Ethics, stem cells and spinal cord repair

Jeffrey V Rosenfeld and Grant R Gillett

ABSTRACT

- Attempted repair of human spinal cord injury by transplantation of stem cells depends on complex biological interactions between the host and graft.
- Extrapolating results from experimental therapy in animals to humans with spinal cord injury requires great caution.
- There is great pressure on surgeons to transplant stem cells into humans with spinal cord injury. However, as the efficacy of and exact indications for this therapy are still uncertain, and morbidity (such as rejection or late tumour development) may result, only carefully designed studies based on sound experimental work which attempts to eliminate placebo effects should proceed.
- Premature application of stem cell transplantation in humans with spinal cord injury should be discouraged.

MJA 2004; 180: 637–639

STEM CELLS CREATE HOPE that we can not only repair but also regenerate damaged and impaired bodily tissues to restore the functions of the healthy body when crucial organs are compromised. This ability would be particularly welcome for spinal cord injury where supportive care rather than any attempt at repair or recovery of function has been the rule. However, spinal cord repair is very complex and includes restoring or enhancing local spinal reflex arcs and reconnecting regenerating axons from above. Neurite outgrowth in the central nervous system (CNS) also requires that inhibitory molecules on oligodendrocytes be eliminated. Moreover, gliosis may block the axon outgrowth.[1]

Neural stem cells are multipotent neural progenitor cells. The main strategies for spinal cord repair using stem cells are:

- to have them act as a cellular bridge providing chemical and mechanical cues for axons to traverse the bridge into the spinal cord below the injury site;
- to provide a source of new neurons which may repair damaged circuits in the spinal cord; and
- to secrete neurotropic substances which promote repair.[1]

Olfactory ensheathing cells (OECs) are unique in sharing properties of Schwann cells and astrocytes and ensheathing olfactory neurons throughout their course. When transplanted, OECs may overcome the inhibition of neurite growth in the CNS. Thus, these cells can be used as an alternative to stem cells for transplantation. They act as a cellular bridge through which corticospinal axons can grow distal to the injury with the aim of restoring some motor function. This has been achieved in experiments in animals.[1,2] Transplantation of autologous olfactory ensheathing cells for chronic spinal cord injury in humans has commenced in Queensland.[3] It is too early to assess the results of these interventions.

Stem cells alone may not be enough to improve functions in a damaged spinal cord. Future strategies for human spinal cord repair will probably be multifaceted, with enhancement of axonal growth and reconnection, replacement of cellular elements, and the reversal of demyelination all being necessary for success. The connective tissue matrix, the degree of glial scarring and the central myelin inhibitory factors (elimination of which is required for axon outgrowth) are all important. The balance of these factors may be as important as the stem cells and very difficult to optimise.

Department of Neurosurgery, Alfred Hospital, Melbourne, VIC.
Jeffrey V Rosenfeld, MS, FRACS, Professor and Director.
Otago Bioethics Centre, University of Otago Medical School, Auckland, New Zealand.
Grant R Gillett, PhD, FRACS, Professor of Medical Ethics.
Reprints: Professor Jeffrey V Rosenfeld, Department of Neurosurgery, Alfred Hospital, PO Box 315, Prahran, Melbourne, VIC 3181.
j.rosenfeld@alfred.org.au

The application of stem cells in neurosurgery, and the biology of cellular transplantation for spinal cord injury, have been reviewed elsewhere.[1,4,5] The ethical issues that are raised in relation to neural stem cells are representative of ethical problems throughout the field of stem cell research. The purpose of this article is to discuss the ethical issues of cell transplantation in repairing the injured human spinal cord. We do not address the ethical problems of embryonic stem-cell harvesting or the genetic engineering of stem cells.

Ethical issues in the clinical use of stem cells

Selection of patients

Extrapolating the results of animal experiments to humans is problematic. Extrapolations should be made from animal models which closely resemble the human injury. Neural transplants into the damaged spinal cords of young or neonatal animals may produce better results than if the host is an adult because of the plasticity of repair in the young animal. It is also important to distinguish return of spinal cord reflex activity below the level of the experimental lesion with that of recovery of complex behaviour, coordination and balance, which depend on repair and regeneration at the level of the spinal cord injury. Special tests have been designed to assess this return of function.[6] The timing of the neural transplantation into the injured spinal cord is also important, as the biology of repair in a chronic injury is also very different from transplantation early after injury.

The clinical application of stem cells to spinal cord injury is problematic in that the less neurologically impaired the patient, the greater the likelihood that manipulation of the spine will produce a worsening of function. Thus, patients with partial spinal injury have more to lose from surgery than those with complete injury. This problem is intensified if, as some theorise, the procedure with the greatest chance of success is the creation of a clean transection with the use of a matrix-and-stem-cell suspension to potentiate repair. Evidence for a high probability of anatomical and functional improvement would be required before embarking on such a surgical transection — theoretical considerations alone would be insufficient. On the other hand, if one were to work solely with patients who have had complete transection, it would be possible to miss (because of the enormity of the reconstructive task) small but important gains which could be stepping stones for interventions offering more chance of viable repair.

The placebo effect

Unfortunately, some of the minimal but significant gains in spinal function reported with techniques such as late decompression of spinal injury are subjective (even though they may indicate a way forward to more substantial gains). Therefore, the ethical issue of subjecting paraplegic and quadriplegic patients to sham spinal surgery for the purpose of controlled comparisons has to be faced. This may be justified where the sham surgery is innocuous and clear distinction between genuine and placebo outcomes is not only crucial, but impossible without surgery. These issues are hotly debated by ethicists and surgeons.[7]

Pressure to apply stem-cell techniques

Surgeons working in this area are constantly being pressured to perform the surgery required as soon as it looks promising. This pressure comes from patients, biotechnology companies and universities with interests in any new area of medical innovation. Scientific objectivity may be further diminished by the egos and commercial imperatives of the proponents. However, whatever the source of such pressure, clinicians need to maintain independent clinical judgement.

These problems were vividly illustrated when many patients with Parkinson's disease travelled to Mexico to have adrenal medulla transplanted to the caudate nucleus in the hope of a miracle treatment, only to be disappointed; some also suffered serious complications. Subsequently, Goetz et al reported the results of adrenal medullary transplantation in 61 Canadian and United States patients who underwent surgery in 13 US centres. Only 19% of patients were considered to have shown improvement at 2 years, and there were significant rates of morbidity and mortality from this surgery.[8,9]

The media should accept some responsibility for raising the expectations of patients with the promise of a significant new advance. The issue of media reports creating false hope for cancer sufferers has recently been examined in the Journal,[10] but also applies to use of stem cells. It is important that researchers explain their work to the media in simple but accurate terms.

Even in animal studies we are increasingly finding that neural repair is a prolonged process, and that we may need to wait months or years for any indication that an intervention has produced any clear benefit. However, the pressure to help suffering patients is so intense that waiting for the results of interventions before recommending their more general use is difficult. This is especially so in patients with spinal injuries, for whom just maintaining function is a major exercise.

Long-term risks to patients

Immunological rejection of non-autologous stem cells may occur in the CNS, as elsewhere in the body, and can cause the loss of the graft. The use of immunosuppressant drugs may prevent such rejection.[1] Of concern is the possible late development of neural tumours arising from implanted stem cells. Genetically engineered stem cells may harbour oncogenes, which could also theoretically induce late tumour development in the graft. However, tumours have not developed in any cultures of human stem cells or after transplantation into animal models, and further experiments are required to determine the risks.[5] The first tentative steps with a new technology such as stem-cell repair must be undertaken with great caution and anticipation of possible risks.

Conclusions

Stem-cell-based technology offers amazing possibilities for the future. These include the ability to reproduce human tissues and potentially repair damaged organs (such as the heart,[11] liver,[12] brain and spinal cord[13,14]), where, at present, we mainly provide supportive care to prevent the situation from becoming worse. This potential almost silences the sternest critics of such technology, but the fact remains that the ethical challenges are daunting. It is encouraging that, in tackling these challenges, we stand to reflect a great deal about the ethics of our profession and our relationships with patients, industry, and each other. The experimental basis of stem-cell or OEC transplantation should be sound before these techniques are applied to humans with spinal cord injury.

Competing interests

None identified.

References

1. Barami K, Diaz FG. Cellular transplantation and spinal cord injury. *Neurosurgery* 2000; 47: 691-700.
2. Ramon-Cueto A, Cordero MI, Santos-Benito FF, Avila J. Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing cells. *Neuron* 2000: 25; 425-435.
3. Smith W. Trial offers hope to paraplegics. *Herald-Sun* 2002; 11 July: 2.
4. Bruce JN, Parsa AT. Why neurosurgeons should care about stem cells. *Neurosurgery* 2001; 48: 243-244.

5. Galvin KA, Jones DG. Adult human neural stem cells for cell-replacement therapies in the central nervous system. *Med J Aust* 2002; 177: 316-318.
6. Zang D, Cheema SS. Leukemia inhibitory factor promotes recovery of locomotor function following spinal cord injury in the mouse. *J Neurotrauma* 2004. In press.
7. Gillett G. Unnecessary holes in the head. *IRB* 2001; 23(6): 1-6.
8. Goetz CG, Stebbins GT, Klawans HL, et al. United Parkinson Foundation on adrenal medullary transplants: presurgical, and 1- and 2-year follow up. *Neurology* 1991: 41; 1719-1722.
9. Greene P, Fahn P. Fetal tissue transplantation for the treatment of Parkinson's disease. In: Tarsy D, Vitek JL, Lozano AM, editors. Surgical treatment of Parkinson's disease and other movement disorders. Totowa, NJ: Humana Press Inc, 2003: 313-328.
10. Ooi ES, Chapman S. An analysis of newspaper reports of cancer breakthroughs: hope or hype. *Med J Aust* 2003; 179: 639-643.
11. Raeburn CD, Zimmerman MA, Arya J, et al. Stem cells and myocardial repair. *J Am Coll Surg* 2002; 195: 686-693.
12. Kobayashi N, Okitsu T, Nakaji S, Tanaka N. Hybrid artificial liver: establishing a reversibly immortalized human hepatocyte line and developing a bioartificial liver for practical use. *J Artif Organs* 2003; 6: 236-244.
13. Kondziolka D, Wechsler L, Achim C. Neural transplantation for stroke. *J Clin Neurosci* 2002; 9: 225-230.
14. Kilpatrick TJ, Butzkueven H, Grigg A. Prospects for stem cell transplantation in multiple sclerosis. *J Clin Neurosci* 2002; 9: 361-367.

(Received 15 Jan 2003, accepted 19 Feb 2004) ❑