Spinal cord bypass surgery using peripheral nerve transfers: review of translational studies and a case report on its use following complete spinal cord injury in a human

Experimental article

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Spinal cord injury has been studied in a variety of in vitro and in vivo animal models. One promising therapeutic approach involves the transfer of peripheral nerves originating above the level of injury into the spinal cord below the level of injury. A model of spinal cord injury in rodents has shown the growth of peripheral nerve fibers into the spinal cord, with the subsequent development of functional synaptic connections and limb movement. The authors of this paper are currently developing a similar model in felines to assess the cortical control of these novel repair pathways. In an effort to determine whether these neurotization techniques could translate to spinal cord injury in humans, the authors treated a patient by using intercostal nerve transfer following complete acute spinal cord injury. The case presented details a patient with paraplegia who regained partial motor and sensory activity following the transfer of intercostal nerves, originating above the level of the spinal cord injury, into the spinal canal below the level of injury. The patient recovered some of his motor and sensory function. Notably, his recovered hip flexion showed respiratory variation. This finding raises the possibility that intercostal nerve transfers may augment neurological recovery after complete spinal cord injury. (DOI: 10.3171/FOC.2009.26.2.E6)

Key Words • cauda equina • intercostal nerve • nerve transfer • neurotization • paraplegia • spinal cord injury

ESTIMATES of the incidence of spinal cord injuries vary from 30 to 40 new cases per million persons annually in the US, and the average age of the victim of spinal cord injury is < 40 years.29 Approximately one-quarter of these injuries result in complete paraplegia.18,29 A simple technique that facilitates the recovery of some lower-extremity motor and sensory activity after a complete paraplegic spinal cord injury would have tremendous value. The rehabilitation potential, cost of care, risk of complications and/or death, and quality of life could all improve on recovery from a complete to partial spinal cord injury.

Neurotization, or nerve transfer, is most commonly used to treat brachial plexus injury by connecting a donor nerve, such as the spinal accessory or intercostal nerves, to a denervated peripheral nerve target.7,28 After the transfer, axons grow from the donor nerve into the recipient nerve, innervating previously denervated muscles. For example, nerve transfers can permit recovery of shoulder abduction and arm flexion even in a flail arm.

In experimental studies, researchers have used nerve transfers to bypass spinal cord injury. In brief, an intercostal nerve originating above the level of injury is separated from its target muscle and transferred to nerve roots or into the spinal cord below the level of spinal cord injury. In an effort to explore the potential of this strategy in the clinical setting, we performed an intercostal nerve transfer into the spinal canal below the level of injury in a patient undergoing surgery for treatment of a complete spinal cord injury.

Illustrative Case

History and Examination. This 48-year-old man sustained an injury as the result of a fall from a ladder. Motor and sensory examinations were consistent with a complete T-11 level spinal cord injury. Spinal CT re-
Revealed a T11–12 fracture dislocation with complete canal compromise (Fig. 1).

**Operation.** Forty-eight hours after injury, the patient underwent a T11–12 laminectomy and a T-9 to L-1 posterior instrumented fusion. Before implanting the instrumentation, the T-11 nerve roots were identified and dissected ~2 cm distal from the canal. A partial costotransversectomy was performed bilaterally to unroof these roots. The origin of the T-11 roots was visualized just above the level of the cord injury. The roots were cut distally and transferred into an elliptical incision made into the dura of the spinal cord just below the level of the injury. The implantation was angled so that the roots would point inferiorly into the canal (Fig. 2). No attempt was made to directly attach the roots or fascicles to either the distal spinal cord or any of the roots of the cauda equina.

**Postoperative Course.** Postoperatively, the patient remained paraplegic with an unchanged sensory level and a neurogenic bladder. He subsequently spent 8 weeks at an inpatient rehabilitation unit where he was taught to self-catheterize and use a bowel regimen. Urinary tract infections and a deep venous thrombosis complicated his clinical course. At 5 months postoperatively, the patient began to report a vague awareness of sensation in his thighs. Sensation below the knees was absent. No motor function in the lower extremities was observed. At 10 months postoperatively, the patient began to demonstrate recovery of hip adduction (MRC Grade 2/5) and flexion (MRC Grade 2/5). The patient noted that he could induce more powerful adduction by exhaling firmly. Spontaneous movement of his legs was observed in cycle with respirations. No clinical improvement in urinary or bowel function was reported.

**Discussion**

**The Spinal Cord Injury Problem**

Primary spinal cord injury results from the physical disruption of the spinal cord structure at the time of initial injury due to penetrating objects, bone fragments, hematoma, or other mechanisms. Secondary injury represents additional damage that occurs in a delayed fashion in the tissues surrounding the primary injury. Tissue ischemia, excitotoxicity, inflammation, apoptosis, and free radical injury are all mechanisms contributing to secondary injury. Unfortunately, after injury the CNS neurons display little tendency for regeneration; and even if they did, the extracellular matrix is laden with growth-inhibition substances that restrict nerve cell regeneration. Moreover, the site of spinal cord injury is typically replaced with a dense glial scar, providing a mechanical barrier against regenerative processes. One strategy to treat spinal cord...
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injury is to bypass the site of injury with functional nerve bridges.

Spinal Cord Bypass: Animal Studies

Early efforts to supply innervation to more caudal structures below a level of injury date back to 1907 when lumbar nerve roots were anastomosed to the ventral sacral roots in dogs. Stimulation of the transferred roots produced bladder contraction and micturition. Similar studies decades later involved the use of related strategies to enable the recovery of lower-extremity function in dogs and erectile function in baboons. In an experiment in cats, the researchers used an L7–S1 peripheral nerve root transfer to recover bladder function. After an appropriate period of recovery, invasives pressures showed respiratory variation, stimulation of the transferred nerves led to bladder contraction, sectioning of the transferred nerves abolished this function, and histological analysis confirmed growth of the transferred axons down the target nerves.

Intercostal nerves were chosen as the donor nerves for transfer to the lumbar roots in canine experiments. Following a T-11 transfer to L-6, some animals were eventually able to ambulate without a limp. A histological follow-up analysis in these animals revealed axon growth from the donor to the target nerves as well as morphological changes in the muscle consistent with denervation and subsequent reinnervation. Later studies in rabbits and dogs demonstrated the feasibility of transferring multiple intercostal nerves to a single lumbar nerve root and to multiple lumbar roots in rats. A second study showed partial recovery of limb function following the transfer of multiple intercostal nerves to multiple lumbar nerve roots in the rat.

A variant of a spinal cord bypass without using nerve transfers has been developed in rats and later in primates. In this model, the proximal terminus of peripheral nerve autografts is implanted into the ventral horn of the spinal cord below the level of injury, whereas the distal ends are anastomosed to the lumbar ventral nerve roots. Data from this model have suggested that anterior horn motor neurons send recovering axons down the nerve grafts to reinnervate the distal lumbar nerve-supplied targets.

Spinal Cord Bypass: Human Cadaver Studies

A feasibility study in human cadavers has shown that the T-11 intercostal nerve can be readily transferred to the L-5 nerve root in both infants and adults. Intercostal nerves have been reported to be acceptable donor nerves for transfer to the sacral nerve roots at an intraspinal level in a cadaver study. A more extensive set of studies in adult cadavers has revealed that the T9–11 intercostal nerves can be sufficiently harvested and transferred to targets within the cauda equina.

Spinal Cord Bypass: Human Clinical Studies

The first description of a nerve transfer to treat a human following a spinal cord injury dates back to 1912. In that case report, a patient who had sustained an L-2 level injury underwent transfer of 1 of the extradural L-1 nerve roots to the S-3 and S-4 roots within the cauda equina. The patient apparently regained some functional bladder control 8 months later. There is a brief description of another series of patients with high lumbar spinal column injuries who underwent intercostal to lumbar nerve root anastomosis. Of the 8 patients in the series, only 1 showed improvement, but few details of either the surgical technique or the patient characteristics were described. In an early case report, a child with myelomeningocele and a neurogenic bladder was treated with neural plate excision and anastomosis of 1 pair of thoracic intercostal nerves to 2 pairs of sacral nerve roots. Although the bladder was initially atonic, by 8 months the patient recovered reflex micturition. A second report by the same group of researchers details the treatment of 2 patients with complete L-1 spinal cord injury following T12–L1 fractures. In both patients, the bilateral T-12 intercostal nerves were transferred to the bilateral S2–3 nerves below the level of injury within 2 weeks of injury. Both patients recovered some sacral sensation and voluntary voiding and had low postvoid residual volumes.

Two patients with myelomeningocele underwent T10–11 intercostal nerve transfer to the lumbosacral nerve roots distal to the congenital lesion. Although minimal follow-up data were reported, both patients apparently experienced reinnervation of select lower-extremity muscles, as noted on electrodiagnostic studies and clinical examination. Another adult patient suffered a traumatic L1–2 fracture, resulting in a complete spinal cord injury at the T-12 level. The bilateral T8–9 intercostal nerves were transferred to the bilateral L-2 and (presumably) S-1 nerve roots. Although this report showed the feasibility of this technique, no follow-up data were included.

A reasonably large series of patients with spinal cord injury underwent 1 of 2 types of nerve transfer surgery. In the first treatment group, several pairs of lower intercostal nerves were anastomosed to the lumbosacral nerve roots within the cauda equina. In the second group, several pairs of intercostal nerves were anastomosed to the L2–4 nerve roots in the retroperitoneal lumbar plexus. Although most of these patients had sustained a complete spinal cord injury, many recovered some, albeit modest, motor function. Specifically, 5 of the 21 patients in the study experienced recovery of lower-extremity muscle power ranging from MRC Grade 1 to 3. Another series of patients who had suffered low thoracic spinal cord injury—all but 1 with complete injury—underwent transfer of the 2–4 intercostal nerves above the level of injury to the L1–4 nerve roots within the spinal canal below the level of injury. More than three-quarters of the patients recovered sufficient lower-extremity motor function to permit ambulation with an assistive device. Nerve transfers were used in a series of 11 patients following L-1 complete spinal cord injuries. One year after transferring the bilateral T11–12 intercostal nerves to the bilateral S2–3 nerve roots, patients had significant improvements in bladder function, sacral sensations, and sacral reflexes.

The group that created the model of spinal cord bypass in which peripheral nerve autografts are implanted proximally into the ventral spinal cord rostral to the level

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of injury and distally into the ventral lumbar nerve roots attempted this technique in a human. This patient had sustained a complete T-9 level spinal cord injury 3 years before the bypass surgery. He received peripheral nerve autografts, which were inserted into the T7–8 ventral spinal cord proximally and anastomosed to the L2–4 lumbar roots within the spinal canal distally. Several months postoperatively, the patient recovered modest thigh adhesion and knee extension on clinical and electrodiagnostic examination.

A New Approach to Spinal Cord Bypass

The transfer of peripheral nerves originating above the level of spinal cord injury to peripheral nerve targets below the level of injury has limitations. For example, the axons must grow from the site of anastomosis to the target muscles, a process that may require years, depending on the length of the target nerve. Moreover, the availability of donor axons is limited, thus hindering the degree to which 1 or more targets can be reinnervated.

If the peripheral nerve donors were transferred directly into the spinal cord, then they could potentially tap into existing spinal cord circuits below the level of injury. A relatively small donor nerve could exert control over a somewhat limited set of muscles within a restricted peripheral distribution. Direct transfer might enhance the extent of fiber growth into the periphery, given that those pathways are already in place. In the literature there is an early report of intercostal transfer to the spinal cord. An adult male patient had sustained a gunshot wound to the spinal cord, resulting in complete transection at about the T-11 level. Four months later he underwent a bilateral T-8 and T-10 intercostal nerve harvest. One pair of intercostal nerves was transferred to clumps of sacral nerve roots, whereas the second pair was inserted into the substance of the conus medullaris via midline stab incisions. Unfortunately, the patient died before the acquisition of meaningful follow-up data. However, postmortem findings did demonstrate axonal growth into the recipient sacral nerves past the anastomoses and, notably, into the substance of the conus. This model of spinal cord bypass surgery recently has been investigated in a rodent model. An intercostal nerve was transferred into the spinal cord caudal to the level of injury. It is our opinion that the incisions needed to insert the nerves into the cord may cause unacceptable damage to a partially injured spinal cord in the acute setting, and thus compromising its ability to recover.

Nevertheless, in the illustrative case herein described, the patient recovered some hip flexion. Curiously, the muscle movements were associated with respiratory variation, which would be expected if under control by the intercostal (respiratory) nerves. Additionally, electromyographic studies of the hip flexor muscles showed characteristic respiratory variation. Although there was no way to know for certain that this patient was not going to recover some of this function anyway, the respiratory variation in the recovered muscles suggests that a portion of this function is controlled by the intercostal nerves.

Why peripheral axons grow into the CNS so well, whereas central axons do not, is a mystery but likely stems from phenotypic differences between the 2 types of fibers. Stimulation of the transferred peripheral nerve results in limb movement when sufficient recovery time has elapsed in a rodent model. Intermittent stimulation produces intermittent leg movement through these novel spinal cord synapses, not through another pathway, such as via the spinal nerve roots. There is no evidence to suggest that the growth of a peripheral nerve directly into the spinal roots even occurs. In fact, such a pathway would be anatomically impossible in the animal models, because the transferred axons would have no way of entering the intact spinal nerve roots. Similarly, it would be difficult to imagine a feasible pathway for the peripheral axons from the transferred nerves in our patient to find their way for a couple of segments caudally and to enter otherwise undamaged spinal nerve roots to exert their effects.

Our patient gained leg movement with respiratory muscle contraction. Sectioning the peripheral nerve bridge in animal models abolishes limb movement. We suspect that a similar result would occur if our patient underwent an appropriate intercostal nerve block. Unfortunately, in the absence of any reasonable expectation of a clinical benefit, this procedure would be unethical, and we have not advocated it.

Obviously, there is no way to prove that our patient’s recovery was due solely to the nerve transfer, as opposed to some recovery of intrinsic spinal cord function. Nevertheless, the presence of respiratory variation in the muscle contractions is certainly suggestive of at least a contribution by the transferred intercostal circuitry. This problem will always be encountered when studying this population of patients. Thus, within a population of spinal cord–injured patients, there would be no way to reliably determine if the outcome for any given patient is due to spontaneous recovery or to the treatment itself. We advocate the exploration of this problem in a larger clinical study so that meaningful differences between treatment groups can be revealed if present.

Conclusions

A spinal cord bypass utilizing intercostal nerve transfers to spinal cord targets caudal to the level of injury may represent a viable approach in treating complete spinal
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cord injury in humans. Future animal studies and subsequent clinical trials in humans will, we hope, delineate the utility of this treatment strategy.

Disclaimer
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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