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Authors

Harrop, James S

Kim, Kee D

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Acute Implantation of a Bioresorbable Polymer Scaffold in Patients With Complete Thoracic Spinal Cord Injury: A Randomized Controlled Trial (INSPIRE 2.0)

James S. Harrop, MD, MSHQS [‡**], **Kee D. Kim, MD** [§*], **David O. Okonkwo, MD, PhD** [‖], **Ira M. Goldstein, MD** [¶#], **K. Stuart Lee, MD** [**], **Richard M. Toselli, MD** [††]

[‡]Department of Neurological and Orthopedic Surgery, Division of Spine and Peripheral Nerve Surgery, Delaware Valley SCI Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; **(Continued on next page)**

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*James S. Harrop and Kee D. Kim contributed equally to this work.

Correspondence: James S. Harrop, MD, MSHQS, Department of Neurological and Orthopedic Surgery, Division of Spine and Peripheral Nerve Surgery, Delaware Valley SCI Center, Thomas Jefferson University, 909 Walnut St—third floor, Philadelphia, PA 19107, USA. Email: james.harrop@jefferson.edu and Kee D. Kim, MD, Department of Neurological Surgery, UC Davis, 4860 Y St, Suite 3740, Sacramento, CA 95817, USA. Email: kdkim@ucdavis.edu

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BACKGROUND AND OBJECTIVES: Traumatic spinal cord injury (SCI) remains a devastating condition with no proven effective treatment options available. In a prior single-arm study of patients with thoracic complete SCI (INSPIRE; ClinicalTrials.gov, NCT02138110), acute implantation of an investigational bioresorbable polymer scaffold (Neuro-Spinal Scaffold [NSS]) appeared to be safe through 24 months postimplantation and was associated with an American Spinal Injury Association Impairment Scale (AIS) conversion rate that exceeded historical controls. Here, we evaluated whether NSS implantation demonstrates probable benefit for safety and neurological recovery in patients with thoracic complete SCI vs standard-of-care spine surgery.

METHODS: INSPIRE 2.0 was a randomized, controlled, parallel, multicenter study conducted at Level I trauma centers in the United States (ClinicalTrials.gov, NCT03762655; funded by InVivo Therapeutics Corporation). Patients with AIS grade A, thoracic (T2-T12), nonpenetrating SCI requiring spine surgery ≤7 days postinjury were randomized (1:1, computer-generated allocation) to undergo NSS implantation or spine surgery alone (control group). Patients and follow-up International Standards for Neurological Classification of SCI assessors were blinded. A predefined study success criterion required the proportion of patients with improvement of ≥1 AIS grade at 6 months postsurgery (primary endpoint) to be ≥20% higher in the NSS group than in the control group.

RESULTS: Target enrollment was reached (N = 20) with 10 patients randomized and analyzed in each group. At 6 months postsurgery, an improvement in the AIS grade was reported in 2 NSS patients (20%; both to AIS C) and 3 control group patients (30%; to AIS B [n = 2] or AIS C [n = 1]). No serious or unanticipated adverse device effects were reported. The study was closed to further follow-up because of not meeting its primary endpoint.

CONCLUSION: In this small group of patients with thoracic complete (AIS A) SCI, implantation of an intraparenchymal bioresorbable scaffold did not produce probable clinical benefit. However, this study provides evidence that surgical intervention in an injured spinal cord parenchyma may be performed safely.

KEY WORDS: Absorbable implants, Biopolymers, Clinical trial, Randomized controlled trial, Spinal cord contusion, Spinal cord injuries, Tissue scaffolding

ABBREVIATIONS: ADEs, adverse device effects; **AEs,** adverse events; **AIS,** American Spinal Injury Association Impairment Scale; **FDA,** Food and Drug Administration; **INSPIRE,** InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold for Safety and Neurological Recovery in Patients with Complete Thoracic SCI; **ISNCSCI,** International Standards for Neurological Classification of SCI; **NLI,** neurological level of injury; **NSS,** Neuro-Spinal Scaffold; **SOC,** standard-of-care; **US,** United States.

Supplemental digital content is available for this article at neurosurgery-online.com.

Traumatic spinal cord injury (SCI) is a devastating condition with ~18 000 new cases presenting annually in the United States (US) and no proven effective treatment strategies available.[1-4]

The Neuro-Spinal Scaffold ([NSS]; InVivo Therapeutics Corporation), an investigational device with Humanitarian Use Device designation, is a highly porous bioresorbable polymer comprising poly(lactic-co-glycolic acid)-b-poly-(L-lysine),[5] a synthetic biomaterial widely used in US Food and Drug Administration (FDA)–approved devices. It was developed to facilitate spinal cord repair after intraparenchymal implantation by providing a structural support that is conducive to cellular attachment and growth.

Preclinical data that led to clinical evaluation of the NSS were compelling.[6-9] In a rat contusion model, NSS implantation significantly reduced cyst volume and increased tissue sparing and new tissue formation at 12 weeks vs controls.[6] Remodeled tissue was rich in neuropermissive extracellular matrix. In a prior single-arm study (INSPIRE; ClinicalTrials.gov, NCT02138110), acute NSS implantation appeared to be safe through 24 months postimplantation in patients with thoracic complete SCI and was associated with a 6-month American Spinal Injury Association Impairment Scale (AIS) conversion rate (44%) that exceeded historical controls (14%-21%).[10-15]

The primary objective of this study was to evaluate whether NSS implantation is safe and demonstrates probable benefit vs standard-of-care (SOC) spine surgery in patients with thoracic complete SCI.

METHODS

Study Design and Oversight

INSPIRE 2.0 was a randomized, controlled, parallel-group, multicenter Humanitarian Device Exemption probable benefit trial conducted in the United States (ClinicalTrials.gov, NCT03762655). Within the Humanitarian Device Exemption regulatory pathway, Humanitarian Use Devices are exempt from effectiveness requirements but must be determined not to expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device must outweigh the risk of injury or illness. Table 1 summarizes key planned study assessments. This preplanned analysis reports data through the 6-month primary endpoint follow-up visit.

This study was conducted following the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and applicable regulatory requirements. All patients provided signed written informed consent before study enrollment or undergoing any study procedure. Each institution's respective Institutional Review Board/Research Ethics Board approved the protocol and all relevant study forms. An independent Data and Safety Monitoring Board conducted unblinded monitoring of all patients.

Eligibility

Eligible patients were aged 16 to 70 years and had complete (AIS A) traumatic SCI at T2-T12 neurological level of injury (NLI) with a requirement for spine surgery, allowing access to the injured spinal cord, ≤7 days from injury as part of standard treatment. The SCI was nonpenetrating (contusion injury) and ≥4 mm in diameter by MRI. Additional inclusion criteria were Injury Severity Score ≤45 at screening, Glasgow Coma Scale (GCS) score ≥14 at screening (GCS score ≥10 for intubated patients), GCS score of 15 within 2 hours before surgery (GCS score ≥10 for intubated patients), and 8 hours of hemodynamic stability (systolic blood pressure >90 mm Hg) before surgery. Notable exclusions were >1 discrete SCI, complete spinal cord transection, clinically significant neurological or respiratory comorbidities, significant traumatic brain injury or coma, requirement for long-term ongoing mechanical ventilation, and evidence of clear and significant somatosensory-evoked potentials transmission through the injury site. All study sites were Level 1 trauma centers and were selected based on SCI case volume and experience from the INSPIRE study.

Randomization and Blinding

On induction of anesthesia, patients were randomly assigned (1:1) to undergo SOC spine surgery followed by NSS implantation (NSS group) or SOC spine surgery alone (control group). The computer-generated random allocation sequence was not stratified, and a permuted block method was used (block size of 4). The Interactive Web Response System vendor created the randomization list and enrolled participants. The Interactive Response Technology system assigned patients to the appropriate treatment arm during the randomization visit. Patients and follow-up International Standards for Neurological Classification of SCI (ISNCSCI) assessors were blinded to treatment assignment for the study duration. A patient unblinding form allowed for emergency unblinding by the Interactive Web Response System vendor, which would trigger notification to study management. All study staff conducting ISNCSCI examinations had to provide documentation of training by approved trainers within 2 years of each study assessment. Study sites were encouraged to have a single assessor perform all follow-up examinations.

Study Interventions and Surgical Procedures

All patients underwent SOC spine surgery (eg, decompression, fusion, and stabilization). The same team of neurosurgeons could perform surgeries in either treatment group. Intraoperative ultrasound was performed to confirm the contusion size and location, and the presence or absence of a cavity, as initially assessed by the preoperative MRI. Investigators ensured patients continued to meet eligibility criteria before proceeding to implantation (NSS group) or after completion of spine

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[§]Department of Neurological Surgery, UC Davis, Sacramento, California, USA; [‖]Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; [¶]Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, New Jersey, USA; [#]Current affiliation: Department of Neurosurgery, Hackensack Meridian School of Medicine, Nutley, New Jersey, USA; **Division of Neurosurgery, ECU Health, Greenville, North Carolina, USA; [††]InVivo Therapeutics Corporation, Cambridge, Massachusetts, USA

TABLE 1. Summary of Preplanned Study Assessments

Assessment	Details	Timing
Neurological status	• Neurological status was assessed by the investigator or a designated trained medical professional using the ISNCSCI[16] and ASIA 2015 worksheet. • The 5-grade AIS was used to determine the completeness of the patient's injury as follows: ○ AIS A (complete; no motor or sensory function in the lowest sacral segments S4-S5) ○ AIS B (sensory incomplete; sensory but not motor function is preserved below the level of injury and includes sacral segments S4-S5) ○ AIS C (motor incomplete; motor function is preserved below level of injury; voluntary anal contraction or sparing of motor function 3 levels below injury) ○ AIS D (motor incomplete—similar to AIS C, but with ≥50% of key muscles below injury functioning against gravity) ○ AIS E (normal function) • NLI refers to the lowest spinal cord level that shows normal bilateral sensory and motor function. • Sensory scores were assessed on a scale from 0 to 2 for each sensory point tested on each side of the body (maximum pin prick score = 112 and maximum light touch score = 112); total sensory score = light touch + pin prick score; higher scores indicate better function. • Motor scores were assessed on a scale from 0 to 5 for each myotome tested on each side of the body (maximum UEMS = 50 and maximum LEMS = 50); total motor score = UEMS + LEMS; higher scores indicate better function.	• Screening • Presurgery (<8 h before spine surgery to confirm a reliable ISNCSCI examination and AIS A classification) • Postsurgery (at hospital discharge and 3, 6, 12, and 24 mo)
Spinal cord anatomy	• MRI studies were performed without contrast. • Characteristics of spinal cord anatomy assessed included spinal cord dimensions, lesion size and location, cyst presence or absence including size and location, if present. A cyst was defined as a well-defined, fluid-filled area of tissue loss within the spinal cord that is isointense with cerebrospinal fluid. • All MRIs were performed at the study site and images were sent to an independent central core radiology laboratory for storage and analysis by an independent board-certified neuroradiologist central reader.	• Screening • Postsurgery (at 72 h and 3, 6, 12, and 24 mo)
Safety event monitoring	• MedDRA (version 20.1 or higher) was used to classify all safety events. • An AE is a safety event not related to the investigational device or its implantation procedure. • An ADE is any safety event that was at least possibly related to the investigational device or its implantation procedure.	• Presurgery • Intraoperative • Postsurgery • At 72 h postsurgery, hospital discharge, and at 3, 6, 12, and 24 mo • Annually from 3 to 10 y postsurgery[a]

ADE, adverse device effect; AE, adverse event; AIS, ASIA Impairment Scale; ASIA, American Spinal Injury Association; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; LEMS, lower extremity motor score; MedDRA, Medical Dictionary for Regulatory Activities; NLI, neurological level of injury; UEMS, upper extremity motor score.
[a]Conducted through telephone to collect general health information, including any serious safety events.

stabilization and before surgical site closure (control group). Prophylactic antibiotics were administered perioperatively per institutional practice. A pulmonary embolism prophylaxis protocol was implemented and documented postsurgery through hospital discharge and had to include mechanical prophylaxis modalities and anticoagulation therapy. All patients participated in a comprehensive rehabilitation program after hospital discharge.

For the NSS group, an illustrative example of the surgical procedure including implantation is provided in Figure 1. Further details, including an example intraoperative video, were published previously.[10] To standardize the NSS implantation procedure, all implanting neurosurgeons were trained on the proper storage, handling, and use of the NSS, using individual and SCI model training. A slide deck and instructional video were also available for reference before surgery.

Outcomes

The primary endpoint was the proportion of patients with an improvement of ≥1 AIS grade from baseline at 6 months postsurgery. Key secondary efficacy endpoints were changes in NLI, sensory scores (total, light touch, and pinprick), motor scores (total, lower extremity, and upper extremity), and changes in spinal cord anatomy as determined by MRI. ISNCSCI endpoints were assessed at hospital discharge and 3 and 6 months postsurgery. MRI endpoints were evaluated at 3 and 6 months postsurgery. For this 6-month analysis, all safety events with start dates on or before Day 181 were included.

Statistical Considerations

For the study to be deemed a success, the proportion of patients who demonstrated an improvement of ≥1 AIS grade at 6 months

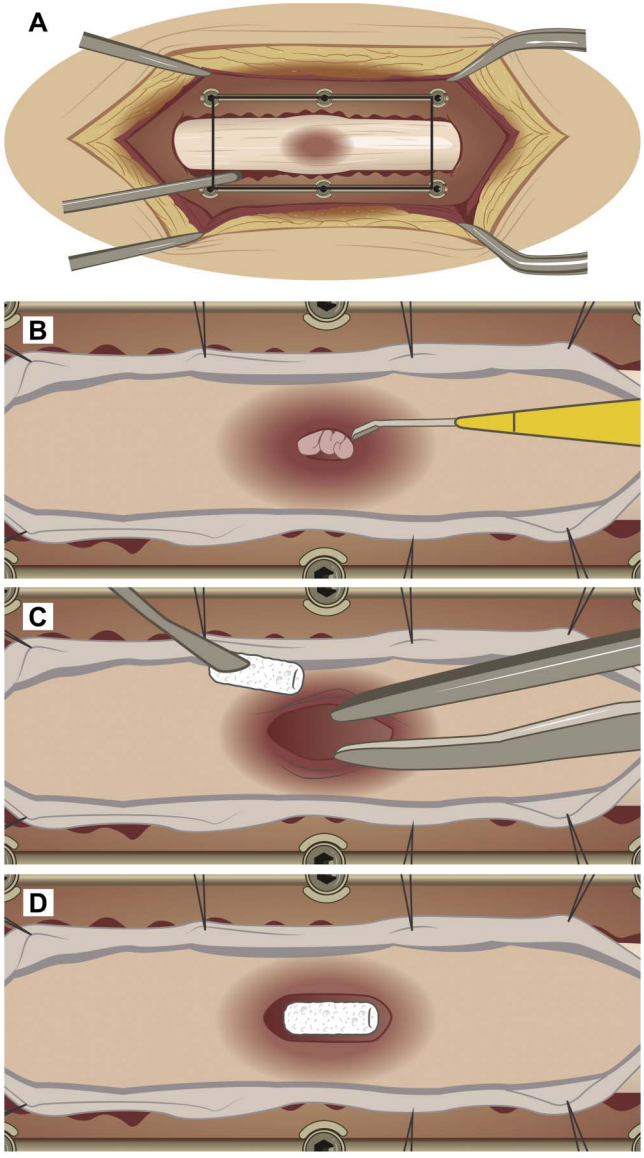

FIGURE 1. *Illustration of Neuro-Spinal Scaffold Implantation Procedure.* **A**, *After spinal decompression and stabilization with pedicle screws, as needed, a durotomy was performed, or an existing dural injury was extended to expose the contusion site. The injured spinal cord was then irrigated with isotonic saline to wash away any superficial hemorrhagic material or devitalized tissue.* **B**, *If needed, an arachnoid/pial incision was made over the contusion, allowing direct access to the injured parenchyma with the full extent of the cavity exposed by myelotomy. The cavity was then irrigated with isotonic saline to remove any additional necrotic spinal tissue or fluid that may exude.* **C**, *After completion of the debridement, the NSS was briefly wetted in isotonic solution and gently implanted lengthwise into the postirrigation intraspinal contusion cavity. The NSS (3 mm diameter) was available in 3 sizes (6, 8, or 10 mm length), which were determined using INSPIRE data (unpublished). Scaffold size selection was based on contusion cavity size as determined by the screening MRI, intraoperative ultrasound, and visual inspection. Investigators selected the appropriate NSS size to provide an optimal fit within the cavity without causing undue tension on the spinal cord surrounding the contusion site.* **D**, *The NSS is in place within the contusion cavity before the dura is closed. INSPIRE, InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold for Safety and Neurological Recovery in Patients with Complete Thoracic Spinal Cord Injury; NSS, Neuro-Spinal Scaffold.*

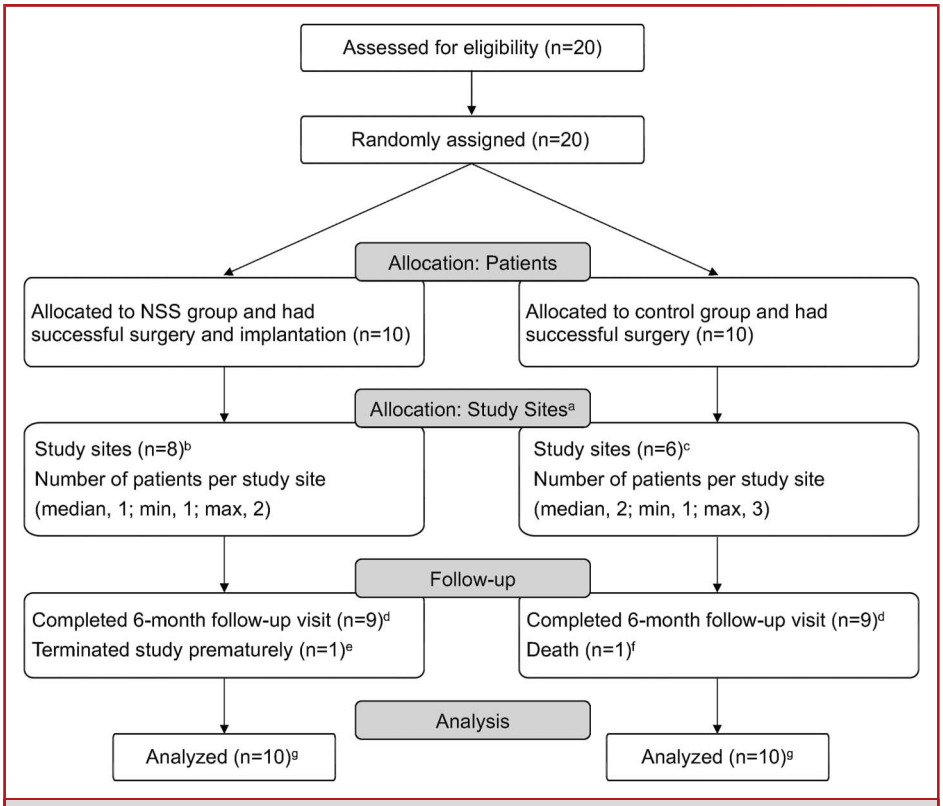

FIGURE 2. *Consolidated Standards of Reporting Trials flow diagram. ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; NSS, Neuro-Spinal Scaffold; SCI, spinal cord injury. [a]Most of the neurosurgeons who performed the surgeries had undergone spine fellowship training, while others had long-standing SCI surgery experience. [b]Principal investigators had a median of 22 years of experience, not including fellowship training (range, 17-33 years). [c]Principal investigators had a median of 23 years of experience, not including fellowship training (range, 17-43 years). [d]ISNCSCI examination was not completed in 1 patient in each treatment group because of COVID-19 restrictions. [e]Patient withdrew consent after their 72-hour follow-up visit and subsequently died due to acute respiratory failure unrelated to the Neuro-Spinal Scaffold or study-related procedures. [f]Patient missed their 3-month follow-up visit and subsequently died due to sepsis unrelated to the Neuro-Spinal Scaffold or study-related procedures. [g]All patients had successful surgery according to their treatment arm, and there were no major protocol violations; therefore, all randomized patients were included in the Safety, Intent-to-Treat, and Primary Efficacy Analysis Sets, respectively.*

(primary endpoint) had to be ≥20% higher in the NSS group than the control group. This predefined criterion was determined based on INSPIRE study data and historical data (including CONTEMPO Registry Study data, which evaluated patients closely matched to INSPIRE inclusion criteria).[10,12,13,15] A sample size of up to 35 patients was selected to make it highly probable that there would be 10 patients in each study arm. Based on AIS conversion rates from INSPIRE (44%) and best natural history data available at the time of study initiation (SCI Model Systems and European Multicenter Study about SCI registries; both 16%), the study was underpowered.[10,13,15]

The ISNCSCI examination performed within 8 hours of surgery was used as the baseline for ISNCSCI endpoints, and the screening MRI was used as the baseline for changes in spinal cord anatomy. Patients who did not complete the 6-month primary endpoint follow-up visit were considered not to have an improvement in the primary efficacy analysis. No other missing data were imputed. No formal statistical hypothesis testing was performed because of the small sample size. Descriptive statistics were used for all efficacy and safety analyses. Data were analyzed using SAS® for Windows® version 9.4. SAS Inc.

Data availability

Statement requests can be made to review the study protocol, and qualified researchers may request access to additional study documents and data (submit requests to: rtoselli@invivotherapeutics.com). Individual anonymized patient data supporting this study cannot be made available because participants did not consent to have their data shared.

RESULTS

Patients and Follow-up

Twenty patients (of 20 screened) were enrolled at 11 study sites between May 21, 2019, and June 1, 2022 (Figure 2).

TABLE 2. Demographics and Baseline Clinical Characteristics of Randomized Patients

Characteristic	Neuro-Spinal Scaffold (N = 10)	Control (N = 10)
Mean age (range), y	37 (19-61)	36 (16-69)[a]
Sex, n (%)		
Female	2 (20)	0
Male	8 (80)	10 (100)
Race, n (%)		
Black or African American	2 (20)	0
White	8 (80)	9 (90)
Other	0	1 (10)
Ethnicity, n (%)		
Hispanic or Latino	2 (20)	2 (20)
Non-Hispanic or Latino	8 (80)	8 (80)
Mean weight (range), kg	83 (56-106)	100 (72-127)
Mean height (range), cm	178 (168-191)	180 (163-193)
Mean BMI (range), kg/m^2	26 (18-38)	31 (20-38)
Cause of injury, n (%)		
Vehicular	4 (40)	7 (70)
Sport	1 (10)	0
Fall	4 (40)	1 (10)
Other	1 (10)	2 (20)
NLI before surgery, n (%)[b]		
T2-T5	5 (50)	8 (80)
T6-T9	3 (30)	1 (10)
T10-T12	2 (20)	1 (10)
Mean sensory score before surgery (range)[b,c]		
Total	114 (80-156)	100 (77-140)
Light touch	58 (40-78)	51 (40-70)
Pinprick	56 (40-78)	50 (36-70)
Mean ISS at screening (range)[d]	23 (0-43)	27 (1-54)
Mean GCS score before surgery (range)[e]	14 (10-15)	15 (11-15)

BMI, body mass index; GCS, Glasgow Coma Scale; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; ISS, Injury Severity Score; NLI, neurological level of injury.

[a]For the patient aged 16 y, assessment of skeletal maturity showed Risser Stage 4 by iliac crest x-ray (apophysis over >75% of the iliac crest).

[b]Based on the ISNCSCI examination performed within 8 h before spine surgery.

[c]Calculated based on available data (Neuro-Spinal Scaffold group [n = 9]; control group [n = 10]).

[d]Calculated based on available data (Neuro-Spinal Scaffold group [n = 8]; control group [n = 10]).

[e]Based on assessment performed within 2 h of spine surgery.

Target enrollment was reached with 10 patients assigned to each treatment group, and the 6-month primary endpoint follow-up analysis was completed as planned. With US FDA approval, subsequent follow-up of included patients ceased on September 30, 2023, and the study was terminated by the sponsor because of not meeting its primary endpoint as of December 31, 2023.

Demographics and clinical characteristics seemed to be balanced across treatment groups (Table 2). All patients had successful surgery according to their treatment arm, and there were no major protocol violations; therefore, all randomized patients were included in the Safety, Intent-to-Treat, and Primary Endpoint Analysis Sets. Protocol deviations are detailed in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E475). Median time from injury to start of surgery was 29.9 hours (range, 9.3-104.4 hours) for the NSS group and 20.6 hours (range, 7.0-89.7 hours) for the control group, with 40% (4/10) and 60% (6/10) of patients undergoing spine surgery <24 hours after injury, respectively. Intraoperative ultrasound confirmed the contusion size and location in 100% (8/8) and 80% (4/5) of patients with available data, respectively. NSS-treated patients received a 6 mm (n = 1), 8 mm (n = 4), or 10 mm (n = 5) scaffold.

Primary Endpoint

The proportion of patients with an improvement of ≥1 AIS grade at the 6-month follow-up visit was 20% in the NSS group (2/10 patients; both AIS C) and 30% in the control group (3/10 patients; AIS B [n = 2] and AIS C [n = 1]).

Secondary Endpoints

AIS grades in individual patients are presented in Table 3. In the NSS group (N = 10), 1 patient each first converted to AIS C by 3 and 6 months, respectively, both by obtaining voluntary anal contraction. In the control group (N = 10), 2 patients were AIS B at hospital discharge because of the presence of deep anal pressure, including 1 patient who improved to AIS C at 3 and 6 months because of the additional presence of voluntary anal contraction, and 1 patient converted to AIS B at 6 months because of the presence of deep anal pressure. An additional control group patient was AIS B at hospital discharge but was AIS A at subsequent assessments. The remaining ISNCSCI secondary endpoints are presented in Table 4, with further detail provided in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E475).

Among NSS and control group patients with available data (n = 7 for each group), intraparenchymal spinal cord cysts were documented at 6 months postsurgery in 2 (29%) and 3 (43%) patients, respectively (further details are provided in **Supplemental Digital Content 1** [http://links.lww.com/NEU/E475]). There was no evidence of spinal cord adhesion in either treatment group.

TABLE 3. AIS Grades in Randomized Patients

Pt	Age group	Baseline NLI	Time to Surgery (h)	AIS grade		
				Hospital discharge	3 mo Postsurgery	6 mo Postsurgery
Neuro-Spinal Scaffold				N = 10	N = 10	N = 10
1	Adult	T3	32	Withdrew[a]	Withdrew[a]	Withdrew[a]
2	Adult	T4	11	A	A	A
3	Adult	T3	28	A	A	A
4	Adult	T4	77	A	A	A
5	Pediatric[b]	T7	57	A	Unable to assess[c]	A
6	Adult	T4	104	A	A	A
7	Adult	T12	21	A	A	A
8	Adult	T6	9	A	A	C
9	Pediatric[b]	T7	55	A	e-visit[d]	e-visit[d]
10	Adult	T11	23	A	C	C
At least 1-grade improvement from baseline,[e] n (%)				0	1 (10)	2 (20)
Control				N = 10	N = 10	N = 10
11	Pediatric[b]	T3	18	B	A	A
12	Pediatric[b]	T9	21	B	C	C
13	Adult	T4	20	A	A	A
14	Adult	T2	90	A	Not done	B
15	Adult	T5	40	A	Missed visit[f]	Death[f]
16	Adult	T5	11	B	B	B
17	Adult	T11	13	A[g]	A	A
18	Adult	T5	42	Not done	Missed visit	A
19	Adult	T2	7	A	A	A
20	Pediatric[b]	T3	42	A	A	Missed visit[d]
At least 1-grade improvement from baseline,[e] n (%)				3 (30)	2 (20)	3 (30)

AIS, American Spinal Injury Association (ASIA) Impairment Scale; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; NLI, neurological level of injury.
[a]Patient withdrew consent (final study visit 72 h postsurgery) and subsequently died due to acute respiratory failure assessed as not related to the study device or study-required procedure.
[b]Defined as age 22 y or younger.
[c]S2-S5 could not be assessed because of the impracticality of repositioning the patient.
[d]Owing to COVID-19 restrictions; ISNCSCI examination was not performed.
[e]Per study protocol, patients with missing AIS grade for any reason were treated as having not improved from baseline.
[f]Patient missed their 3-mo follow-up visit and subsequently died due to sepsis assessed as not related to the study device or study-required procedure.
[g]ISNCSCI examination was conducted 1 d before hospital discharge.

Safety

Safety events are summarized in Table 5, with further detail provided in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E475). Most adverse events (AEs) were of mild or moderate severity (60/68 events [88%] in the NSS group and 107/122 events [88%] in the control group). The most common AEs by Medical Dictionary for Regulatory Activities preferred term (defined as those occurring in ≥30% of patients in either the NSS group [N = 10] or control group [N = 10]) were urinary tract infection (60% vs 40%), nausea (0 vs 30%), pulmonary embolism

TABLE 4. Changes in Neurological Level of Injury, Sensory Scores, and Motor Scores at 6 mo Postsurgery in Randomized Patients

ISNCSCI outcome	Neuro-Spinal Scaffold (N = 10)	Control (N = 10)
Change in NLI	n = 8	n = 8
Overall, n (%)		
Improved	1 (10)	3 (30)
No change	2 (20)	0
Worsened	5 (50)	5 (50)
Number of levels,[a] n (%)		
2	0	0
1	1 (10)	3 (30)
0	2 (20)	0
−1	2 (20)	3 (30)
−2	2 (20)	1 (10)
<−2	1 (10)	1 (10)
Mean (SD)	−1.8 (3.1)	−1.1 (2.6)
Median (min, max)	−1.0 (−9, 1)	−1.0 (−7, 1)
Change in total sensory score	n = 7	n = 8
Overall, n (%)		
Improved	2 (20)	5 (50)
No change	0	0
Worsened	5 (50)	3 (30)
Mean (SD)	1.6 (14.8)	6.5 (16.7)
Median (min, max)	−2.0 (−16, 31)	4.5 (−12, 36)
Change in sensory LT score	n = 7	n = 8
Overall, n (%)		
Improved	2 (20)	5 (50)
No change	0	0
Worsened	5 (50)	3 (30)
Mean (SD)	1.0 (8.5)	4.8 (12.0)
Median (min, max)	−1.0 (−9, 18)	2.5 (−8, 30)
Change in sensory PP score	n = 7	n = 8
Overall, n (%)		
Improved	2 (20)	5 (50)
No change	1 (10)	0
Worsened	4 (40)	3 (30)
Mean (SD)	0.6 (6.4)	1.8 (5.8)
Median (min, max)	−1.0 (−7, 13)	2.0 (−6, 12)
Change in total motor score	n = 8	n = 8
Overall, n (%)		
Improved	1 (10)	1 (10)
No change	5 (50)	7 (70)
Worsened	2 (20)	0
Mean (SD)	2.0 (6.9)	0.3 (0.7)
Median (min, max)	0 (−2, 19)	0 (0, 2)
Change in LEMS	n = 8	n = 8
Overall, n (%)		
Improved	1 (10)	1 (10)
No change	7 (70)	7 (70)
Worsened	0	0
Mean (SD)	2.4 (6.7)	0.3 (0.7)
Median (min, max)	0 (0, 19)	0 (0, 2)
Change in UEMS	n = 8	n = 8
Overall, n (%)		
Improved	0	0
No change	6 (60)	8 (80)
Worsened	2 (20)[b]	0
Mean (SD)	−0.4 (0.7)	0 (0)
Median (min, max)	0 (−2, 0)	0 (0, 0)

ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; LEMS, lower extremity motor score; LT, light touch; NLI, neurological level of injury; PP, pinprick; UE, upper extremity motor score; UEMS, upper extremity motor score.

[a]A positive change indicates caudal improvement, whereas a negative change indicates rostral deterioration.

[b]One patient previously underwent left clavicle surgery and had transient shoulder muscle changes that were not associated with their spinal cord injury or associated surgery.

n = Number of patients evaluable at baseline and the respective postbaseline visit. Sensory scores were not calculated if any sensory point was not testable, and motor scores were not calculated if any muscle function was not testable.

(10% vs 30%), muscle spasms (30% vs 30%), pyrexia (10% vs 50%), deep vein thrombosis (10% vs 40%), hypokalemia (10% vs 30%), and decubitus ulcer (30% vs 10%).

Safety events meeting the criteria for study stopping rules were reported in 2 (20%) and 3 (30%) patients in the NSS and control groups, respectively. These patients remained on study at data cut-off, and the Data and Safety Monitoring Board reviewed all study patients and did not recommend stopping the trial at any point.

TABLE 5. Summary of Safety Events Reported 0-6 mo Postsurgery in Randomized Patients

	Neuro-Spinal Scaffold (N = 10)		Control (N = 10)	
Safety Event	**n (%)**	**No. of events**	**n (%)**	**No. of events**
Any AE	9 (90)	68	9 (90)	122
Mild	7 (70)	45	7 (70)	80
Moderate	6 (60)	15	9 (90)	27
Severe	6 (60)	8	6 (60)	15
Serious AE[a]	6 (60)	9	6 (60)	22
Safety event of interest	1 (10)[b]	1[b]	2 (20)[c]	3[c]
ADE	3 (30)[d]	3[d]	1 (10)[e]	1[e]
Serious ADE	0	0	0	0
Unanticipated ADE	0	0	0	0

ADE, adverse device effect; AE, adverse event.
[a]None were deemed to be related to the Neuro-Spinal Scaffold or its implantation procedure.
[b]Mild spinal cord edema possibly related to the Neuro-Spinal Scaffold.
[c]Moderate deep vein thrombosis of the right popliteal and calf vessels (n = 1) and moderate sepsis (n = 1).
[d]Mild muscle spasms possibly related to the implantation procedure (n = 1), mild hypoxia possibly related to the implantation procedure (n = 1), and mild spinal cord edema possibly related to the Neuro-Spinal Scaffold (n = 1), as reported by the investigator.
[e]Moderate constipation possibly related to the Neuro-Spinal Scaffold and its implantation procedure (n = 1), as reported by the investigator.

One NSS-treated patient had ascending NLI of 6 levels to T6 at hospital discharge, which returned to within 2 levels of baseline at subsequent visits. Another patient had ascending NLI of 9 levels to C2 at 6 months. The examination documented decreased light touch sensation at the C4 dermatome, with normal pinprick sensation, which normalized and was most likely due to left clavicle surgery. In the control group, 1 patient had an ascending NLI of 3 levels to T2 at hospital discharge, another patient had an ascending NLI of 3 levels to T1 at hospital discharge and 7 levels to C5 at 6 months, and a third patient had an ascending NLI of 6 levels to C5 at both hospital discharge and 3 months combined with a 20-point and 15-point deterioration in upper extremity motor score at these time points, respectively.

DISCUSSION

Key Results

The INSPIRE 2.0 study did not meet its primary endpoint, which was assessed by the proportion of patients with thoracic AIS A SCI who underwent acute NSS implantation having an improvement of ≥1 AIS grade at 6 months postsurgery compared with the control group (20% vs 30%). However, the device had no apparent safety concerns because there were no serious or unanticipated adverse device effects (ADEs).

Interpretation

Neurological improvement after NSS implantation was less dramatic in this study than in the previously reported INSPIRE study (6-month AIS conversion rates were 20% [2/10 randomized patients] and 44% [7/16 patients who completed 6-month follow-up], respectively).[10,11] Conversely, the control group seemed to overperform relative to natural history in patients with thoracic complete SCI (6-month AIS conversion rate 30% [3/10 randomized patients] vs AIS conversion rates of 14%-21% [follow-up duration varied across studies]).[12-15]

Of note, 2 of the 3 control group patients who had improvement in AIS grade at 6 months were graded AIS B at hospital discharge, which was an earlier timepoint than AIS conversions reported among NSS-treated patients in either of the INSPIRE studies.[10,11] Both patients underwent surgery within 24 hours of injury (11 and 21 hours, respectively). This result may highlight a conundrum of acute SCI clinical trials. While there is a push for earlier surgery,[17] it is important to consider that early examinations can be deceiving.[18,19] Interpretation of INSPIRE 2.0 study data may be further limited by 2 patients (20%) in each treatment group not completing their 6-month primary endpoint ISNCSCI examinations (including 1 patient each because of COVID-19 restrictions).

NLI changes were generally within the range of what would be expected based on natural history and INSPIRE study data,[10-13,15,20] and there was no discernible difference between treatment groups. Owing to the severe neurologic injury from great mechanical forces, spontaneous motor recovery is uncommon in patients with thoracic AIS A SCI.[12,13,15,21] In this study, 1 patient in each treatment group had lower extremity motor score improvement, with the greatest improvement noted at 6 months (NSS: 19 points; control: 2 points).

AEs were consistent for the injury and across treatment groups.[22] Replicating the results from INSPIRE, no unanticipated or serious ADEs were reported.[10,11] Longer-term data from INSPIRE showed that the NSS safety profile was stable through 24 months postimplantation and void of long-term neurological issues.[11] The INSPIRE studies have firmly established the safety of the NSS and its implantation procedure.[10,11] Based on learnings from INSPIRE, inclusion criteria for INSPIRE 2.0 were modified to prevent critically ill patients from being operated on prematurely, and a pulmonary prophylaxis protocol was implemented. The early complications seen in INSPIRE,[10,11] unrelated to the NSS or its implantation procedure, were not observed in INSPIRE 2.0 despite most patients (15/20 patients [75%]) heading to the operating room within 48 hours of injury.

Generalizability

To our knowledge, this is the first randomized clinical trial of a biomaterial placed in an acutely injured spinal cord. From a safety standpoint, there does not seem to be any serious complications related to NSS implantation within the spinal cord. It is acknowledged that it will likely take more than one treatment modality to make a significant impact on outcomes in patients with severe traumatic SCI, eg, neuromodulation, pharmaceutical agents, cell-based therapies, or direct intervention at the site of injury, such as NSS implantation.[2,23] Importantly, this study conducted by experienced spinal neurosurgeons showed that myelotomy can be performed safely in patients with complete (AIS A) injuries.

Limitations

The main limitation of this study was the small sample size. Ideally, clinical trials are enrolled to statistical significance, but this is difficult to achieve for traumatic SCI studies because of the inherent patient enrollment challenges and associated costs.[12,24-26] SOC spine surgery was considered the only appropriate choice for the control group by the US FDA. Double blinding was not feasible; however, patients and assessors performing follow-up ISNCSCI examinations were blinded to treatment group allocation to minimize potential bias. While ISNCSCI training was mandated and study sites were advised to use consistent assessors throughout the study, inter-rater variability cannot be ruled out.

CONCLUSION

In this small randomized controlled trial, implantation of an intraparenchymal bioresorbable scaffold did not produce probable clinical benefit in patients with thoracic complete (AIS A) SCI. While this result is disappointing, the procedure's safety profile remains acceptable, thus supporting the results of previous studies and demonstrating the feasibility of performing a myelotomy on an acutely injured spinal cord without causing serious neurological deterioration.

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Disclosures

James S. Harrop has been a consultant for Depuy Synthes and Ethicon and was an advisor for Abbvie, Spiderwort, and AlaMab Therapeutics. Kee D. Kim has received research funding from AbbVie, Empirical Spine, InVivo Therapeutics Corporation, Medtronic, Seikagaku and Stryker; been a consultant for Seikagaku, GS Medical and ZimVie; received royalties from Precision Spine and ZimVie; and serves on the Board of Directors and holds stock options at Molecular Matrix. David O. Okonkwo has been a consultant for and has received royalties from NuVasive and Highridge. Ira M. Goldstein has been a consultant for and has received royalties from Alphatec Spine and Globus Medical. K. Stuart Lee has served as an Advisory Board (INSPIRE study steering committee) member for InVivo Therapeutics Corporation. Richard M. Toselli serves as Chief Medical Officer/Chief Executive Officer and holds stock options at InVivo Therapeutics Corporation.

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Supplemental digital content *is available for this article at neurosurgery-online.com.*

Supplemental Digital Content 1. Additional Data Tables (5). Table S1. Protocol Deviations. **Table S2**. MRI: Cyst Location and Dimensions. **Table S3**. Changes from Baseline in Neurological Level of Injury, Sensory Scores, and Motor Scores. **Table S4**. Adverse Events. **Table S5**. Serious Adverse Events.

COMMENTS

This paper details an RCT examining safety and efficacy of an implantable bioresorbable polymer scaffold to treat motor complete thoracic spinal cord injury within 7 days of injury. The trial represents a tremendous amount of work consuming a huge amount of resources from multiple institutions over a 3-year accrual period. The authors are to be congratulated for the diligence of their methodology and data reporting and for their objectivity in publishing a negative result.

This is an industry-sponsored trial conceived on the results of the initial INSPIRE study published in parts a few years ago.[1a,2a] Although designed as a safety study, INSPIRE 1.0 anecdotally reported conversions from ASIA grade A to B (n = 5) and A to C (n = 2) in 7 of 16 patients (44%), about 3x higher than historical controls. Soberingly, 50% of patients experienced ascension of their sensory level, perhaps not unexpected when a foreign body is implanted in the middle of an acutely injured spinal cord. Nonetheless these results catalyzed both industry and investigators to undertake the present study, INSPIRE 2.0.

This trial was terminated prematurely because industry sponsorship was withdrawn. Not surprising. Despite low numbers of patients available for follow-up (n = 9 per group), the results showed AIS conversion in 3 control patients (33%) but only 2 scaffold patients (22%), trending in the opposite direction of the desired treatment effect. This would be enough to induce cold feet in any industry partner faced with pouring additional millions of dollars into a trial failing to behave as expected.

It is what it is; an RCT prematurely terminated for funding reasons because of a predictably absent clinical effect. The take home points are as follows: (1) Building expensive RCTs based on magical results from a small number of patients is a risky investment and (2) industry-funded RCTs are also a risky investment. Please note, on February 7, 2024, InVivo Therapeutics Holdings Corp (NVIVQ) filed for Chapter 11 bankruptcy. Nasdaq trading was suspended February 13, 2024. Despite the optimism and enthusiasm of this investigative group, Aguayo's axiom still stands: The CNS is a nonpermissive environment for neuronal regeneration.[3a,4a] I congratulate the authors for their meticulous tenacity. Results like these absolutely need to be reported. We can all learn from them.

R. John Hurlbert
Tucson, Arizona, USA

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