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Original Article

Spinal cord epidural stimulation for motor and autonomic function recovery after chronic spinal cord injury: A case series and technical note

Maxwell Boakye[1], Tyler Ball[2], Nicholas Dietz[1], Mayur Sharma[1], Claudia Angeli[1], Enrico Rejc[1], Steven Kirshblum[3], Gail Forrest[3], Forest W. Arnold[4], Susan Harkema[1]

[1]Department of Neurosurgery, University of Louisville, Louisville, Kentucky, [2]Department of Neurosurgery, Vanderbilt University, Nashville, [3]Department of Physical Medicine Rehabilitation, Rutgers, Newark, New Jersey, [4]Department of Infectious Diseases, University of Louisville, Louisville, United States.

E-mail: Maxwell Boakye - maxwell.boakye@uoflhealth.org; Tyler Ball - tyler.ball@vumc.org; *Nicholas Dietz - nkd25@georgetown.edu; Mayur Sharma - mayur.sharma@uoflhealth.org; Claudia Angeli - claudia.angeli@uoflhealth.org; Enrico Rejc - enrico.rejc@louisville.edu; Steven Kirshblum - skirshblum@selectmedical.com; Gail Forrest - gforrest@kesslerfoundation.org; Forest W. Arnold - f.arnold@louisville.edu; Susan Harkema - susan.harkema@louisville.edu

***Corresponding author:**
Nicholas Dietz,
Department of Neurosurgery,
University of Louisville,
Louisville KY 40202, United States.

nkd25@georgetown.edu

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ABSTRACT

Background: Traumatic spinal cord injury (tSCI) is a debilitating condition, leading to chronic morbidity and mortality. In recent peer-reviewed studies, spinal cord epidural stimulation (scES) enabled voluntary movement and return of over-ground walking in a small number of patients with motor complete SCI. Using the most extensive case series (n = 25) for chronic SCI, the present report describes our motor and cardiovascular and functional outcomes, surgical and training complication rates, quality of life (QOL) improvements, and patient satisfaction results after scES.

Methods: This prospective study occurred at the University of Louisville from 2009 to 2020. scES interventions began 2–3 weeks after surgical implantation of the scES device. Perioperative complications were recorded as well as long-term complications during training and device related events. QOL outcomes and patient satisfaction were evaluated using the impairment domains model and a global patient satisfaction scale, respectively.

Results: Twenty-five patients (80% male, mean age of 30.9 ± 9.4 years) with chronic motor complete tSCI underwent scES using an epidural paddle electrode and internal pulse generator. The interval from SCI to scES implantation was 5.9 ± 3.4 years. Two participants (8%) developed infections, and three additional patients required washouts (12%). All participants achieved voluntary movement after implantation. A total of 17 research participants (85%) reported that the procedure either met (n = 9) or exceeded (n = 8) their expectations, and 100% would undergo the operation again.

Conclusion: scES in this series was safe and achieved numerous benefits on motor and cardiovascular regulation and improved patient-reported QOL in multiple domains, with a high degree of patient satisfaction. The multiple previously unreported benefits beyond improvements in motor function render scES a promising option for improving QOL after motor complete SCI. Further studies may quantify these other benefits and clarify scES's role in SCI patients.

Keywords: Epidural stimulation, Functional recovery, Neuromodulation, Rehabilitation, Spinal cord injury, Spinal cord stimulation, Spinal surgery, Technical note

INTRODUCTION

Traumatic spinal cord injury (tSCI) is a debilitating condition with an annual incidence of 54 cases/million people and an estimated prevalence from 252,000 to 373,000 persons in the United States in 2020.[27,30,36] In addition to functional impairment with limitations in independent living,[2] tSCI also leads to sequalae of dysautonomia with cardiac instability, bowel and bladder retention or incontinence, cardiac disease, metabolic syndrome, and osteoporosis that lead to early morbidity and mortality.[19,32] Unfortunately, no proven pharmacologic treatment to restore neurologic function exists for chronic SCI. In 2011, Harkema *et al.* described spinal cord epidural stimulation (scES) as a novel neuromodulation therapy that enabled lower limb voluntary movement in a research participant with chronic tSCI and complete motor paralysis.[24] Since that publication, scES's ability to activate latent sensorimotor and autonomic networks to improve bowel, bladder, and cardiovascular regulation has been confirmed in a number of studies of small sample sizes.[5,11,14,21,25,48] Most recently, scES enabled over-ground walking with balance assistance in two previously motor complete SCI patients.[3] Gill and colleagues also describe independent stepping with scES after locomotor rehabilitation in an individual with complete sensorimotor lower extremity function loss.[22] Similarly, scES, in conjunction with rehabilitation techniques, have been proven effective for persons with incomplete SCI.[26,47]

Reports in the literature have focused on neurological and physiological outcomes in small numbers of patients.[8,10,15] Neurological and physiological measures help evaluate the effectiveness of scES but may not reflect the full impact of scES on quality of life (QOL) and patient satisfaction. As some authors have raised concerns about potential scES complication rates,[46] there remains a need to examine overall complications in a more extensive series. This paper aims to present surgery and training complication rates, functional, participant satisfaction, and QOL outcomes from 25 individuals who underwent scES implantation at our center as part of previous and ongoing research studies.

MATERIALS AND METHODS

After approval from our local institutional review board (IRB), we monitored and recorded all adverse events (as per the local IRB, Food and Drug Administration standards, and the appointed Data Safety and Monitoring Board reporting requirements). This report describes data from the initial 25 participants with motor complete injuries, graded as American Spinal Injury Association, Impairment Scale A or B, and satisfying the inclusion and exclusion criteria listed in Table 1.

Each participant enrolled in one of three cohorts [Figure 1], with each cohort undergoing one or more of the following:

Table 1: Key inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Over age 18	No painful musculoskeletal dysfunction, unhealed fracture, contracture, pressure sore, or urinary tract infection that might interfere with stand or step training
Nonprogressive SCI above T10	No current anti-spasticity medication regimen
Unable to stand and step independently overground	No clinically significant depression or ongoing drug abuse
Unable to voluntarily move all individual joints of the legs	Painful musculoskeletal function, unhealed fracture, contracture, or pressure sore that might interfere with training
At least 2 years post injury	Cardiovascular, respiratory, bladder or renal disease unrelated to SCI
Segmental reflexes remain functional below the lesion	
Brain influence on spinal reflexes is not clinically detectable	

SCI: Spinal cord injury

practice of lower limb and core voluntary movements with scES (Vol-scES), stand training with scES (Stand-scES), step training with scES (Step-scES), or scES for blood pressure stabilization (CV-scES). The first cohort had two subgroups (Cohorts 1a and b) both receiving a total of 160 training sessions with scES. Those persons in Cohort 1a received 80 daily sessions of step training (stepping on a treadmill with body weight support with manual facilitation as needed) before implantation.[41] Following implantation, they underwent 80 sessions of Stand-scES turned on (Stand-scES) (over ground with a customized frame and manual facilitation as needed) followed by 80 sessions of Step-scES on (Step-scES). Participants in Cohort 1b received 80 sessions of stand and step training before implantation.[3] Following implantation, they received two consecutive sets of 80 sessions of Stand-scES and Step-scES. Participants in Cohorts 2 and 3 received usual care without any activity-based recovery training before implantation. Cohort 2, after implantation, received 80 sessions of CV-scES, then 80 sessions of CV-scES and Vol-scES, and then 80 sessions of CV-scES, Vol-scES, and Stand-scES training.[25] Cohort 3 was randomized into four groups (Cohorts 3a-d). Cohort 3a underwent 80 sessions of CV-scES followed by 80 sessions of CV-scES and Stand-scES. Cohort 3b underwent 80 sessions of Vol-scES followed by 80 sessions of Vol-scES and Stand-scES without CV-scES.[25] Cohort 3c underwent two consecutive 80 sessions of CV-scES and Stand-scES. Cohort 3d underwent two consecutive 80 sessions of Vol-scES and Stand-scES training. The daily and weekly schedule and durations of training are listed in Figure 1.

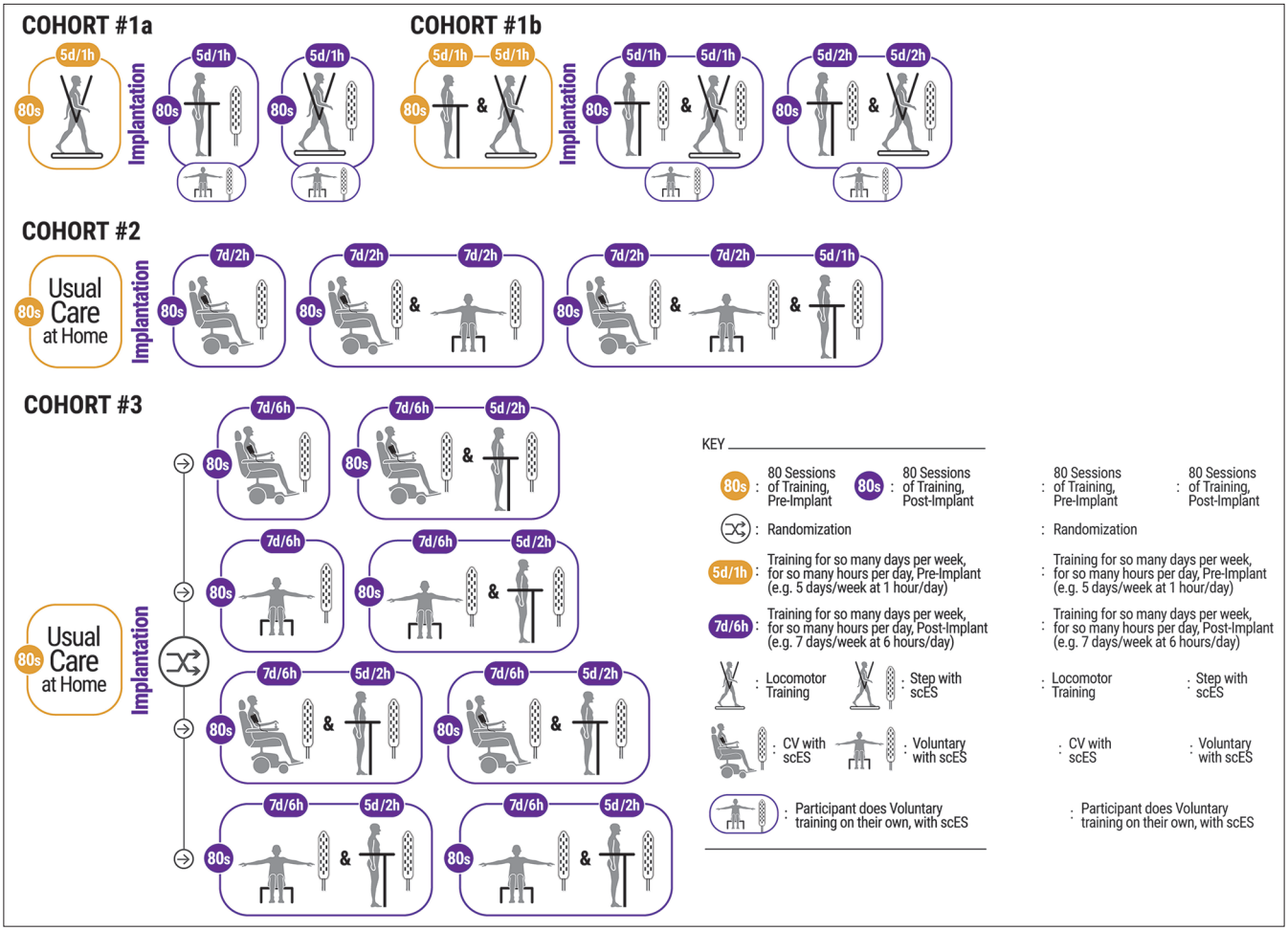

Figure 1: Training protocols for spinal cord epidural stimulation (scES) studies. Cohort 1 (n = 8) was implanted to evaluate motor and functional outcomes, including standing, stepping, and voluntary movement. Cohort 2 n = 5) was implanted to assess cardiovascular function. This cohort also trained for voluntary movement and standing. Individuals in Cohort 3 (n = 12) were implanted as part of a prospective randomized control trial evaluating the effect of scES on cardiovascular function and voluntary movement.

All research participants underwent scES surgery using a 16-electrode epidural paddle and internal pulse generator (IPG) (Medtronic RestoreAdvanced™ or Intellis™). One surgeon performed the first four procedures, and the first author Maxwell Boakye performed the subsequent 21.

Surgical procedure

To reduce infection risk, 11 essential personnel were allowed in the operating room (OR): the anesthesiology attending, anesthesiology resident or nurse anesthetist, attending neurosurgeon, resident neurosurgeon, surgical technologist, circulating nurse, fluoroscopy technician, research principal investigator, research acquisition technician, research engineer, and the Medtronic representative. After surgical incision, only nurses and the anesthesiologist could exit/enter the OR for essential activities. Antibiotics were administered within 30 min of the incision.

Following intubation and induction of anesthesia, the participant was positioned prone on a radiolucent Jackson table with a Wilson frame. A midline incision extending from T11-L2, typically centered on the L1-L2 disc space, was marked using anterior-posterior and lateral fluoroscopy. A subperiosteal exposure of the lamina from T12 to L2 was performed. Fluoroscopy confirmed the L1-L2 disc space. Bilateral laminotomies were executed, usually at L1-L2, though this varied by 1-2 levels based on the level of the conus medullaris. The ligamentum flavum was removed. The caudal edge of the L1 lamina was undercut to enable a shallower approach angle for smooth passage of the electrode array (Medtronic Specify® 5-6-5 lead) into the epidural space [Figure 2]. The electrode was advanced superiorly, and the position was assessed with fluoroscopy [Figure 2]. If the electrode paddle was directed to one side of the midline, a second laminotomy was performed at the

adjacent level superiorly to redirect the paddle. After midline positioning, optimal functional positioning was confirmed electrophysiologically (see the electrophysiological section below). After satisfactory placement, the electrode paddle was secured using 2-–0 silk sutures on a silicon lead anchor. A strain relief loop was used when possible.

Tisseel® fibrin sealant (Baxter, Deerfield, IL, USA) was applied on top of the paddle as an additional means of securing it. Vancomycin-saline irrigation was used throughout the case and before closure. The IPG was placed in a TYRX™ antibacterial envelope (contains Minocycline and Rifampin) starting with patient 12.[4] Before patient 12, Vancomycin powder was sometimes used in the IPG incision, but we discontinued this practice due to concerns about seroma formation since a local hypersensitivity has been reported in the literature.[1,38] Participant 1 had the IPG set in the gluteal region in a single-stage approach, while participants 2–13 had a non-Bluetooth IPG implanted in the lower abdomen. Availability of a Bluetooth-enabled IPG allowed a return to a single-staged approach with the implant in the posterior flank in participants 14–25 [Figure 2].

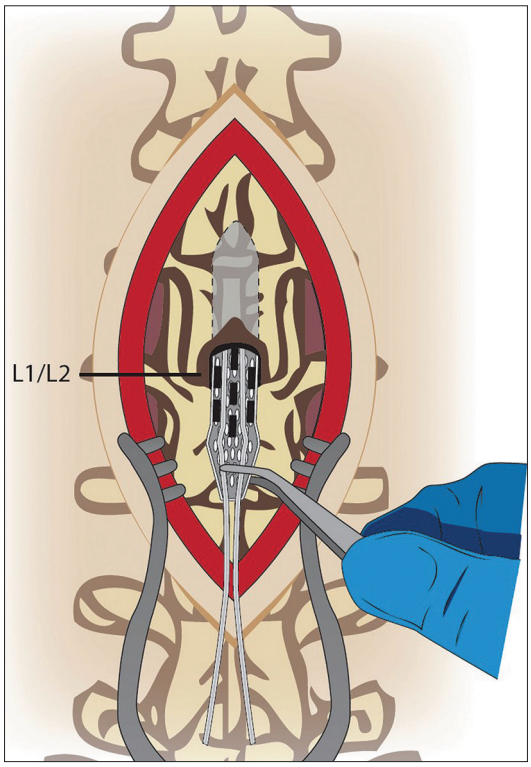

Figure 2: Surgical techniques. Illustration of surgical technique. A laminotomy is performed L1-2 (or adjacent level depending on the level of the conus) to allow passage of the paddle electrode into the epidural space (ribs not depicted). Intraoperative fluoroscopic image showing final midline positioning of the electrode between T11 and L1 vertebrae. Epidural stimulator sleeves shown exiting the epidural space. White silicon anchors secure the leads. A strain relief loop was left between the anchors and the exit point of the epidural space when possible. 2-0 silk sutures anchored the leads to the fascia, where a strain relief loop was typically placed. Leads were tunneled to a posterior flank site for the internal pulse generator Image showing postoperative incisions in midline and posterior flank.

Intraoperative electrophysiological testing

In the preoperative area on the day of surgery, the electrophysiology team placed bilateral surface electrodes over the muscle bellies of the soleus, medial gastrocnemius, tibialis anterior, medial hamstrings, rectus femoris, and vastus lateralis.[18] They inserted bilateral fine-wire electrodes to record electromyography (EMG) from the iliopsoas. EMG was collected at 10,000Hz using a 40-channel hard-wired AD board and custom-written data acquisition software (Labview, National Instruments, Austin, TX). Bipolar electrode selections at various locations along the array were tested to assess the sequence of activation of lower extremity muscles [Figure 3]. If the electrode array had to be adjusted to optimize the muscle activation sequence, a

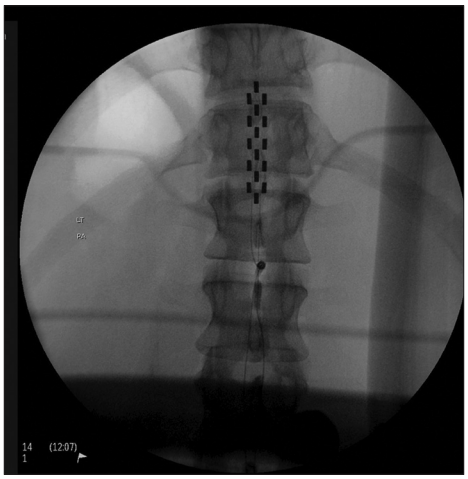

Figure 3: Intraoperative electrophysiology testing. Initial testing of Rostral and Caudal electrode configurations to assess activation sequence of lower extremity muscles. Fluoroscopy shows initial placement of the electrode paddle. Re-testing of rostral and caudal electrode configurations following movement of electrode paddle to optimize activation of rostral muscles. Fluoroscopy shows final placement of electrode paddle. Muscles: IL: Iliopsoas, RF: Rectus femoris, VL: Vastus lateralis, MH: Medial hamstrings, TA: Tibialis anterior, MG: Medial gastrocnemius, SOL: Soleus, STIM: Stimulation pulse.

new fluoroscopy image was obtained, and the position again confirmed electrophysiologically. Bipolar rostral and caudal configurations at 2Hz and 450 μsec were assessed first. Stimulation amplitude was initiated between 0.1V and 0.5V and increased by 0.1V intervals until motor thresholds for key muscles were identified.

Postoperative protocol and follow-up

Perioperative complications are included in Table 2. Two weeks after surgery, research participants were evaluated and cleared for research studies if wounds were healed and there were no postoperative complications. Longer-term adverse events evaluated included implant-related complications (migrations, malfunctioning, etc.) and injuries sustained during training.

Following clearance, spatial-temporal neurophysiological mapping was performed every other day. Functional and physiological mapping were performed as previously described.[3,24,40] Incisions were checked at the end of the first four sessions assessments, followed by weekly checks

Table 2: Participant demographics and injury.

Pub ID	Gender	Age	Time between injury and surgery (years)	Level	AIS	Operative time (min)	End of battery life (cc)	Follow Up (year)	Study	Location of stimulator
B07*	Male	23.8	3.4	T2	B	133	30	9.9	1	Gluteal
A45*	Male	24.2	2.2	T4	A	194	50	8.3	1	Abdominal
B13*	Male	27.3	4.2	C7	B	214	50	8.0	1	Abdominal
A53*	Male	34.0	2.4	T5	A	170	20	6.8	1	Abdominal
A59	Male	26.6	2.5	T4	A	228	50	5.0	1	Abdominal
B23*	Male	32.0	3.3	C5	B	208	50	4.8	1	Abdominal
A41*	Male	24.0	7.2	C4	A	246	20	4.7	2	Abdominal
A60*	Male	23.3	3.2	T3	A	251	50	4.2	1	Abdominal
A68*	Male	35.0	3.8	C5	A	190	50	4.2	2	Abdominal
B21*	Male	31.0	6.9	C4	B	189	20	4.1	2	Abdominal
A77	Female	28.5	10.2	C5	A	256	30	3.2	2	Abdominal
A80*	Female	32.9	7.9	C6	A	250	25	Explant	2	Abdominal
B30*	Female	22.8	3.2	T1	B	220	30	2.2	1	Abdominal
A96*	Female	26.9	3.1	C4	A	309	100	1.4	3	Posterior Flank
A99*	Male	19.9	2.8	C4	A	276	50	1.1	3	Posterior Flank
A101*	Male	31.4	2.4	C2	A	203	20	1.0	3	Posterior Flank
B32	Male	60.6	7.4	C4	B	285	30	0.9	3	Posterior Flank
A105*	Male	33.7	10	C4	A	337	30	0.8	3	Posterior Flank
B24*	Male	25.5	6.7	C6	B	200	20	0.7	3	Posterior Flank
B41*	Male	26.7	8.6	C8	B	150	20	0.6	3	Posterior Flank
A110*	Female	22.0	5.8	C5	A	176	20	0.6	3	Posterior Flank
A82	Male	36.6	7.4	C4	A	159	30	0.5	3	Posterior Flank
A100*	Male	52.0	16.6	C4	A	146	50	0.4	3	Posterior Flank
A123	Male	29.4	7.8	C4	A	198	20	0.4	3	Posterior Flank
B47*	Male	43.3	8.2	C4	B	234	40	0.3	3	Posterior Flank
Mean	n/a	30.9	5.9	n/a	n/a	216.9	36.2	3.0	n/a	n/a

1: (Rejc *et al*. 2017, Angeli *et al*. 2018) 2: (Harkema *et al*., 2018) 3: (Clinical trials number NCT03364660), *Completed phone interview and survey, AIS: American Spinal Injury Association Impairment Scale, A: Grade A, B: Grade B, n/A: not applicable

for 6 weeks. Any erythema or change in the healing process was addressed immediately. Following all post-implantation assessments (mapping and outcome measures), participants initiated their assigned intervention protocol [Figure 1].

Functional outcomes

After the laboratory training portion of the study, participants were assessed for their ability to perform tasks independently outside the laboratory environment. Each participant was asked to demonstrate the safe performance of each task without the assistance of the research team. Stimulation programs for functional and physiological outcomes that they could perform safely and independently were loaded into the participant's IPG for home use.

Patient-reported QOL outcomes

Patient-reported QOL outcomes were collected using an in-house designed survey of impairment domains based on the International Classification of Functioning, Disability, and Health (ICF) model.[21] Participants described scES specific changes that impacted their life. The interview timing ranged from a few months to 9 years post-implant. Three independent investigators evaluated each recorded interview. ICF domains categorized changes[29] and quotes from the interview were transcribed and documented [Table 3].

Assessment of patient satisfaction

Patient satisfaction was assessed using the validated North American Spine Society outcomes questionnaire,[39,42] which evaluated whether scES met their expectations and whether they would undergo the operation again [Table 4].

Statistical methods

Rank biserial correlation coefficient was used to evaluate the correlation of patient satisfaction (ordinal variables) with functional outcomes and complications (binary variables). Spearman's rank-order correlation coefficient was used to assess the correlation of satisfaction with the number of functional outcomes and complications (count variable). The tests were two-sided, and the significance level was set to 5%. Correlation analysis was performed in SAS 9.4 (SAS Inc., Cary, NC).

RESULTS

Of the 25 participants, most (n = 20, 80%) were male with a mean age of 30.9 years (range 19–60 years) [Table 5]. The median interval from SCI to scES implant was 5.9 years (range 2.2–16.6 years). The mean follow-up duration for participants was 3 years (0.3–9.9 years). The mean operative time was 216.9 min (range: 133–337 min), with the majority of the operative time spent performing electrophysiological monitoring. Adjusting electrode position to optimize muscle activation accounted for the variability in operative time. Optimal electrode placement sometimes required extending the laminotomies cranially to remove osteophytes that pushed the paddle off the midline. The mean operative time for the first ten cases was 202 min (range: 133–251 min) compared to 227 min (range:146–337 min) for the subsequent 15. Mean blood loss was 36.2 cc (range: 20–100 cc). All patients had a postoperative length of stay of 1 day. The optimal position of the electrode was generally between T11 and L1 vertebral level.

Table 3: Study related surgical adverse events in chronological order from postoperative period.

Adverse event	Time after implant
Ileus	1 day
Ileus	3 days
Incision site erythema	4 days
Dehiscence resulting in wound washout	2 weeks
Incision site drainage (washout with no infection)	2 weeks
Seroma	2 weeks
Device Infection resulting in device removal	28 days
Cellulitis over incision site	26 days
Dehiscence resulting in antibiotic treatment	1 month and 4 days
Seroma	3 months
Neurostimulator malposition requiring correction	5 months
Rectal pain with stimulator activation requiring repositioning of simulator	5 months
Pain during stimulation resulting in device removal and replacement	6 months
Electrode malfunction	11 months

Perioperative complications within the first 30 days

Two participants (8%) developed infections requiring washout of pus, both approximately 1 month postoperatively [Table 2]. One of these participants required removal of the stimulator. Both participants grew methicillin-sensitive *Staphylococcus aureus* on cultures and were managed with intravenous (IV) nafcillin/oral rifampin (infection at the lumbar site) and IV ceftriaxone (infection at the abdominal site) for 6 weeks. Participants 12–25 were implanted after a new infection prevention protocol was established[4] and did not experience any infections. Three participants required wound washout for wound dehiscence and non-infectious seroma. These resolved without long-term sequelae or need for implant removal. Participant 17 developed an

Table 4: Impairment domains based on ICF model.

	Specifics	Sample comments
Body function domains Mental function	Number of patients reporting (*n*=20)	
	Cognition (*n*=15)	
	Sleep (*n*=7)	"(I am) sleeping better at night."
	Energy and drive functions (*n*=12)	"I always felt crummy; now I can get out of bed – no issue." "(My) daily goal used to be to stay alive. (I have) more energy; before you're tired all the time."
	Body perception (*n*=11)	"I feel connected to my body now. Before, I just felt like a head." "(My) muscle mass has greatly increased. I look like a regular 24-year-old active woman. Expectations of how I can contribute to the world have changed." "Feel empowered – can do more on your own"
Cardiovascular, hematologic, immunological, and respiratory systems		
	Orthostasis (*n*=18)	"Passing out, didn't want to be around people, couldn't engage, now can sit with people all day" "Not dizzy, heart not skipping a beat, not passing out."
	Breathing (*n*=4)	"Respiratory function has improved"
	Thermoregulation (*n*=14)	"I don't feel like I am shivering all the time." "Sweat more." "Hanging out places I want to be without focusing on temperature." "Not cold anymore"
Voice and speech function	Voice (*n*=3)	"Conversations for a long period of time" "(I can) project my voice. Respiratory function has improved: sneezing, coughing, lung capacity. I couldn't get a song out, now I can sing – even without the stimulator"
Genitourinary and reproductive functions		
	Urinary (*n*=7)	"Before implant, I had more accidents. I now have increased sensation so I can avoid accidents" "Better (bladder) sensation, better fullness, better awareness"
	Sexual (*n*=7)	"Before implant, (I used) medications and pumps to get an erection and for intercourse. With the implant, I have not needed anything, when wanted and where wanted to be sexually active and now really essential now moving into having a family" "Increased libido."
Sensory functions and pain		
	Sensation (*n*=7)	"(I) can tell you are touching my foot" "(I) feel different sensations."
	Pain (*n*=5)	"Neuropathic pain in right foot is pretty much eliminated with stimulation and activating the muscles."
Digestive, metabolic and endocrine	Defecation (*n*=10)	"My bowel program went from 2 h to 30 min." "I now go when I need to go, not on a schedule." "(My) bowel program is done in 30 min every day, consistent (ly)."
Neuromuscular and movement related functions	Spasticity (*n*=8)	"(It is) easier for aides to take care of me; not as hard to move around due to spasticity. (My) spasticity is not anywhere near what it was."
Other - Improved health (*n*=19)	- ↓ Meds -↓Physician and Hospital Visits -↑ Healing	"(I) have not been hospital-sick since the implant." "Used to be on a lot of medications for pain and was on Baclofen. (I am now) off all of those."
Activities limitation and participation		

(*Contd*...)

Table 4: (*Continued*).

	Specifics	Sample comments
Interpersonal interactions and relationships	Participation	"I can stay out longer." "Do more things with my family." "Confidence and want to do things."
Other (*n*=13)	Well-being and Empowerment	"Helps my irritability." "Feel empowered – can do more on my own." "(I feel) stronger (and it) makes me want to try new things – reaching for things, bending forward, your riskier, trying new things."
Self-care (*n*=11)	Independence and ↓ caregiver support	"Increased independence, daily routine at home, brushing my teeth, brushing my hair, washing my face, washing half my body putting on my shirts, dressing. Not possible before implant. My mom went back to work. Mom worries less about me." "I feel like I may be able to live by myself. (I no longer) need someone next to me all the time. I can go back to school and to work."

ICF: International Classification of Functioning, Disability and Health, n refers to number of participants

Table 5: Survey responses (*n*=18).

Question	Exceeded	Met	Not met	
Were your expectations met from procedure?	7	8	3	
	Better	Same	Worse	
Did you improve overall after procedure?	14	4	0	
	Quality of life has improved and would undergo procedure again	Quality of life has improved less than I hoped, but would undergo procedure again	Quality of life has improved but would not undergo procedure again	Quality of life has not improved and would not undergo procedure again
Would you undergo procedure again?	15	3	0	0

n: Number of participants

ileus on postoperative day 3 after their initial surgery and postoperative day 2 after the revision surgery, despite extraprecautions taken after the second surgery. There have been no cases of lead migration in this series.

Long-term complications after 30 days during training

Table 5 summarizes all complications. One participant initially had the implant placed with the inferior paddle at the caudal aspect of L2 guided by electrophysiology but was later revised to a more cranial level (T11-T12) after stimulation caused an exacerbation of pre-existing rectal and penile pain. Unfortunately, the participant still had episodes of pain during stimulation after the revision.

One participant in Cohort 1b sustained a femoral neck fracture during the ninth step training session. Their postoperative course was complicated by an infected hematoma at the hip surgical site approximately 2 weeks postoperatively in the setting of a supratherapeutic INR (5.71) while on coumadin for deep venous thrombosis prophylaxis following hemiarthroplasty. This participant required a washout and was treated with 6 weeks of IV antibiotics. Subsequently, this person was placed on medical hold and was followed by the orthopedic service for an additional 9 months, during which time they had multiple washouts and also sustained a peri-prosthetic femoral fracture. After resolution of infection and revision hemiarthroplasty, they returned to training and completed the protocol without any additional complications.

Device-related events

Two participants had their IPGs upgraded due to end of battery life (EBL) 9 years after implantation. Two additional participants had their entire systems replaced after 7 years due to electrode malfunctions and EBL. Another participant had an IPG surgically repositioned due to the inability to recharge.

Primary outcomes

The primary outcomes in these research studies were improvements in motor ability and cardiovascular regulation. Improvements in motor function and blood pressure regulation have been described in the previous papers from our center in a much smaller subset of the patients described here.[5,24,25,40,41] All of the participants achieved voluntary movement in the lower extremities. Two of eight research participants that received step training achieved overground ambulation.[3] In addition, eight of 25 participants who underwent stand training were cleared to stand with stimulation outside the laboratory environment. All participants in the cardiovascular regulation studies (Cohorts 2 and 3) achieved blood pressure regulation within 110–120 mmHg systolic with stimulation and were cleared to continue stimulation at home. All were able to integrate the scES into their daily lives.

QOL improvements and correlation with training, functional improvement, and complications

Impairment domain survey results were available in 20 research participants [Table 3]. Patient satisfaction survey results were available for 20 research participants [Table 4]. All respondents felt that their overall QOL was improved after the procedure, although for 20%, the improvement was less than hoped. All reported that they would undergo the procedure again. For almost all of them (85%), the expectations were met (45%) or exceeded (40%).

All participants in Cohort 1 had their expectations either met (33.3%) or exceeded (66.7%) in an upward trend, compared to other groups, yielding a significant low positive correlation (rank-biserial correlation r = 0.452, $P = 0.0452$). One participant elected not to continue practice of voluntary leg movement. The expectations were not met; however, they reported that QOL had increased and would undergo the procedure again. Those who gained this function had higher probabilities of having their expectations met. There was also one participant who did not gain voluntary core function. This individual reported that the expectations were exceeded, that QOL had increased, and that they would undergo the procedure again. Forty-seven percentages (47%) of those who gained the voluntary core function ($n = 19$) had their expectations met, and for 36.8%, was exceeded.

There were six participants with one complications and one with two complications (a total of 7/20). Six of them had their expectations met or exceed; for three, QOL improved less than they hoped; but they would all undergo the surgery again. There were three individuals for whom expectations were not met. They felt better after the procedure and would all undergo the procedure again. Only one of them had a complication (infection requiring washout and resulting in permanent antibiotic treatment). Overall, there was no correlation between satisfaction and occurrence of complications. For dehiscence resulting in wound washout and seroma complications, the distribution of QOL improvement yielded a high negative correlation between the two events (rank-biserial correlation r = −0.842, $P < 0.0001$), that is, higher probability of having QOL improved as or more than hoped for those who did not experience those complications.

DISCUSSION

In this series of scES for neuromodulation of motor and blood pressure regulation after tSCI, all participants achieved voluntary control of lower limb movement. Two participants achieved overground ambulation. All participants who initially had blood pressure instability at the end of the study could integrate it into their daily lives and regulate blood pressure independently. Improvements in motor and cardiovascular function were consistent with previously reported preliminary results.[24,25,40]All patients reported improvement following scES, with 85% reporting that the procedure either met or exceeded their expectations, and all would undergo the operation again. Most perioperative complications were minor and transient without long-lasting effects and did not influence long-term patient satisfaction with the procedure or willingness to undergo the operation again.

Due to immunological and inflammatory abnormalities and neurogenic immune system dysfunction, persons with SCI are highly susceptible to infections and wound complications. Infections ($n = 2$) and wound dehiscence and seroma ($n = 3$) were the most common complications with one research participant requiring permanent removal of the implant due to infection. The overall infection rate of 8% is comparable to previously reported rates for spinal cord stimulator (SCS) implants in the chronic pain population.[44] Therefore, when using the additional recommendations proposed here, SCS in the SCI population can be performed with comparable infection rates to SCS implants in non-SCI populations. Wound dehiscence/seroma complications responded well to washout with primary wound reclosure without long-term sequelae or need for implant removal. As outlines in enhanced recovery after surgery protocols, good nutritional support with protein supplements in the perioperative period may optimize wound healing and postoperative rehabilitation.[13]

We have previously published our protocol for reducing infections after scES.[4] Key aspects included a panel of laboratories to assess nutritional status and level of systemic inflammation before surgery, identification, and treatment of urinary tract infections, and use of a TYRX antibacterial envelope for the IPG rather than vancomycin powder. Our infection rate dropped to zero after the implementation of

this protocol in the last 14 participants (2/11 infections in the initial protocol, 0/14 in the revised protocol). In the two participants (8%) who developed infections, one required implant removal, and the other required lifelong antibiotics per Infectious Diseases recommendations. When an infection is suspected, the decision to remove implants is a complex decision that involves surgeons, the research participant, and the infectious disease team. In a large multicenter retrospective study involving 2737 spinal cord stimulator implants, the infection rate was 2.45%, of which 77% required removal.[7,44] The most common site of infection was the IPG pocket, while *S. aureus* was the most common organism.[7]

After any intervention, especially one like scES, it is critical to monitor the direct effect of neurological and functional change on the specific outcome measures proposed. ScES improved motor functions previously,[43] but many self-reported benefits and improvements in QOL are not captured in objective neurologic outcome measures. Our post-intervention follow-up survey results show consistent additional improvements in critical domains of QOL, including cardiovascular, thermoregulatory, respiratory, cognitive, bowel, bladder, and sexual-related dysfunction. These "hidden impairments" improvements are essential in the QOL of persons with SCI.[8] All participants stated that they would undergo the operation again. The satisfaction reported in this series compares favorably with patient satisfaction results after other spinal surgery procedures.[16,31,45] Combined, the impairment domain survey data, and the global survey results provide further insight into the overall benefits of scES. They suggest that scES effects extend beyond motor and physiological improvements, with 50% experiencing enhancements in more than ten domains of QOL. Of interest is the data that scES may alleviate some of the widespread cognitive impairments that occur after SCI, a finding that warrants future studies.[10,34,35,37]

The electrode was positioned satisfactorily in most research participants through an L1-L2 laminotomy. Intraoperative electrophysiological mapping guided the optimal position. In addition, and more recently high-resolution, magnetic resonance imaging was used to delineate the conus medullaris [Figure 4].[33] We recommend the paddle span as much of the lumbosacral enlargement as possible [Figure 5].[33] This position seems optimal for volitional lower-limb motor improvements and appears to be sufficient to activate multiple physiological systems [Table 6]. Further research is needed to help refine our understanding of the ideal intraoperative positions for locomotion, cardiovascular, and bowel and bladder functions.

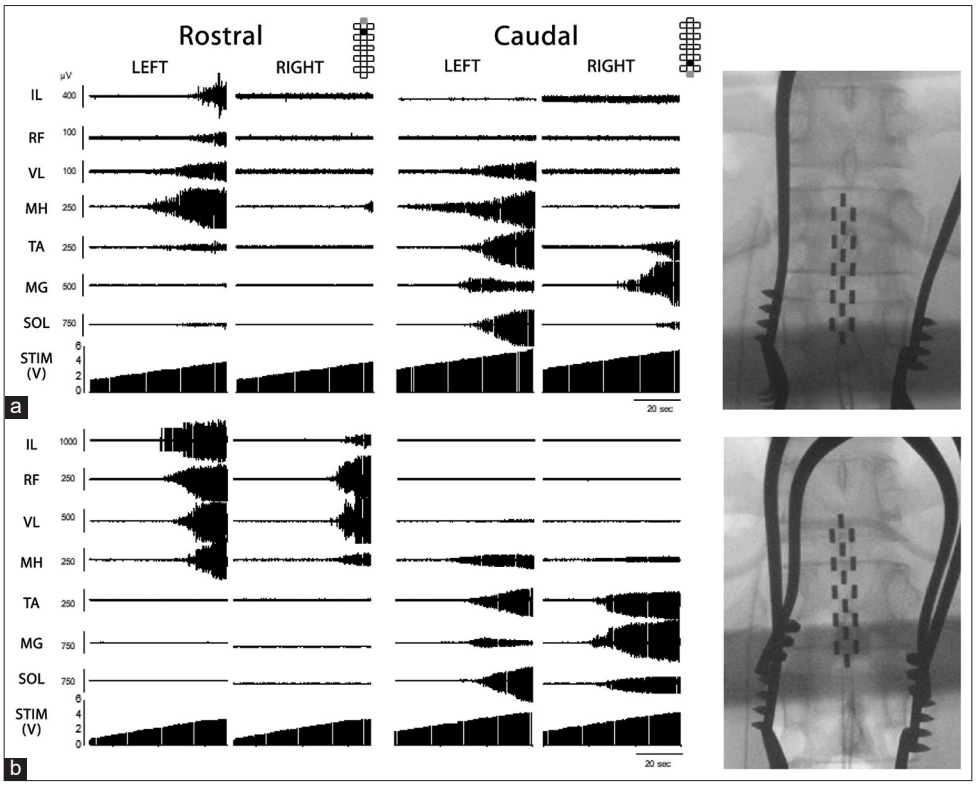

Figure 4: Intraoperative electrophysiology testing assessing rostral and caudal ends of paddle stimulator. Key muscle groups are tested from stimulation parameters. (a and b) panels juxtapose differing outcomes based on positioning.

Table 6: Paddle placement relative to conus.

Patient number	End of conus slice	Electrode placement slices	Distance from end of conus (mm)	Magnetic resonance imaging axial slice thickness (mm)
A59	34/35	16–30	15.52	3.45
B23	33/34	20–34	−1.725	3.45
A41	38	28–42	−13.8	3.45
A60	34/35	17–31	12.075	3.45
A68	33	15–29	13.8	3.45
B21	42/43	29–43	−1.725	3.45
A77	14	8–12/13	15	10
A80	9/10	5/6–10	−5	10
B30	12	6–11	10	10
A96	11/12	8/9–13/14	−20	10
A99	11/12	6/7–11/12	0	10
A101	15/16	10/11–15/16	0	10
A105	16/17	10–15	15	3.45
B24	11/12	6–11	5	10
B41	12/13	7–12	5	10
A110	7/8	13/14–18/19	20	10
A82	12/13	6/7–11/12	10	10
A100	14/15	9–13/14	10	10
C54	16	10–15	10	10

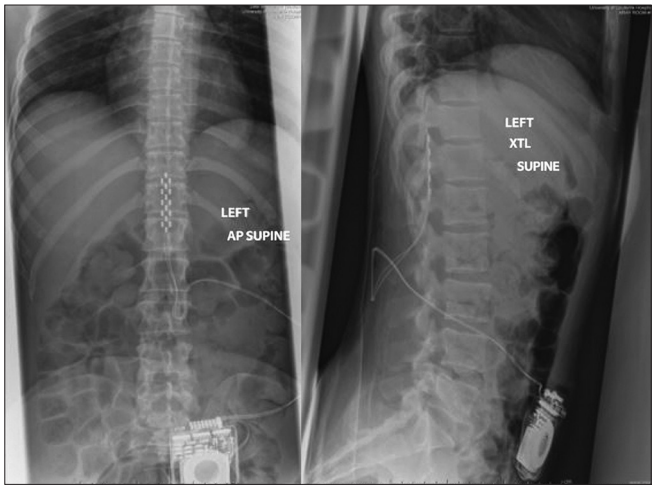

Figure 5: Final lateral and posterior-anterior X-rays demonstrating positing of epidural stimulator and pulse generator.

Overall, except for the hip fracture, most of the complication rates reported here were transient and consistent with reported results after SCS placement for pain.[44] Given pervasive bone mineral density abnormalities, SCI patients undergoing scES with locomotor therapy are at risk for musculoskeletal fractures. The participant who experienced a hip fracture had evidence of heterotopic calcifications before the fracture. Following this complication, we modified our protocol to start scES only once daily, with a high body weight support and slow speed. Loading on legs and treadmill speed was slowly increased throughout the training sessions. Most individuals in cohort 1b did not train twice daily until after 80 sessions with scES.

In contrast to a recent paper,[6] we did not observe any worsening of bladder function associated with scES. However, in that paper, there was uncertainty regarding establishing a cause-and-effect relationship between stimulation-induced changes in detrusor pressure in one participant due to limited assessment time points. The lack of post-implant pre-treatment urodynamics and the absence of representative urodynamic study records limit the ability to understand the reported loss of bladder compliance.

Assessment of risks and benefits is a cornerstone in evaluating neuromodulatory therapies for chronic neurological conditions. Deep brain stimulation, approved for the treatment of movement disorders,[12,23] carries a risk of infection, device removal/replacement, and procedure-related complications such as intracerebral hemorrhages.[12,17,20,28] As a treatment for the sequelae of SCI for which there are currently no effective treatments for paralysis,[15] our results suggest that scES neuromodulation for SCI has a favorable risk-benefit profile in the sense that the risks are mostly transient and does not prevent patients from achieving numerous benefits and satisfaction. Most patients integrate scES into the_RJAir daily lives to improve cognitive functions, overall QOL, perform stand and step exercise, and avoid blood pressure instability, the leading cause of morbidity, mortality.[9] Patients may need to replace the IPG every 7–10 years with outpatient procedures. The results suggest that scES may enable patients to achieve at least a decade of lower-extremity motor control and standing at home with improved cardiovascular regulation to help avoid secondary sequelae of SCI while improving QOL in mental health and cognitive domains.

Strengths and limitations

One of the strengths of this study is the sample size, and it is the first to measure multiple patient-reported outcomes. Although the follow-up was variable, most patients had at least a 1-year follow-up, and 13 had >2-year follow-up. Furthermore, there was 80% survey response rate, so we have no information on outcomes in all participants. Most individuals continue to use the stimulator and report benefits exemplifying the durability of results. Although this is the most extensive series to date, the overall number of research participants is small, and additional multicenter studies are needed. Several other benefits remain to be quantified, including but not limited to benefits on bowel motility, systemic inflammation, metabolic syndromes, bone density, cognitive and mental health, immune health, infection frequency, and overall cost-effectiveness.

CONCLUSION

scES in patients with tSCI achieved numerous functional benefits on lower extremity function, patient-reported outcomes, and patient satisfaction, making it a most promising therapeutic strategy. Postoperative complications were primarily minor (except the hip fracture) and transient and have not influenced longer-term satisfaction with the procedure. Strict adherence to a preoperative, intraoperative, and postoperative protocol minimized postoperative infections and postoperative seromas. Utilization of high level of body weight support and slow speeds during the initial sessions of Step-scES is recommended to minimize fractures. Well-designed clinical trials are needed to build on these results to elucidate the role of scES in tSCI and ultimately streamline regulatory approval and make scES more accessible to patients with tSCI.

Data availability statement

Data are available on reasonable request from the authors.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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