First Human Implantation of a Bioresorbable Polymer Scaffold for Acute Traumatic Spinal Cord Injury: A Clinical Pilot Study for Safety and Feasibility

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BACKGROUND AND IMPORTANCE: A porous bioresorbable polymer scaffold has previously been tested in preclinical animal models of spinal cord contusion injury to promote appositional healing, spare white matter, decrease posttraumatic cysts, and normalize intraparenchymal tissue pressure. This is the first report of its human implantation in a spinal cord injury patient during a pilot study testing the safety and feasibility of this technique (ClinicalTrials.gov Identifier: NCT02138110).

CLINICAL PRESENTATION: A 25-year-old man had a T11-12 fracture dislocation sustained in a motocross accident that resulted in a T11 American Spinal Injury Association Impairment Scale (AIS) grade A traumatic spinal cord injury. He was treated with acute surgical decompression and spinal fixation with fusion, and enrolled in the spinal scaffold study. A 2 × 10 mm bioresorbable scaffold was placed in the spinal cord parenchyma at T12. The scaffold was implanted directly into the traumatic cavity within the spinal cord through a dorsal root entry zone myelotomy at the caudal extent of the contused area. By 3 months, his neurological examination improved to an L1 AIS grade C incomplete injury. At 6-month postoperative follow-up, there were no procedural complications or apparent safety issues related to the scaffold implantation.

CONCLUSION: Although longer-term follow-up and investigation are required, this case demonstrates that a polymer scaffold can be safely implanted into an acutely contused spinal cord. This is the first human surgical implantation, and future outcomes of other patients in this clinical trial will better elucidate the safety and possible efficacy profile of the scaffold.

KEY WORDS: Myelotomy, Scaffold, Spinal cord injury, Spinal cord rehabilitation

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The treatment of traumatic spinal cord injury (SCI [tSCI]) has advanced markedly from the standpoint of correcting spinal instability. However, little clinical progress has been made in treating the underlying nervous system pathology to ultimately improve outcomes in these patients. There has been preclinical success with use of different pharmacologic and cell-based therapies.[1,2] The Neuro-Spinal Scaffold (InVivo Therapeutics Corp, Cambridge, Massachusetts) is a proprietary bioresorbable polymer scaffold that acts by appositional healing to spare white matter, decrease posttraumatic cyst formation, and potentially improve functional recovery as tested in animal models of spinal cord hemisection (Figure 1).[3,4] The Neuro-Spinal Scaffold is composed of US Food and Drug Administration–approved poly (lactic-co-glycolic acid) covalently conjugated to poly(L-lysine) to facilitate favorable cell-material interactions. Spinal cord hemisection is a rarity in clinical medicine, and these therapeutic strategies have been adapted in animal models of spinal

ABBREVIATIONS: AIS, American Spinal Injury Association Impairment Scale; **SCI,** spinal cord injury; **tSCI,** traumatic spinal cord injury

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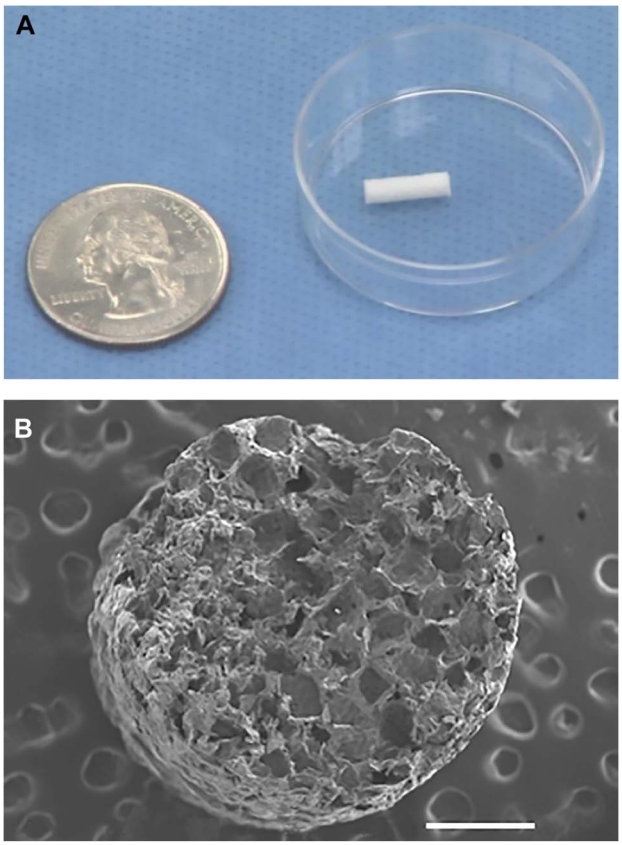

FIGURE 1. **A**, *photograph of a Neuro-Spinal Scaffold (InVivo therapeutics Corp, Cambridge, Massachusetts) adjacent to a coin (US quarter) to demonstrate its size (2 mm in diameter by 10 mm in length).* **B**, *electron microscopic image of the scaffold demonstrating its highly porous nature, which provides structural support for recovering neural tissue and allows for the seeding of stem cells. Scale bar, 500 μm. Used with permission from InVivo Therapeutics Holdings, Corp.*

cord contusion to assess safety and feasibility to support the application of this technology in a human clinical trial. Although preclinical studies show that this technology may represent a viable treatment option, future applications may include the addition of other agents, such as stem cells. Herein, we report the first human implantation of the polymer scaffold directly into the SCI site of a patient.

The study was approved by the US Food and Drug Administration (ClinicalTrials.gov Identifier: NCT02138110) and by the Institutional Review Board of St. Joseph's Hospital and Medical Center. The objective was primarily to evaluate whether the Neuro-Spinal Scaffold is safe and feasible for the treatment of complete functional SCI, as determined by no degradation in paralysis level or sensory motor neurological function beyond that typically seen in patients with American Spinal Injury Association Impairment Scale (AIS) grade A injuries.

Secondarily, the study was geared to gather preliminary evidence of the clinical effectiveness of the scaffold, including improvement in AIS grade, sensory scores, motor scores, bladder and bowel function, neurological tests, and the Spinal Cord Independence Measure III. Inclusion criteria for the study were signed informed consent, age 18 to 65 years, AIS grade A tSCI (T3-T12/L1) confirmed by a neurosurgeon, injury occurring within the previous 21 days, and nonpenetrating contusion injury no less than 4 mm in diameter and limited to 2 contiguous vertebral levels. Exclusion criteria included incomplete SCI (AIS grade B, C, D, or E), terminal illness, severe spinal conditions other than the lesion to be treated, associated traumatic brain injury, long-term mechanical ventilation, penetrating trauma, and radiographic evidence of parenchymal disassociation or transection in which the contusion completely bridged a full cross section of the spinal cord.

CLINICAL PRESENTATION

Patient Presentation

A 25-year-old man with no underlying medical problems presented to our institution after a motocross accident that ejected him from his dirt bike. He experienced immediate paralysis, and his spine was immobilized by first responders. He had no documented hypotension or hypoxia immediately after the accident. He had complete flaccid paralysis of his legs, and the lowest level of normal sensation was at the T11 dermatome, with complete lack of sensation below L1. The patient had no voluntary anal contraction and had lost sensation to deep anal pressure, indicating a lack of sacral sparing; therefore, his injury was classified as a T11 AIS grade A complete injury. The patient had a Glasgow Coma Scale score of 15 and had no other traumatic injuries. A computed tomographic (CT) scan of the thoracic spine demonstrated a fracture dislocation at T11-12, with bilateral jumped facets (Figure 2). To improve spinal cord perfusion, we immediately began administering an intravenous infusion of norepinephrine to maintain a mean arterial pressure of 85 mm Hg, in accordance with the Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries from the Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.[5]

Magnetic resonance imaging demonstrated extensive spinal cord damage at the T11-12 level, with ongoing compression from the fracture dislocation (Figure 3). A bright area of spinal cord parenchyma was on T2-weighted magnetic resonance imaging, but there was no radiographic evidence of cyst or hemorrhage. Given the degree of spinal cord compression, as well as our institution's general practice of acute decompression and fixation for all SCI patients, informed consent was obtained for surgery. Informed consent concerning the Investigational Device Exemption for the intraparenchymal implantation of the Neuro-Spinal Scaffold was also obtained from the patient and his family.

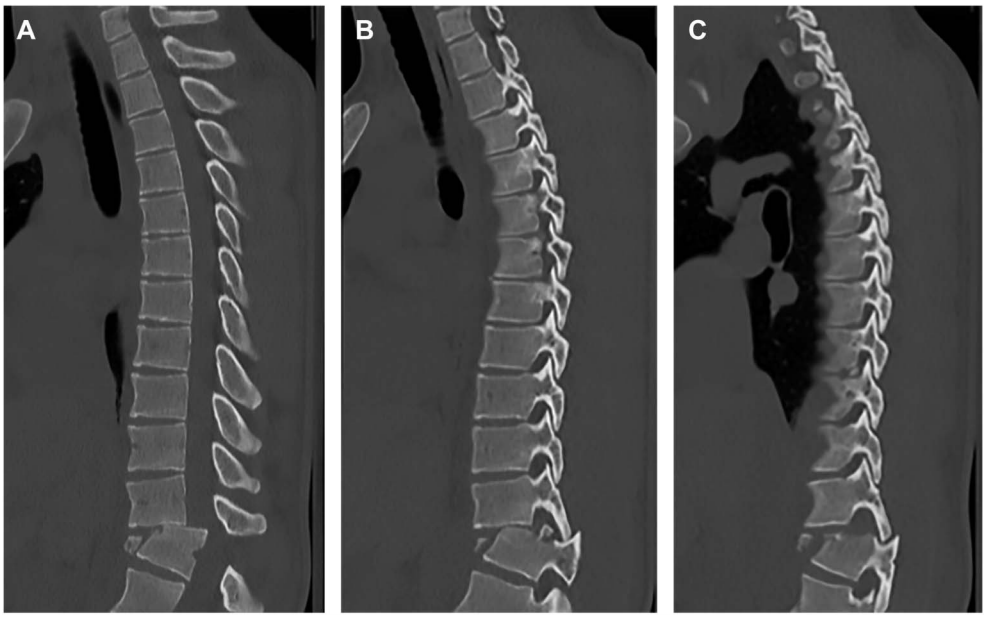

FIGURE 2. *Preoperative computed tomographic scans of the thoracic spine: Midsagittal (A) and parasagittal (B and C) views. Evidence indicated a fracture-dislocation injury with bilateral jumped facet joints at T11-12, with bony retropulsion into the spinal canal. Used with permission from InVivo Therapeutics Holdings, Corp.*

Surgical Description

Approximately 8 hours after the injury, the patient was brought to the operating room, where he received general endotracheal anesthesia. He was placed prone on a Jackson table, and neutral spinal alignment was maintained. A midline incision was made over the thoracolumbar region, and subperiosteal dissection was completed in a standard fashion. There was clear evidence of bilateral T11 to 12 facet dislocation. An intraoperative CT scan was performed for spinal navigation, and bilateral pedicle screws were placed at all levels from T10 through L1. T11 and T12 laminectomies were performed, along with medial facetectomies, and the spine was gently reduced to normal alignment with the application of a temporary titanium rod through the left pedicle screws for temporary segmental fixation. Given the marked instability of the spine, this temporary rod was provisionally tightened with set screws.

The dura of the spinal cord appeared intact; however, the right T11 nerve root sleeve was avulsed, without obvious egress of cerebrospinal fluid. The spinal cord appeared adequately decompressed by the laminectomies and open reduction of the fracture dislocation. A Woodson device passed freely along the ventral dura, and there was no evidence of ongoing or additional compression. Ultrasonography was then used to visualize the area of contused spinal cord directly beneath the dorsal dura. A midline durotomy was sharply performed, and the spinal cord was inspected. The spinal cord had no gross damage, hemorrhagic pial staining, or lacerations, but the cord did appear diffusely swollen and absent pulsations. The spinal cord was again evaluated with ultrasound, which helped identify the caudal end of the contusion and the associated cavity. In addition, this ultrasound interrogation demonstrated increased contusion on the left side of the spinal cord. Given that there were several large surface vessels in the midline on the dorsal surface of the spinal cord, and that the injury appeared slightly predominant on the left, we opted for a left-sided dorsal root entry zone approach. Small vessels were mobilized from the dorsal surface, and the spinal cord was sharply entered with a No. 11 blade. Microscissors and microforceps were used to gently expand what appeared to be a large cavity within the spinal cord (Figure 4A). Gentle saline irrigation into this cavity washed out small pieces of loose necrotic debris. The overall turgor of the cord decreased, and normal pulsations of the spinal cord returned.

Before implantation, the scaffold was placed in sterile saline for 10 minutes according to the manufacturer's protocol. The myelotomy and cavity were sized, and a 2 mm (diameter) by 10 mm (length) scaffold device was selected for implantation. Gentle spreading of the cavity opening allowed tensionless insertion of the scaffold (Figure 4B). **Video 1** (**Supplemental Digital Content 1**, http://links.lww.com/NEU/A859) demonstrates the microsurgical portion of the operation, including scaffold insertion.

Once the scaffold was placed, the surrounding spinal cord gently closed around it so that the cavity was no longer visible through the myelotomy. Intraoperative ultrasonography confirmed correct

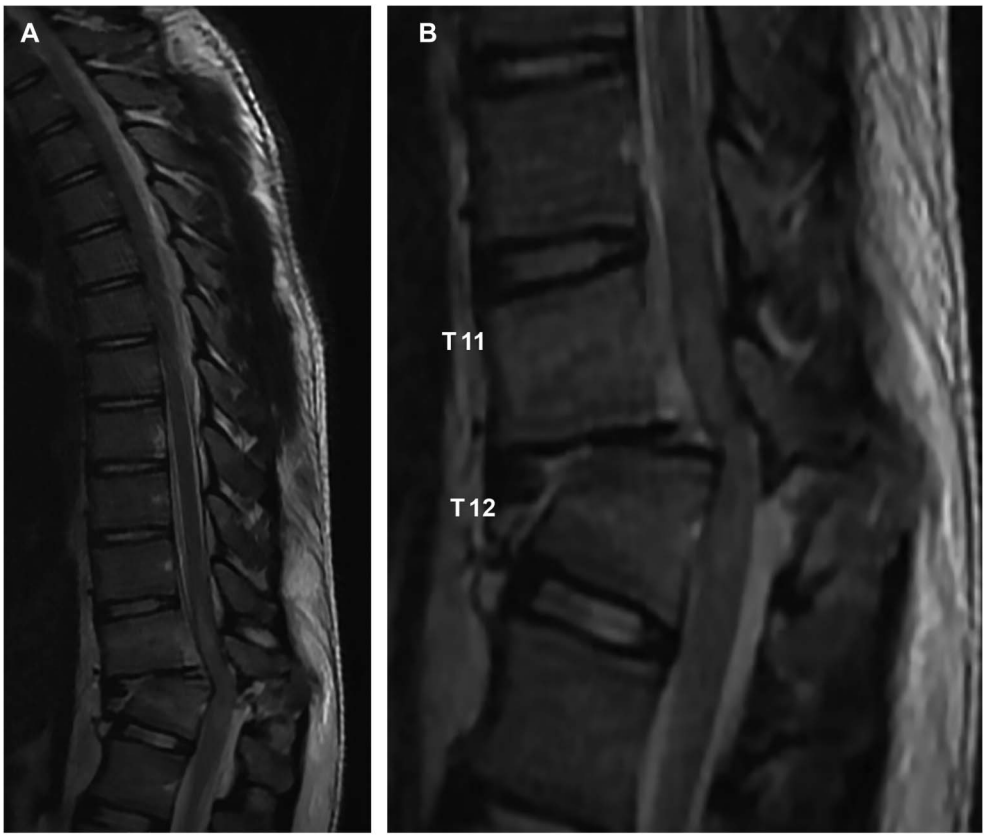

FIGURE 3. *Preoperative T2-weighted magnetic resonance imaging of the thoracic spine. Sagittal views without (A) and with (B) magnification over the injury site at T11-12 demonstrate expected spinal cord compression and edema within the cord parenchyma. Used with permission from InVivo Therapeutics Holdings, Corp.*

placement of the scaffold device, with the polymer scaffold appearing hyperechoic relative to the surrounding spinal cord tissue and maintaining its longitudinal orientation (Figure 5). The subarachnoid space was irrigated copiously with bacitracin solution. Polypropylene suture was used to close the dura in a watertight fashion, followed by fibrin glue reinforcement. The temporary rod was removed, and permanent titanium rods were contoured, placed, and tightened bilaterally to perform definitive segmental fixation. The bony surfaces from T10 to L2 were decorticated with the use of a high-speed air drill, and a mixture of the patient's own bone (from the laminectomy) and demineralized bone matrix was packed into the interstices bilaterally from T10 through L2 for posterolateral fusion. Vancomycin powder was sprinkled in the wound, and a drain was left for spontaneous drainage. The wound was closed in standard fashion with absorbable suture. Estimated blood loss from the procedure was 500 mL. The total operative time was approximately 200 minutes.

Postoperative and Extended Recovery

The patient was kept intubated immediately after surgery, with extubation on the first postoperative day. His motor examination did not change, but he did report altered sensation in the L1 dermatomes bilaterally. His mean arterial pressure was kept elevated above 85 mm Hg for 6 days after surgery. As expected, the patient had postsurgical and neuropathic pain, which was treated aggressively with medication. In addition, he developed a urinary tract infection shortly after discharge from the hospital, which was treated with antibiotics. Neither complication (pain or urinary tract infection) appeared to be directly related to the experimental portion of the surgery, because these are both common complications of this injury after a standard decompression with fixation and fusion. After 11 days in the hospital, the patient was discharged directly to our SCI rehabilitation hospital, where he continued to recover before returning home 20 days later. He received the standard physical therapy for this injury both during his hospital stay and as an outpatient.

Three months after the surgery, the patient had evidence of sacral sparing, with intact voluntary anal contraction and sensation of deep anal pressure. In addition, his sensation was normal at and above the L1 dermatomes bilaterally. The patient's motor function also improved to 3/5 strength in the hip flexors and to 1/5

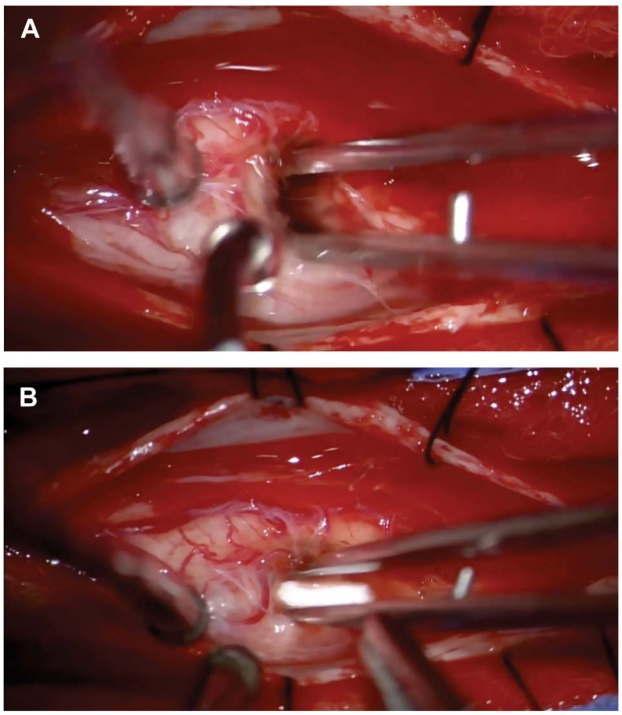

FIGURE 4. *Intraoperative photographs of the spinal cord injury site preparation and scaffold implantation under microscopic magnification.* **A**, *after completion of a left-sided dorsal root entry zone myelotomy at the caudal end of the injury site, gentle dissection was performed with suction and microforceps. Approximately 2 mm below the pial surface, a small cavity was encountered. Necrohemorrhagic material was removed from the cavity to prepare it for scaffold implantation.* **B**, *the 2 × 10 mm scaffold was inserted with microforceps into the cavity in the spinal cord. The scaffold was implanted without extensive friction or tension on the surrounding friable spinal cord tissue. Used with permission from InVivo Therapeutics Holdings, Corp.*

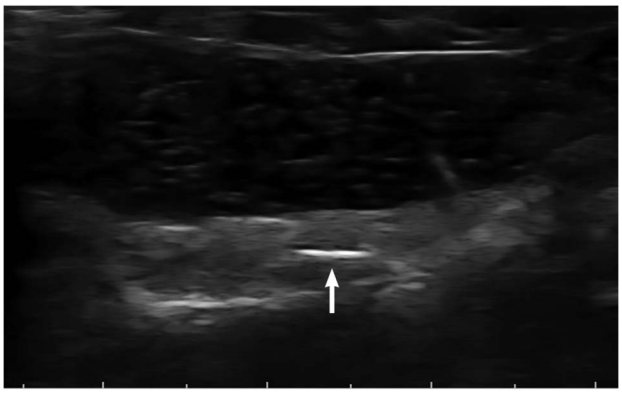

FIGURE 5. *After implantation of the scaffold, intraoperative sagittal ultrasonography was performed. Note the hyperechoic scaffold (***arrow***) within the surrounding spinal cord parenchyma. Used with permission from InVivo Therapeutics Holdings, Corp.*

FIGURE 6. *Follow-up imaging was performed 3 months after surgery. Sagittal T2-weighted magnetic resonance imaging demonstrates a slightly expanded contusion or cavity at the T11-12 injury site compared with preoperative imaging as seen in Figure 3A. Used with permission from InVivo Therapeutics Holdings, Corp.*

strength in the knee extensors. Given this clinical improvement, the patient's injury status was reclassified as an L1 AIS grade C incomplete SCI. Repeat magnetic resonance imaging showed a relatively stable appearance of high signal within the spinal cord at the injury site without evidence of syrinx formation (Figure 6). Ultrasonography over the surface of the back did not identify the presence of the scaffold.

At the patient's 6-month follow-up, he reported continued urinary tract infections, but he had complete resolution of both postsurgical back pain and neuropathic pain, and he no longer required any analgesics. His knee extension strength had improved to 2/5, with overall stability of his L1 AIS C incomplete SCI (Figure 7). The patient had perineal sensation to deep pressure and pinprick. He also had voluntary anal sphincter contraction. He was able to partially empty his bladder but was continuing with intermittent self-catheterization. Magnetic resonance imaging remained consistent, with no evidence of

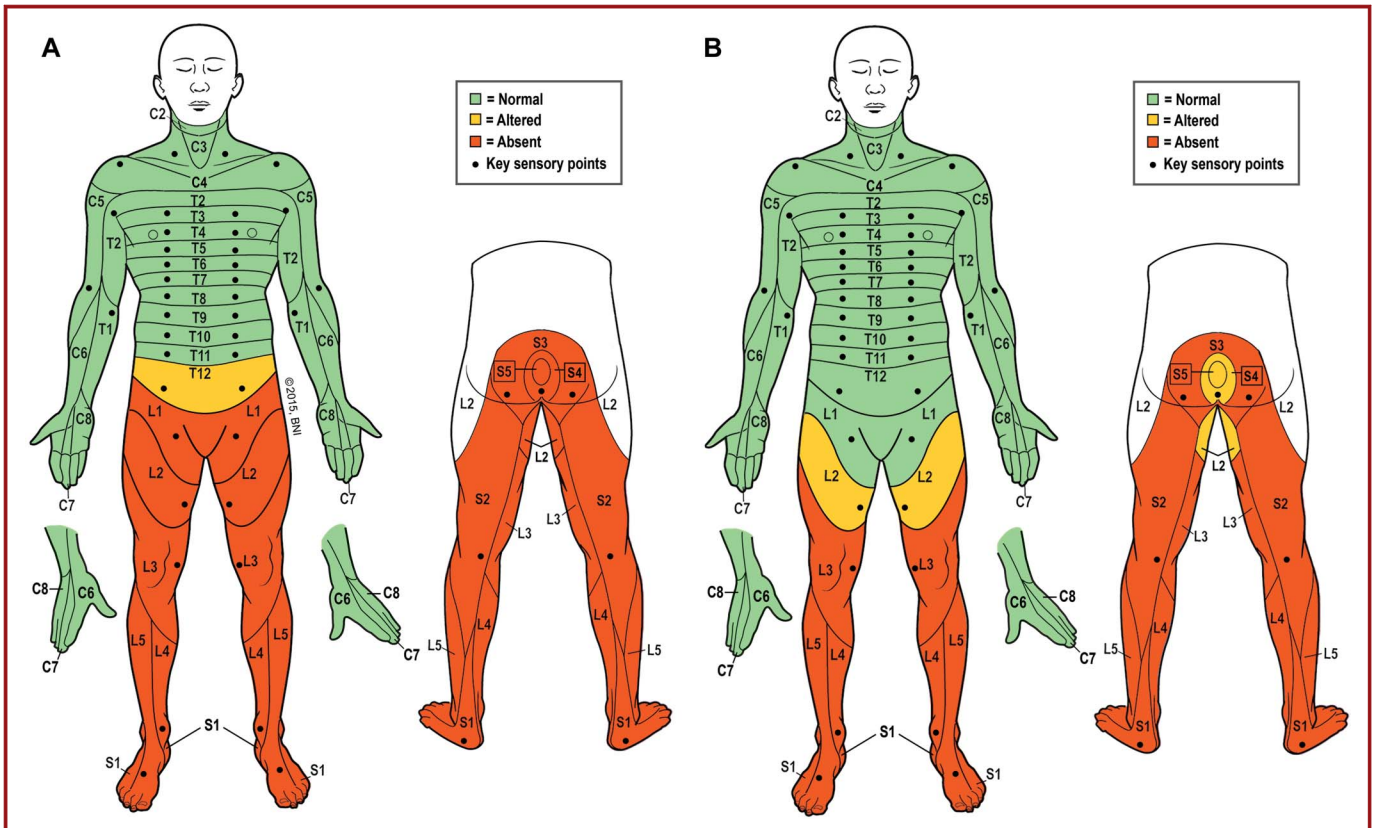

FIGURE 7. *Preoperative (A) and 3-month postoperative (B) score sheets adapted from the* American Spinal Injury Association Impairment Scale (AIS): International Standards for Neurological Classification of Spinal Cord Injury *(revised 2013; updated 2015) demonstrated improvement in the patient's sensory examination. Preoperatively, he had no deep anal pressure sensation or voluntary anal contraction and a T11 sensory level with no motor function below that level, indicating a T11 AIS grade A complete spinal cord injury. At 3-month follow-up, he had regained deep anal pressure sensation and voluntary anal contraction. In addition, he had regained normal sensation down through the L1 dermatomes bilaterally and had regained some strength in the hip flexors and knee extensors, indicating conversion to an L1 AIS grade C incomplete injury. Orange indicates areas with no sensation, yellow indicates areas with diminished sensation, and green indicates areas with normal sensation. Modified from the score sheets of the American Spinal Injury Association, Atlanta, Georgia. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.*

radiographic sequelae from the implanted scaffold. Radiographs revealed evidence of early bony fusion across the posterolateral elements (Figure 8).

DISCUSSION

This case demonstrates the safe and feasible implantation of an innovative polymer scaffold into the parenchyma of a patient with an acutely injured spinal cord. In general, patients with tSCI experience a low rate of conversion from AIS grade A complete injury to incomplete injury. Large studies have cited 10% to 20% of patients with complete cervicothoracic injuries converting to motor incomplete injuries at 12 months but only 2% gaining functional motor strength below the injury level.[6,7] Given these historical conversion rates, our patient might have converted to an incomplete injury with standard decompression and fixation surgery, without durotomy, myelotomy, and scaffold implantation. Although there was notable improvement in the patient's neurological function (ie, T11 AIS grade A to L1 AIS grade C), this improvement cannot be attributed solely to the implanted scaffold. In this case, we elected to operate on the patient acutely (within 8 hours) because he had no evidence of spinal cord transection and there was obvious ongoing compression.

An additional explanation for this patient's clinical improvement may have been decompression of the intradural compartment secondary to the traumatic nerve root avulsion or surgical durotomy. Similar to cranial decompression, the laminectomy and durotomy will lower the subarachnoid pressure locally around the injured spinal cord and may improve perfusion and, possibly, recovery.[8] Furthermore, the myelotomy and subsequent debridement of the necrohemorrhagic cavity with gentle irrigation and suction may also have enhanced local recovery, but because this is not the standard of

FIGURE 8. *Lateral radiograph of the surgery site at 6-month follow-up. The pedicle screws and rods are in the proper location, and there is evidence of early bony fusion across the facet joints from T10 to L1 from the posterolateral fusion. There was no early adverse effect of the implantation of the scaffold on spinal alignment, instrumented fixation, and fusion that was performed as the standard of care. Used with permission from InVivo Therapeutics Holdings, Corp.*

care for patients with tSCI, its potential benefits and risks are unknown. Finally, it should be noted that patients with injuries to the conus medullaris do tend to have a better recovery than patients with spinal cord injuries of the thoracic and thoracolumbar spine.[9] The underlying hypothesis for this difference is the higher proportion of lower motor neurons in the conus region. Despite the clinically significant confounding factors that may have led to this patient's favorable recovery, there are preclinical data supporting the potential effectiveness of the scaffold in improving outcomes.

The concept of spinal cord internal decompression and evacuation of necrohemorrhagic tissue after SCI through a myelotomy was proposed over 100 years ago.[10,11] In canine experiments, Allen[10,11] noted "the much better state of preservation of the substance of the cord in this sectioned case" (with, rather than without, myelotomy). Many hypotheses have been proposed for improved function in animals after myelotomy in addition to laminectomy for decompression after SCI, including reduction in aquaporin expression.[12] Despite good experimental evidence for the benefits of myelotomy after acute injury, this practice has largely been abandoned and is not the standard treatment for patients with acute traumatic injuries.

An often-cited concern is that removal of necrohemorrhagic tissue could lead to a detrimental collapse of the spinal cord architecture. Specifically, in his 1923 treatise, Thompson stated: "Evacuation removes the support and the walls of the cavity cave in like the sides of a sand pit or the banks of a river when the waters recede."[13] In the present study, we filled the empty cavity created by myelotomy and debridement with a biomaterial scaffold that may have provided structural support and thus limited the collapse of the spinal cord architecture.

Limitations

An additional limitation of this case study was the relatively short follow-up of 6 months. However, the stated goal of this first implantation was to evaluate safety. In a future case series with a larger number of patients, extended follow-up should be possible. In addition, we did not include evaluation using standardized scales for pain or electrophysiologic measures but will consider them for future studies.

CONCLUSION

The novel surgery described in this report demonstrates the feasibility of implanting a polymer scaffold directly into the injured spinal cord of a human. Throughout 6 months of clinical and radiographic follow-up, no complications were attributable to the scaffold itself or to the additional surgical steps required for its implantation. The patient had a fortunate outcome, with notable improvement in sensorimotor function, as well as resolution of commonly encountered neuropathic SCI pain. Outcomes from other patients enrolled in this clinical trial will better elucidate the safety profile of the scaffold. This report gives cause for cautious optimism about the effectiveness of intraspinal implantation of polymer scaffolds to treat patients with tSCI.

Disclosures

Kristin Neff and Lou Vaickus, MD, are employees, and Thomas R. Ulich, MD, is an employee and stockholder, of InVivo Therapeutics Corp., Cambridge, Massachusetts. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors present the first successful and safe human implantation of a bioresorbable polymer scaffold in a patient with severe traumatic spinal cord injury. Although the results of this study provide encouraging data on the feasibility of the technique and tolerability of the implant, outcomes from future patients enrolled in this study are necessary to validate the safety and elucidate the effectiveness of this polymer scaffold.

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