Review Article

Recovery and Regeneration after Spinal Cord Injury: A Review and Summary of Recent Literature

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Abstract

Introduction: Spinal cord injury (SCI) often results in significant neurologic dysfunction and disability. An annual incidence of 15 to 40 traumatic SCI cases per million population has been reported worldwide, and a conservative estimate for Singapore would be 23 cases per million. With continued improvements in medical care, an increasing prevalence of SCI patients is expected, with corresponding need for comprehensive rehabilitation services led by specialist rehabilitation physicians. Methods: A literature search, review, and summary of findings of recent studies relating to factors associated with recovery, as well as interventions for rehabilitation and promotion of healing of the injured spinal cord was performed. Conclusions: Many SCI patients show improvements in motoric and neurologic level, but those with complete injuries have poor chance of improving American Spinal Injury Association (ASIA) scores. SCI of violent aetiology tends to be more neurologic complete, and those without sacral sparing less likely to improve. Older patients generally do well in activities of daily living. Women have better motor score improvement, although men have better Functional Independence Measure (FIM) scores generally. Electrodiagnostic tests such as somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) can help with prognostication, as can imaging techniques such as magnetic resonance imaging (MRI). Immediate surgery for spinal decompression may improve recovery, but whether routine surgery after SCI improves function remains unclear, as does the timing. Methylprednisolone and similar agents appear to help limit secondary injury processes. Rehabilitation interventions such as functional electrical stimulation (FES) and body-weight supported treadmill ambulation training may be effective, as may neural-controlled prostheses and devices. Substances that promote repair and regeneration of the injured spinal cord such as GM-1, 4-AP, BDNG, GDNF, Nogo and MAG-inhibitors, have been studied. Transplanted tissues and cells, such as blood macrophages, bone marrow transplant with GM-CSF, olfactory ensheathing cells, fetal tissues, stem or progenitor cells, have been reported to produce neurological improvements.

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Introduction

Spinal cord injury (SCI), whether of traumatic or non-traumatic aetiology, often results in significant and catastrophic dysfunction and disability. It physically and psychologically affects not only the individual, but also the family and society. Early rehabilitation in an organised multidisciplinary SCI care system has been shown to be beneficial, with lower mortality, decreased pressure sores, slightly greater chance of neurologic recovery, and shorter lengths of stay with lower hospital charges.[1] Nevertheless, continued functional dependency, healthcare needs and costs, as well as caregiver burden and stress often remain tremendous. Not surprisingly, there is a constant search for ways and means to enhance recovery and cure SCI.

In 2004, the National Spinal Cord Injury Statistical Center (NSCISC), University of Alabama at Birmingham, USA, reported an annual incidence of 11,000 cases of new traumatic SCIs or 40 per million population (upper end of the 15 to 40 cases per million seen worldwide), with a prevalence of 250,000 cases.[2] In descending order, patients discharged from the Model Spinal Cord Injury Systems (MSCIS) supported by the National Institute on Disability and Rehabilitation Research, had incomplete tetraplegia (34.1%), complete paraplegia (23.0%), complete tetraplegia (18.3%), and incomplete paraplegia (18.5%). Less than 1% had complete neurologic recovery.[3] In the Asia Pacific region, Australia with a 2003 population of 20 million reported an incidence of 300 to 400 new cases per year or

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15 to 20 per million, and a prevalence of 10,000 persons with SCI.[4]

A study from Tan Tock Seng Hospital, then the only facility in Singapore offering structured SCI medical rehabilitation services to the "more severely injured", showed 813 admissions from 1973 to 1984. With a population of about 3 million then, this was an incidence of 68 new cases per year, or 23 cases per million. This figure did not include the less severely injured, nor those admitted to other hospitals. The most common causes of SCI were industrial injuries (34.5%) and road traffic accidents (33.1%). Forty-four per cent had cervical injuries, 29.6% had thoracolumbar injuries, and 20.8% had lumbar injuries.[5] A subsequent study on patients admitted to the same centre between 1990 to 1995 showed that of the 86.3% gainfully employed before injury, only 21.6% returned to some form of vocation within 1 year.[6]

The actual cost of care for a patient with SCI in Singapore is unknown, although the US MSCIS have estimated lifetime costs for a 25 year-old high-tetraplegia patient as much as US$2.9 million.[3] Significant cost-structure differences here include those for inpatient services, outpatient services, and nursing homes, with assistive devices, equipment, and home modifications usually paid for out-of-pocket. Assistance from family, financial and otherwise, and relatively affordable foreign domestic workers as fulltime caregivers are local phenomena that affect care costs.

Traumatic SCI is thus a relatively uncommon problem but one with a young average onset age, and often with significant impairment, disability, and care costs. With improving emergency services and acute healthcare capabilities, the prevalence of patients will grow with a corresponding need for comprehensive medical rehabilitation services. This paper reviews and summarises some of the more recent literature on recovery and healing of spinal cord injured individuals.

Predictors of Recovery after Spinal Cord Injury

Patient characteristics such as age, gender, severity, and aetiology of injury may provide an indication of prognosis for recovery. Clinical assessment, electrodiagnostic tests, and imaging techniques may also be helpful.

i) Patient Characteristics

Data on 987 subjects from the 16 MSCIS locations showed that 94.4% of subjects with neurological complete SCI at 1 year remained so at the 5-year post-injury evaluation. Only 3.5% improved from American Spinal Injury Association (ASIA) grade A (complete motor and sensory) to grade B (sensory incomplete including S4-5), up to 1.05% improved from grade A to C (motor incomplete, less than half of key muscles below the neurological level with power of 3 and above) with another 1.05% to grade D (motor incomplete, half or more of key muscles with power of 3 and above). Nevertheless, approximately 20% showed some improvement in motor power and neurologic level of injury from year 1 to year 5.[7]

SCI from violent causes were more likely to result in complete injuries. Motor complete individuals, even with extended zones of sensory preservation but without sacral sparing, were less likely to improve (at 13.3%) to motor incomplete status than those with sacral sparing (53.6%). At 1 year, motor score improvements were found related to severity of injury, with greater increases for higher initial ASIA grades (except grade D, presumably because of a ceiling effect).[8] It would appear that in complete SCI no neurologic recovery occurs below the injury level, although there may be varying motor recovery within the zone of partial preservation.[9]

In a retrospective study of 284 traumatic and non-traumatic SCI subjects, older individuals >50 years were found to do well with independence as per activities of daily living (ADL) scales, and had shorter lengths of stay. However, they had less favourable outcomes with walking, bladder and bowel independence, and a higher rate of complications.[10] Whether the good outcomes were due to older individuals having greater probability for less severe, incomplete tetraplegia of non-traumatic origin,[10] and tendency for a presumably less traumatic fall instead of a motor vehicle crash[2] with its attendant complications e.g., multiple injuries, is uncertain.

Based on 14,433 subjects from the MSCIS, women had significantly greater ASIA total motor scores improvement at 1-year then men. However, men had higher Functional Independence Measure (FIM) motor scores at rehabilitation discharge among those with motor-complete injuries, except for those with C1-4 and C-6 neurologic levels.[11] All things being equal, the typically stronger limb-body musculature in men may have allowed for greater ADL independence.

ii) Clinical Assessment, Electrodiagnostic, and Imaging Tools

In a review of the MSCIS database and other multicentre studies, the importance of an accurate baseline examination in the first days following injury was emphasised as this correlated with neurological and functional recovery. Neurologic preservation and recovery correlates to increase in self-care and walking, with a prediction possible based on the initial 1-week sensory-motor examination. The Walking Index for Spinal Cord Injury, a 20-level ambulation scale over a distance of 10 m that includes ambulation device used and assistance required, can also be used.[12]

Electrodiagnostic examination may be useful in the prognostication of SCI. The ambulatory capacity of 70 SCI

subjects, following rehabilitation discharge at least 6 months after trauma, was found to be related to both initial ASIA scores and somatosensory evoked potentials (SSEPs) of the tibial and pupendal nerves. The ambulatory capacity was best related to the pudendal SSEP in acute tetraplegia, and ASIA motor score in acute paraplegia. SSEP may be of additional value to clinical examination for prognostication of incomprehensible or uncooperative patients.[13] Another study showed the ASIA protocol and motor evoked potentials (MEPs) of the upper and lower limb muscles to both be significantly related to ambulatory capacity and hand function.[14]

With respect to imaging techniques, post-surgical patients with median haemorrhage lengths less than 4 mm on MRI within 2 weeks of injury had incomplete SCI and a good prognosis. Conversely, patients with complete SCI had median haemorrhage lengths of 10.5 mm, and no improvement 24 to 65 months later.[15] A larger series of 191 patients with magnetic resonance imaging (MRI) within 72 hours of injury showed that compared to haemorrhage and contusion, cord oedema was the strongest predictor of reduced motor function and light touch at 6 weeks.[16] Oedema length was also found to be inversely related to the admission and discharge FIM scores. Patients without spinal cord haemorrhage on MRI had significant improvement in self-care and mobility scores, although haemorrhage was not shown to significantly affect locomotion and sphincter control scores. High-cervical haemorrhagic lesions were predictive of complete dependence on caregivers and equipment.[17]

Surgical Intervention

The National Spinal Cord Injury Database concluded that those undergoing surgery for spinal stabilisation were more likely to be paraplegic women in motor vehicle crashes. Those not requiring surgery were older in mean age and had more incomplete injuries. With greater incompleteness and neurologic preservation, it was not surprising that motoric improvements were more likely in non-surgical groups. Those undergoing late surgery had increased acute and total lengths of stay with higher incidences of pneumonia and atelectasis. There were no significant differences in neurologic level changes between the early surgery, late surgery, and no surgery groups.[18] A comparison between another 2 cervical SCI groups, one randomised to early surgery <72 hours, and the other late or >5 days after spinal cord injury (SCI), also did not show any significant neurologic benefit to early intervention.[19] There was again no evidence that routine early surgical intervention or decompression improved neurologic outcomes in a retrospective review of 412 traumatic incomplete cervical SCIs.[20]

However, a prospective study on 91 patients out of a tertiary centre supported early surgery. Fifty per cent of cervical SCI patients undergoing immediate spinal cord decompression treatment protocol improved from their admitting Frankel grade, versus only 24% of reference patients. Twelve per cent of the protocol but none of the reference patients improved from complete motor (grade A or B) to independent ambulation (grade D or E). The protocol group also required shorter intensive care unit and total hospital stays. It should be noted though that the reference group needed other emergent surgical treatment, had contraindications to MRI, or specific surgeon opinion regarding "futility" of emergent treatment, all possible indicators of greater injury severity and hence poorer prognosis.[21] A review of data from 50 patients with traumatic central cord syndrome who underwent early (24 hours or less after injury) surgery for acute disc herniation or fracture-dislocation revealed significantly greater overall motor improvement, shorter ICU and hospital lengths of stay.[22]

A retrospective multicentre study from 36 North-American institutions compared early and late decompressive surgery in 585 acute or cauda equina SCI patients. Only half of patients met the inclusion criteria, and results were inconclusive due to great variations in extent and type of scanning performed, and timing of surgery that varied from less than 24 hours to more than 5 days post-injury.[23]

Steroids for Acute Injury

The National Spinal Cord Injury Study (NASCIS) trials I, II and III on early steroids to limit the amount of cellular damage from secondary injury processes such as lipid peroxidation had a tremendous impact on the management of acute traumatic SCI. The conclusions from these trials have been challenged for reasons including relatively modest neurologic improvements compared to risks of high-dose steroids. The trial design, including choice of an 8-hour treatment window, data analysis, reliance on sensory-motor assessments rather than functional outcomes, efficacy and effect size have also been questioned.[24] Nevertheless, the early use of high-dose steroids has practically become the standard of care in acute traumatic SCI.

NASCIS I compared efficacy of high-dose intravenous methylprednisolone (MP) at 1,000 mg bolus/day versus standard-dose 100 mg bolus/day for 10 days. There was no difference in motor or sensory recovery between the 2 groups 6 weeks and 6 months after injury. There was a greater early case fatality although not statistically significant, and more prevalent wound infection in the high-dose group.[25]

NASCIS II compared intravenous MP at 30 mg/kg bolus followed by 23 hours of infusion at 5.4 mg/kg per hour, against naloxone bolus of 5.4 mg/kg with 4.0 mg/kg per

hour for 23 hours, and placebo bolus with infusion. After 6 months, those treated with MP within 8 hours of injury had significant improvement in motor and sensory function compared to placebo. There was no difference in neurologic outcome in those given naloxone or MP more than 8 hours after injury, as compared to placebo. The 3 groups had similar mortality and major morbidity (gastrointestinal bleed, wound infection, delayed healing) rates.[26]

In NASCIS III, all patients received intravenous MP bolus of 30 mg/kg and were subsequently divided into 3 groups. Group 1 received MP infusion at 5.4 mg/kg per hour for 24 hours, group 2 the same for 48 hours, and group 3 received tirilazard mesylate (a 21-aminosteroid lacking glucocorticoid receptor-mediated activity) 2.5 mg/kg bolus infusion every 6 hours for 48 hours. The patients treated with MP for 48 hours showed improved motor recovery over those with MP for 24 hours. This result was significant for those started on MP between 3 and 8 hours after injury, but they also had more severe sepsis and pneumonia than the 24-hour group. Those treated with tirilazard for 48 hours had motor recovery equivalent to the patients treated with MP for 24 hours.[27]

Rehabilitation Intervention

Traditionally, rehabilitation focuses on functional restoration by maximising residuals or returns through therapeutic exercise, or by overcoming losses with compensation techniques and use of devices and equipment. However, evidence for both motor and sensory recovery even years after the injury is increasing. The concept of reversing learned non-use and rediscovery of a central pattern generator (an autonomous network of neurons capable of generating a locomotor pattern independent of supraspinal inputs) has led to keen research in this area,[28] especially in the study of patterned locomotor activity.[29]

i) Functional Electrical Stimulation

In a prospective single-case study, it was demonstrated that recovery of function was possible in a complete C2, ASIA "A" injury 5 years after injury. The subject underwent an activity-based recovery programme with an integrated computer-assisted functional electrical stimulation (FES) induced cycling bicycle with the hypothesis that patterned neural activity might stimulate the central nervous system to become more functional. Over a 3-year period, the patient improved from ASIA "A" to "C" with reversal of osteoporosis, reduction in spasticity, medical complications, and improved quality of life.[30]

Presently, electrical stimulation is used in various neuroprostheses to substitute for non-recovered motor-sensory functioning, including the anterior sacral root stimulator for bladder dysfunction,[31] FES system for improving hand function in tetraplegics,[32] and FES cycling to improve cardiovascular function.[33]

ii) Body Weight Support Treadmill Training

Interest in body weight support treadmill (BWST) training gained impetus with reports of functional improvement after ambulation training on a treadmill. Previously absent voluntary electromyographic (EMG) activity became recordable during flexion and extension movements in 8 incomplete SCI persons who underwent intensive BWST ambulation training wearing harness supports for 30 to 60 minutes, 5 days a week. In 4 severely paralysed patients, reflexive flexion developed in the paralysed limbs as well as knee extension during stance. Significantly, after training, patients were able to walk 100 to 200 m on a static surface despite absent voluntary activity in the paralysed limb at rest. The authors concluded that bipedal stepping with knee extension and stabilisation could be restored even after complete or near complete paralysis, suggesting the presence of spinal-level complex reflex motor patterns.[34]

Functional magnetic resonance imaging (fMRI) of 4 subjects before and after BWST training revealed greater activation in sensorimotor cortical regions (S1, S2) and cerebellar regions, suggesting that task-specific training could promote supraspinal plasticity in locomotion motor centres. There was also a connection between increased cerebellar activation and improvement in over-ground ambulation as measured by Walking Index for Spinal Cord Injury II and gait speed.[35]

Other groups have reported positive results,[36] even after brief training in people with incomplete spinal cord injuries.[37] A small longitudinal prospective study, with 13 chronic incomplete SCI subjects completing the 144 training sessions, showed that all improved in treadmill walking ability with decrease in need for body-weight support, increased speed and distance, and 6 of the subjects had improved over-ground walking capacity. Eight months post-training, most of these improvements were maintained.[38]

A multicentre study with 146 subjects within 8 weeks of SCI comparing efficacy of BWST with defined over-ground mobility therapy did not show any difference in FIM locomotion scores, walking speed or distance. However, this was explained by the unexpectedly high percentage of ASIA "C" subjects who probably would have achieved functional walking regardless of intervention.[39] Combination epidural spinal cord stimulation (ESCS) of dorsal structures at T10-T12 with partial weight bearing treadmill therapy resulted in treadmill and over-ground ambulation in an individual with chronic incomplete tetraplegia. Partial weight-bearing therapy alone had not been sufficient to achieve functional ambulation over ground though treadmill ambulation improved significantly,

suggesting that ESCS augmented the use-dependent plasticity stimulated by partial weight bearing therapy.[40]

Robotic devices have been integrated into neuro-rehabilitation programmes with promising results, and use of automated driven gait orthosis ambulation training has been proposed to significantly reduce the load on therapists during ambulation training.[41] However, a comparison between treadmill ambulation and robotic-assisted Lokomat (TM) walking showed significantly higher swing-phase quadriceps-hamstring activity and reduced ankle flexor-extensor activity in the latter. It would appear that walking within a limiting robotic orthosis altered naturally occurring muscle activation patterns.[42]

The benefits of such therapies were thought to be limited to incomplete paraplegics who had better postural control. However, it was recently reported that the restoration of locomotor function might paradoxically be better in cervical SCIs.[43] At this time, the efficacy of BWST training is still being debated, with few large well-controlled studies and mixed results.

iii) Neural-activity Controlled Prostheses

Recent developments in the field of neural prosthesis include improvements in the important area of brain-machine interface (BMI). The ability to use brain neural activity to directly control a machine such as a word-processor, environmental control unit, wheelchair, or hand prosthesis would be invaluable in compensating for loss of limb function. Problems abound, however, at the BMI, such as undesirability of electrodes implanted directly into the brain, or difficulty in converting weak fluctuating neuronal recordings into definite, discrete and specific commands for the machine. The use of non-invasive electrodes placed over the scalp or head has its own limitations, particularly with resultant weakness and loss of specificity of neural signals. The use of a variety of cognitive (e.g., goal and predicted value of an action) and motor signals (e.g., hand trajectory) may maximise the control signals. Local field potentials as additional signals to the usual electroencephalograms or spike activity recordings have also shown promise.[44] Mathematical analysis of neural population codes as opposed to single-neuron recording has been demonstrated to allow extraction of precise motor signals in real-time to directly control robot-arm movements.[45]

Healing and Regeneration of the Injured Spinal Cord

Various bioactive agents, neurotrophic factors, transplanted neuro-cellular and other tissues are being investigated for efficacy either for limiting the amount of secondary damage, or promoting healing and regeneration of the injured spinal cord. At this time, most of these studies have either been in animal models or have not been proven by way of large randomised controlled studies.

i) Bioactive Agents and Neurotrophic Factors

Monosialotetrahexosylganglioside (GM-1) sodium intravenously for 18 to 32 doses with the first taken within 72 hours of injury in 34 patients has been shown to produce a significant difference in Frankel grades from placebo at 1-year follow-up. The GM-1 group also had significantly greater mean improvement in ASIA motor score. Analysis of individual muscles attributed recovery to initially paralysed muscles regaining useful motor strength, rather than paretic muscles just getting stronger.[46]

Various other substances have been studied using animal models, especially rat. These include application of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) to the spinal cord. These, especially when used in combination 60 or 90 minutes after SCI, have resulted in significant reduction of motor dysfunction and spinal cord pathology.[47] However, transplantation of fibroblasts genetically modified to produce neurotrophic factors BDNF or neurotrophin-3 (NT-3) onto rat spinal lesion did not show advantage in sensorimotor recovery to either grafting with gelfoam or gelfoam plus fibroblasts, other than improvement of heat-induced hyperalgesia.[48]

Certain endogenous inhibitors are known to limit the amount of recovery and plasticity after central nervous system injury. These include Nogo (neurite outgrowth inhibitor) and MAG (myelin-associated glycoprotein). Various therapeutic approaches to overcome these inhibitors and enhance regeneration have been studied, such as targeting against the inhibitory protein, antagonising the known receptor, and inhibiting intracellular signal transduction of these substances.[49] Spinal cord injured rats given highly purified anti-Nogo-A monoclonal IgG antibodies showed enhanced histological corticospinal axon regeneration, compared to those receiving unspecific IgGs. The former also showed significant cortical responses to hindpaw stimulation on fMRI, implying enhanced neurologic regeneration and reorganisation.[50]

The antioxidant compound H-290/51 produced markedly attenuated immediate early gene expression (c-fos) and motor dysfunction. There was evidence of neuroprotection with the blood-spinal cord barrier permeability, oedema formation, and cell injuries mildly but significantly reduced.[51] Antiserum to dynorphin A (1-17) significantly attenuated neuronal nitric oxide synthesis (NOS) up-regulation in adjacent segments of the injured levels with less marked spinal cord oedema and cell injury.[52]

The omega-3 polyunsaturated fatty acids (PUFA) alpha-linolenic acid and docosahexaenoic acid (DHA) have been

shown to significantly improve locomotor performance and neuroprotection when injected 30 minutes after SCI. There was decreased lesion size and apoptosis, and increased neuronal and oligodendrocyte survival. However, rats treated with an omega-6 PUFA, arachidonic acid, had worse outcomes.[53] Adenosine A2A receptor activation with ATL-146e (a selective A2A agonist) in the rabbit SCI has been demonstrated to be at least as effective as MP in preserving function and spinal cord tissue structure.[54]

4-aminopyridine (4-AP), a potassium-channel blocking agent that enhances axonal conduction through demyelinated nerve fibres has undergone human trials with good results. However, there have not been adequately strong trials or sufficient evidence of efficacy for the drug to be approved for the routine use in patients with SCI or multiple sclerosis.[55] Earlier trials with small subject numbers supported 4-AP as producing neurologic benefits in some SCI patients.[56] A more recent prospective, randomised, double-blind, placebo-controlled crossover trial with 15 chronic ambulatory SCI patients showed no statistical or clinical differences in lower limb muscle force and objective gait analyses between placebo and 4-AP.[57]

ii) Transplanted Cells and Tissues

The challenges to recovery have been stated to be the following: i) cell survival; ii) axon regeneration or growth; iii) correct targeting by growing axons; and iv) establishment of correct and functional synaptic appositions. The solutions proposed include intraspinal transplants with fetal cells or progenitor cells to restore the intraspinal circuitry or to function as relays for damaged axons. The physiologically disrupted but anatomically preserved axons can be remyelinated by Schwann cells, oligodendrocytes, and olfactory ensheathing cells. In particular olfactory ensheathing cells have been demonstrated to promote excellent axonal growth by cell adhesion molecules and secretion of neurotrophic growth factors that encourage axonal migration.[58]

Transposition of pedicled omentum has been tried in chronic traumatic SCI patients. Although 6 of 13 subjects self-reported enhanced function at 1 year, their SSEPs and MEPs showed no change. There were also no significant changes on ASIA and International Medical Society of Paraplegia (IMSOP) scoring. Moreover, the operated patients suffered 1 postoperative death from pulmonary embolus, as well as other significant complications.[59]

In a small study with 8 complete SCI patients, macrophages obtained by isolating monocytes from patient blood and incubated ex-vivo with autologous dermis were injected immediately caudal to the spinal injury. Three of the patients went on to recover significant motor and sensory function, progressing from ASIA "A" to "C".[60]

Six complete SCI patients who underwent autologous bone marrow cell transplantation (BMT) in conjunction with granulocyte macrophage-colony stimulating factor (GM-CSF) noted immediate sensory improvements. Six to 18 months after the procedure, there was significant motor improvement with 4 patients going from ASIA "A" to "C", one to "B", and the last remaining "A". MR imaging 4 to 6 months after injury showed slight enhancement within the zone of BMT but no evident syrinx formation.[61]

Olfactory ensheathing cells (OECs) appear to have great potential for aiding recovery after SCI although most studies have been in non-humans. Rats with transected spinal cords which 4 weeks later had olfactory lamina propria transplanted into the area had significantly improved locomotor activity compared to controls, with brainstem raphe axons across the transplant site.[62] Tissue protectors including MP and interleukin-10 (IL-10), in combination with Schwann cells plus OECs significantly improved gross motor performance in contused rat spinal cord compared to injury-only controls.[63]

Olfactory ensheathing glia (OEG) has been transduced with adenoviral (AdV) vectors encoding rat BDNF, NT-3, or bacterial marker protein beta-galactosidase (LacZ) and implanted into rat SCI. The results included smaller lesion volumes for all OEG transplants, significantly so in the neurotrophin factor transduced OEG grafts. There was enhanced regenerative sprouting of the rubrospinal tract, better locomotion and hind limb function, suggesting that genetic engineering of OEG resulted in a more effective cell for promoting axonal outgrowth.[64]

Spinal cord transplants and exogenous neurotrophins 2 weeks after rat SCI dramatically increased amount of axonal growth and functional recovery, with both supraspinal and propriospinal projections caudal to the transaction reestablished. The authors proposed that after SCI, the circuitry underlying rhythmic alternating stepping movements are still present caudal to the lesion but devoid of supraspinal control. Restoring even relatively small amounts of input allowed supraspinal neurons access to this circuitry and this, along with reorganisation of segmental circuitry improved motor function.[65]

The hope of a cure for SCI has been revitalised with the advent of neural stem cells. A non-human primate study involved transplantation of in vitro-expanded human neural stem/progenitor cells (NSPCs) into contused marmoset spinal cords. Eight weeks later, histologic analysis showed that the NSPCs had differentiated into neurons, astrocytes, and oligodendrocytes, with cavities smaller than controls. Functionally, these animals had significantly higher bar grip power and spontaneous motor activity.[66]

There have been phase I clinical trials showing the safety of OECs grown and purified in vitro from nasal biopsies

and injected into the injured human spinal cord. Three chronic SCI subjects reviewed 1 year after transplantation did not appear to have medical or surgical complications such as spinal cord damage from the procedure, cyst, tumour, syrinx formation, neuropathic pain, change in psychological status, or evidence of neurological deterioration.[67]

Six-to-nine-week post-conception human fetal spinal cord tissues have been implanted into 8 progressive post-traumatic syringomyelia patients after surgical dethetering, cyst drainage, and immunosuppression with cyclosporine initiated a few days before surgery and continued 6 months. From the preliminary 2 patients who had 18 months of follow-up, the procedure appeared safe with stable neurological status, and solid tissue at the graft sites without evidence of donor tissue overgrowth on MRI.[68] Fetal nervous and haemopoietic tissues of gestational age 16 to 22 weeks and minimally manipulated were implanted into 15 patients with severe traumatic SCI 1 month to 6 years after injury. Between 1 and 4 cell-transplantations were done and in 11 cases were combined with operative partial disruption of a connective tissue cyst and implantation of a spinal cord fragment with OEC. The patients were ASIA grade "A" before intervention but subsequently 6 improved to "C", 5 improved to "B", and 4 remaining unchanged.[69]

Relatively large series of patients with transplants have been reported from China. One hundred seventy-one SCI patients aged 2 to 64 years who underwent intraspinal OECs transplantation had improved ASIA scores 2 to 8 weeks later with increase in motor, light touch, and pin prick perception regardless of age.[70] The same group subsequently reported on 300 patients (222 with complete and 78 incomplete chronic SCI) 6 months to 31 years after injury, who were transplanted with trypsinised human OECs from aborted human fetuses. Two to 8 weeks after transplantation, there was significant improvement of motor, light touch, and pin prick scores but no significant difference of these in relation to the age, sex, duration after injury, injury degree and level.[71] Some of these same patients, presumably, were studied with MRI before and 29 to 42 months after transplantation. The MRIs did not reveal any development of optic glial tumour, tumour-like mass, new haemorrhage, oedema, expanding cyst, new cyst formation, infection, or disruption of neural structure at transplant site.[72]

There was subsequently a commentary and observational study with MRI, ASIA protocol, change in disability, and detailed history of the perioperative course of 7 of the SCI patients who had undergone fetal brain tissue transplant in the studies above. The patients had received preoperative, and now had postoperative assessments up to 1 year after the transplants. It highlighted many issues with the transplant protocol, such as unclear inclusion and exclusion criteria with subjects varying from ASIA "A" through "D", and having diverse SCI aetiologies. The sites for cell injection did not always correlate with the injury, with 1 high cervical SCI subject injected in the frontal lobes of the brain. Serious complications included meningitis in 5 subjects. The authors felt that transient postoperative hypotonia might have accounted for some of the subjects' physical changes as no clinically useful sensorimotor, disability, or autonomic improvements were found. They also felt that the procedure should not be recommended as it did not meet international trial standards for either safety or efficacy.[73]

Conclusion

Following SCI, an accurate baseline clinical assessment is important and correlates with self-care and walking scores. Those with complete SCI have a poor chance of moving up the ASIA grades, but a good number of patients show some motoric and level of neurologic injury gains. Those without sacral sparing were less likely to improve neurologically. Although older patients generally do well in ADLs, those of younger age have better walking, bowel and bladder independence. Women have better motor score improvement but men have better FIM scores, except with C1-4 and C-6 complete injuries. Electrodiagnostic tests such as SSEPs of the tibial and pudendal nerves, and MEPs of the upper and lower limbs can help with prognostication. Imaging techniques can be useful with cord haemorrhagic lengths <4 mm, absence of haemorrhage, and less rostral oedema on MRI having better prognosis.

Whether surgery improves recovery is unclear, and may be dependent on whether the indication is for decompression or for stabilisation, possibly helpful in the former. Studies on the best timing of surgery are inconclusive but routine early surgery may not improve neurological outcome. Methylprednisolone as per the NASCIS protocol appears helpful in limiting secondary injury processes and has become a common intervention.

Rehabilitation strategies such as use of FES for the urinary bladder, hand and for therapeutic exercise have been studied. BWST ambulation training may also be helpful, possibly by activation of preserved rhythmic-stepping circuitry caudal to the spinal injury, or by promoting supraspinal plasticity in locomotion centres. The use of brain neural activity to control machines and devices is an exciting development still in infancy.

The search for SCI healing continues with attempts to find substances or cellular transplants capable of regenerating the injured spinal cord. GM-1 and 4-AP have been used in humans with significant improvement in motor scores and neurological function. An alphabet soup

of various other substances have been used in animal studies with positive results, including BDNG, GDNF, NT-3, H-290/51, antiserum to dynorphin A (1-17), alpha-linolenic acid, docosahexaenoic acid, and Atl-146e, Nogo and MAG-inhibitors, among others.

Transplanted tissues and cells such as blood macrophages, and bone marrow transplant in conjunction with neurotrophic GM-CSF appear to improve recovery in the small number of human subjects tested. OECs or OEG has been promising in animal studies, and in a small phase I trial appears to be safe for humans. Transplantation of fetal tissues, stem or progenitor cells, is a new field that brings up possible ethical issues to be addressed. Fetal spinal cord, other nervous and hemopoietic tissues, OECs have been reported to produce significant neurological improvements. Nevertheless, the promising results of the largest human series with some 400 patients injected with fetal OECs have been questioned for failing to meet international standards of scientific protocols and evidence.

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