cytokines as well.
- miRNA also plays a fundamental role in spinal cord recovery.

Functional recovery with microRNAs

- For the first time, it is hoped that the recovery in SCI can lead to measurable improvement in function with the use of miRNA.
- The overwhelming evidence that miRNAs are intricately involved in the processes of both SCI pathophysiology and recovery makes miRNA very promising as a therapeutic strategy in SCI.

Plasmid containing miRNA

- miRNA levels may be increased by administering DNA based plasmids at the site of injury.
- This strategy has not so far been used in SCI model. In stroke it has helped to reduce the size of infarct.
- Plasmid is a molecule in the cell which can be separated from chromosomal DNA and made to multiply independently in a cell which can then be tagged with miRNA.

A plea from the Founder and Past President of Neuro Trauma Society of India
Conclusion

I urge all concerned to formulate guidelines on the use of stem cells in the management of SCI and propagate it more among the people rather than doctors.