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Motor and autonomic concomitant health improvements with neuromodulation and exercise (MACHINE) training: a randomised controlled trial in individuals with spinal cord injury

Claire Shackleton ,[1,2] Soshi Samejima ,[1,2] Alison MM Williams,[1,3] Raza N Malik,[1,2] Shane JT Balthazaar,[1,4] Abdullah Alrashidi,[1,5] Rahul Sachdeva,[1,2] Stacy L Elliott,[1,6,7,8] Thomas E Nightingale,[1,9,10] Michael J Berger,[1,2] Tania Lam ,[1,3] Andrei V Krassioukov [1,2,6]

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TL and AVK are joint senior authors.

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For numbered affiliations see end of article.

Correspondence to
Dr Andrei V Krassioukov; andrei.krassioukov@vch.ca and Dr Tania Lam; tania.lam@ubc.ca

ABSTRACT

Introduction Motor and autonomic dysfunctions are widespread among people with spinal cord injury (SCI), leading to poor health and reduced quality of life. Exercise interventions, such as locomotor training (LT), can promote sensorimotor and autonomic recovery post SCI. Recently, breakthroughs in SCI research have reported beneficial effects of electrical spinal cord stimulation (SCS) on motor and autonomic functions. Despite literature supporting the independent benefits of transcutaneous SCS (TSCS) and LT, the effect of pairing TSCS with LT is unknown. These therapies are non-invasive, customisable and have the potential to simultaneously benefit both sensorimotor and autonomic functions. The aim of this study is to assess the effects of LT paired with TSCS in people with chronic SCI on outcomes of sensorimotor and autonomic function.

Methods and analysis Twelve eligible participants with chronic (>1 year) motor-complete SCI, at or above the sixth thoracic segment, will be enrolled in this single-blinded, randomised sham-controlled trial. Participants will undergo mapping for optimisation of stimulation parameters and baseline assessments of motor and autonomic functions. Participants will then be randomly assigned to either LT+TSCS or LT+Sham stimulation for 12 weeks, after which postintervention assessments will be performed to determine the effect of TSCS on motor and autonomic functions. The primary outcome of interest is attempted voluntary muscle activation using surface electromyography. The secondary outcomes relate to sensorimotor function, cardiovascular function, pelvic organ function and health-related quality of life. Statistical analysis will be performed using two-way repeated measures Analysis of variance (ANOVAs) or Kruskal-Wallis and Cohen's effect sizes.

Ethics and dissemination This study has been approved after full ethical review by the University of British Columbia's Research Ethics Board. The stimulator used in this trial has received Investigation Testing Authorisation from Health Canada. Trial results will be disseminated through peer-reviewed publications, conference presentations and seminars.

Trial registration number NCT04726059.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The techniques employed to assess sensorimotor and autonomic functions are validated for individuals with spinal cord injury and will be performed by a collaborative, multidisciplinary team of experienced clinicians and researchers.
⇒ This clinical trial includes an extensive intervention period of 12 weeks of transcutaneous spinal cord stimulation with an inclusive optional open-label follow-up to allow all participants to experience the intervention.
⇒ This clinical trial includes a sham stimulation group as a comparison for active stimulation to assess placebo effects.
⇒ A limitation to this trial is the lack of a follow-up time point for physiological outcomes to ascertain whether favourable adaptations persist beyond the intervention period.

INTRODUCTION

Spinal cord injury (SCI) results in sensorimotor and autonomic dysfunctions, which include cardiovascular (CV), lower urinary tract (LUT), bowel and sexual dysfunction.[1–3] These sensorimotor and autonomic dysfunctions are widespread among people with SCI and can cause persistent health complications, reduce independence and health-related quality of life (HRQoL) and increase mortality risk.[4] Motor paralysis and autonomic dysfunctions have been

identified as key priorities for recovery by individuals with SCI.[5 6] Addressing these dysfunctions may ultimately improve functional independence and daily activity, reduce CV disease risk factors in this at-risk population,[7–9] and in turn, translate to improved HRQoL.[5 10]

Activity-based therapies, including locomotor training (LT), seek to 'provide activation of the neuromuscular system below the level of injury with the goal of retraining the nervous system'.[11–14] Recent studies have demonstrated that body-weight supported gait training facilitates recovery of motor function, ambulation and balance following SCI.[15 16] LT can also facilitate general health maintenance[17] and improvements in autonomic function, including enhancement of blood pressure (BP) control, and bladder, bowel, and sexual functions.[15 16 18–21]

More recently, breakthroughs in SCI rehabilitation have been observed using electrical spinal cord stimulation (SCS). Promising results indicate the potential of epidural SCS to enable significant recovery of motor and autonomic function[22–29]; however, there are a lack of randomised controlled trials to support these findings, and participants are required to undergo invasive and expensive procedures to participate in this therapy. Transcutaneous SCS (TSCS) is a potentially simple, safe and effective treatment for restoring these functions, without requiring expensive and invasive surgery.[30] The effect of TSCS is postulated to be through increasing the excitability of spinal circuits through dorsal root afferents.[31] Therefore, TSCS may modulate the central nervous system by targeting dormant spinal cord circuits for motor recovery and potentially, the neurocircuitries involved in CV, bladder, bowel and sexual function.[31–37] In addition, a recent systematic review determined that 43/46 studies on TSCS reported an improvement in bowel, bladder, and sexual function, as well as HRQoL.[38]

Pairing LT with TSCS may further enhance the beneficial effect of each independent intervention, by combining task-specific training together with plasticity-augmenting stimulation.[33 39] However, the outcome of the combination of electrotherapeutics and rehabilitative training on individuals with SCI needs to be further explored. Based on our review of the literature, there are currently no therapeutic approaches that combine LT with TSCS in individuals with motor-complete SCI and also have the potential to simultaneously benefit both sensorimotor and autonomic functions.[34 40–44] Furthermore, no studies have controlled for placebo effects using sham stimulation and randomisation to test the efficacy of TSCS with LT. This paired approach offers a viable, novel and non-pharmacological treatment option for SCI recovery. Additionally, the flexibility of the paired intervention (ie, easily movable electrodes and adaptable stimulation/LT characteristics) allows the simultaneous targeting of both motor and autonomic dysfunctions, thus serving the priorities of individuals with SCI and improving their HRQoL. Insight into efficacy of combined treatments will be of great importance to offer precise treatment parameters for restoration of functional activities and autonomic regulation in individuals with SCI. Therefore, the purpose of this study is to determine the efficacy of LT in combination with non-invasive TSCS to promote recovery of sensorimotor function, autonomic function and HRQoL in individuals with chronic, motor-complete SCI.

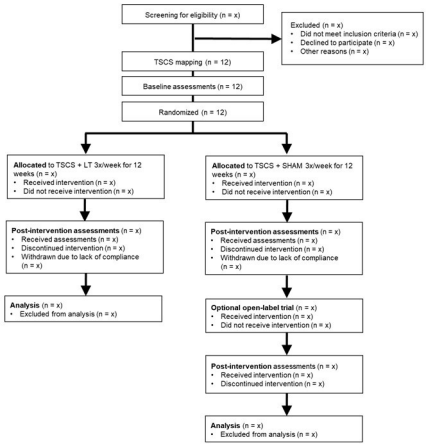

Figure 1 Flow chart for the randomised controlled trial, with an optional open-label follow-up. SHAM, sham transcutaneous spinal cord stimulation; TSCS, transcutaneous spinal cord stimulation.

METHODS AND ANALYSIS

Study design

This study is a single-blind, randomised, sham-controlled trial, with an inclusive optional open-label follow-up. This protocol is approved by the University of British Columbia Clinical Research Ethics Board (CREB; H20-01307) and Health Canada for investigational device exemption for the TESCoN class II medical device used in this clinical trial (#336767). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[45] checklist can be found in the online supplemental material (Research Checklist). Protocol amendments are available on request from the corresponding author. This study will be performed at the International Collaboration on Repair Discoveries (ICORD), in the Blusson Spinal Cord Centre, University of British Columbia, Vancouver, Canada. An overview of the experimental design is illustrated in figure 1.

Participants

This study seeks to enrol 12 adults to undergo the intervention and all required assessments. Participants must be able to attend 12 weeks of clinical visits and undergo a simple screening process. A full list of inclusion and exclusion criteria is provided in table 1. Due to the paucity of available literature looking at the impact of LT paired with non-invasive neuromodulation, in motor-complete SCI, on the primary outcome of interest, it was not possible to perform a sample size calculation. Consequently, our proposed sample size (n=12) is informed by previous studies with a similar sample size (n=12–13).[46–48] Participants will be recruited from various advertisements

Table 1 Participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Resident of British Columbia, Canada with active provincial medical services plan 2. 18–60 years of age 3. Chronic traumatic SCI at or above the T6 spinal segment 4. >1 year post injury, at least 6 months from any spinal surgery 5. American Spinal Injury Association Impairment Scale Grade A or B 6. Able to tolerate an upright posture for 30 min (with or without breaks) 7. Willing and able to comply with all clinic visits and study-related procedures 8. Able to understand and complete study-related questionnaires (must be able to understand and speak English or have access to an appropriate interpreter as judged by the investigator) 9. No painful musculoskeletal dysfunction, unhealed fracture, pressure sore or active infection that may interfere with testing activities 10. Stable management of spinal cord related clinical issues (ie, spasticity management) 11. Medication dosage must be stable for period of 4 weeks prior to participation 12. Women of childbearing potential must not intend to become pregnant, or be currently pregnant, or lactating: – Women of childbearing potential must have a confirmed negative pregnancy test prior to the baseline visit. During the trial, all women of childbearing potential will undergo urine pregnancy tests at their monthly clinic visits as outlined in the schedule of events – Women of childbearing potential must agree to use adequate contraception during the period of the trial and for at least 28 days after completion of treatment. Effective contraception includes abstinence 13. Sexually active males with female partners of childbearing potential must agree to use effective contraception during the period of the trial and for at least 28 days after completion of treatment 14. Must provide informed consent	1. Ventilator dependent 2. Clinically significant, unmanaged, depression (PHQ-9 above 15) or ongoing drug abuse 3. Use of any medication or treatment that in the opinion of the investigator indicates that it is not in the best interest of the participant to participate in this study 4. Intrathecal baclofen pump 5. Presence of severe acute medical issues that in the investigator's judgement would adversely affect the participant's ability to participate in the study. Examples include but are not limited to clinically significant renal or hepatic disease; acute urinary tract infections; pressure sores; active heterotopic ossification; newly changed antidepressant medications (tricyclics); or unstable diabetes 6. Cardiovascular, respiratory, bladder or renal disease unrelated to SCI or presence of hydronephrosis or presence of obstructive renal stones 7. Severe anaemia (haemoglobin <8 g/dL) or hypovolaemia 8. Oral baclofen dose or other anti-spasticity medications greater than 30 mg per day 9. Any implanted metal (other than dental implants) in the skull or presence of pacemakers, implantable defibrillators, neurostimulators or drug delivery pumps in the trunk 10. History or risk of osteoporosis, low bone mineral density, or fragility fractures in the lower limbs 11. Participant is pregnant 12. History of seizures/epilepsy or recurring headaches 13. Any implanted metal in trunk or spinal cord under the electrode application sites 14. Participant has swollen, infected and inflamed areas or open wounds on the area of stimulation 15. Participant has undergone electrode implantation surgery 16. Participant is a member of the investigational team or his/her immediate family

PHQ-9, Patient Health Questionnaire-9; SCI, spinal cord injury.

in Spinal Cord Injury BC's Spin Magazine, ICORD website and GF Strong Rehabilitation Centre bulletin board, and from lists of individuals who have previously participated in research in our laboratories and have consented to be contacted about future research opportunities.

Interventions

Following screening and provision of written informed consent (online supplemental material, Patient Consent Form), participants will be enrolled in the trial. This trial will involve LT, using body-weight supported manually assisted or robotic-assisted gait training, paired with TSCS or sham stimulation. Participants will be randomly assigned, using a computer-generated simple randomisation approach, to the intervention group (active TSCS) or the control group (sham stimulation). The allocation sequence will be concealed using the sequential numbered, opaque, sealed envelope technique.[49] Envelopes will only be opened after a participant has completed all baseline assessments and is ready to be allocated to an intervention. Enrolled participants will attend 44 visits at ICORD over the expected duration of participation of 18 weeks. Participants will come to ICORD for either LT+TSCS or LT+Sham stimulation 3 days per week for 12 weeks, for a total of 36 sessions, after which an additional 36 session optional open-label trial will be available for the control group. The details of the trial visits and timeline are depicted in figure 2.

Locomotor training

LT will be delivered using body-weight supported treadmill training. All participants will train 3 times per

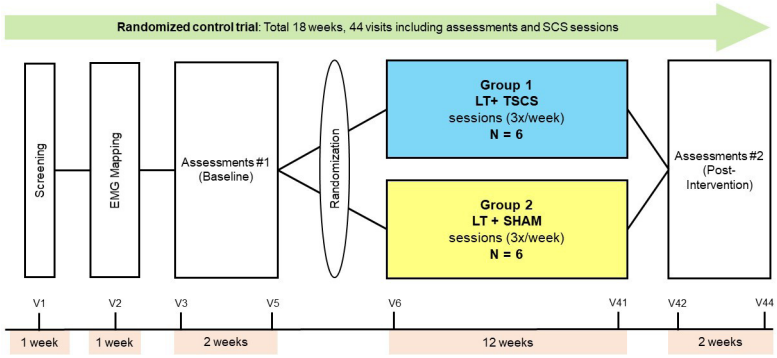

Figure 2 The clinical trial timeline showing each study visit and the study duration. EMG electromyography; LT, locomotor training; SHAM, Sham transcutaneous spinal cord stimulation; TSCS, transcutaneous spinal cord stimulation.

week for 12 weeks with a target to reach 45 min of gait training in each session.[50] Participants will begin with a high degree of body-weight support (BWS; ≥50% of body weight) and a slow walking speed (≤2.0 km/hour). Participants will progress with training through individualised goals set weekly by the research team. Progression will include increasing the walking duration, reducing rest time, increasing walking speed and reducing BWS, while still maintaining proper stance limb kinematics. Walking performance cues will also be provided to the participant to encourage them to engage with the therapy. Training sessions will be divided into three, 15 min blocks. At the end of each 15 min block, BP and heart rate will be recorded, and the participant will be asked to report their rating of perceived exertion using the Borg 6–20 scale as used in previous trials.[51–53] The total distance walked, total time walked, amount of BWS and treadmill speed will be recorded from each session. The data collected at these time points will be used in part by the research team to set goals for the following week.

Transcutaneous spinal cord stimulation

TSCS will be delivered using a non-invasive central nervous system stimulator (TESCoN, SpineX, California, USA). Stimulation will be delivered by a 2.5 cm standard round self-adhesive electrode placed midline at the T11 and L1 spinous processes as the cathodes, and two 5.0×10.2 cm^2 rectangular electrodes placed symmetrically on the skin over the iliac crests as anodes. The two active cathodes will share the same anode pair. Stimulation will involve charge balanced monophasic rectangular waveforms with 1.0 ms pulses, administered at 30 Hz, with a carrier frequency of 10 kHz,[36 40] and a current ranging from 10 to 130 mA for up to 45 min during the gait training.

TSCS will be delivered simultaneously with LT during each training session, 3 times/week for 12 weeks. As the goal is to receive the full 45 min of TSCS therapy, stimulation will remain active (ie, switched on) during the full duration of each training session (45 min), including rest periods. TSCS intensity will be delivered at or above the motor threshold for each participant while still maintaining comfort and BP stability. In the occurrence of an adverse event, such as autonomic dysreflexia, TSCS will be terminated immediately.

Sham stimulation

The experimental set-up, procedures and training will be identical for participants randomised to the sham stimulation group, except that they will receive sham TSCS during the training sessions. The sham stimulation is designed to control for placebo effects associated with the perception of the intervention. Sham stimulation will be administered at the same anatomical location as therapeutic TSCS (T11 and L1 spinous processes). Such sham stimulation has been successfully incorporated as the control treatment in previous studies for neural control of balance[54] and walking function.[35] We have adapted these procedures to reduce the possibility that participants will be able to determine (or guess) their group allocation. The intensity of electrical stimulation will be briefly ramped up to a level at which the participants report perceiving the stimulation (ie, sensory threshold), then ramped down and turned off for the remainder of the intervention.

Assessments

Prior to baseline assessment testing, participants will undergo baseline mapping of TSCS to optimise stimulation parameters based on the EMG responses at various frequencies (1 and 30 Hz) and current amplitudes (10–130 mA).[32 33 55] Surface EMG will be recorded using surface electrodes (Delsys, Natick, USA) as per an established protocol to record muscle activation during mapping with and without TSCS.[25 28] The EMG sensors will be affixed to the skin over each muscle using medical-grade adhesives. Potential motor targets include rectus abdominis, rectus femoris, vastus lateralis, tibialis anterior, biceps femoris, medial gastrocnemius, soleus and the levator ani muscles. EMG signals will be sampled at 2000 Hz and stored for offline analysis using custom MATLAB routines (MathWorks, Natick, USA). Evoked responses to the varying stimulation parameters in this mapping session will inform the stimulation parameters used in the intervention.

All assessments will be performed before (ie, baseline) and after (ie, 12 weeks) each intervention arm. Additionally, the same assessments will be performed before and after the optional open-label 12-week trial for the individuals in the control group. Continuous BP monitoring will be used as a safety measure to detect and record potential adverse CV events, such as autonomic dysreflexia, during TSCS delivery and outcome assessments. Specific outcome measures for each aim are listed in online supplemental table 1 (online supplemental material).

Outcome measures

Primary and secondary outcomes were selected based on a review of previous studies investigating the benefits of LT and TSCS in individuals with SCI, as well as based on the key priorities for recovery in the SCI community. Outcome measures, in the absence of TSCS, will be assessed at baseline prior to randomisation and 12 weeks after randomisation. Participants in the sham stimulation group will also be assessed again after the optional open-label follow-up. Assessments will be completed by independent assessors with experience in treating individuals with SCI and proficient in assessing the outcome measures. Adverse events directly related to the treatment will also be monitored throughout the trial.

Primary outcome measures

Attempted voluntary motor activation (while supine and during walking)

Supine voluntary activation: while lying in the supine position, participants will attempt six motor manoeuvres to determine if voluntary activity can be elicited in muscles below the injury—trunk flexion, hip flexion, knee flexion, knee extension, ankle dorsiflexion and ankle plantar flexion. Each manoeuvre will be attempted twice, bilaterally. EMG recordings will be taken from the rectus abdominis, rectus femoris, biceps femoris, vastus lateralis, tibialis anterior, soleus and gastrocnemius. The mean root mean square (RMS) EMG amplitude from each muscle during rest and the attempted contraction for each participant and each trial will be calculated. If the mean RMS EMG amplitude during a contraction is >2 SD above rest, muscle activity will be considered 'present'. An activation score will be given to each participant for each muscle; one point will be awarded for each trial with muscle activity present during the attempted contraction (possible score of 0–2).[56–58] *Walking voluntary activation*: participants will complete a series of gait trials using the Lokomat robotic exoskeleton (Hocoma AG, Volketswil, Switzerland). Participants' lower limbs will be passively moved through the gait cycle using the Lokomat. Participants will attempt to walk actively together with the Lokomat's movements. We will record bilateral EMG activity from seven muscles during the Lokomat-assisted walking—rectus abdominis, rectus femoris, biceps femoris, vastus lateralis, tibialis anterior, soleus and gastrocnemius. Force sensitive resistors will be inserted into the participants' shoes to record data related to heel strike and toe off for the purposes of identifying these gait events for later analysis.

Lower limb proprioceptive sense

Lower limb proprioceptive sense will be quantified using previously validated assessments of joint position sense (JPS) and movement detection sense (MDS) using custom software of the Lokomat.[59 60] Participants will be suspended in the air with a BWS harness system and attached to the Lokomat robotic gait orthosis (Hocoma AG). Vision of the lower limbs will be blocked throughout the testing procedure to prevent visual cues. JPS will be tested bilaterally for the hip and knee joints using custom software control of the Lokomat. The Lokomat will move the leg into a predetermined test position (eg, target angle of 25° flexion or 25° extension) and then to a distractor position. The participant will have to use a joystick to return their limb to the suspected test position. MDS will also be tested, where the leg is moved (either at the hip or knee) ~10° by the Lokomat from a random starting position. The participant will have to indicate when the movement is detected and whether the movement is 'up' or 'down' (ie, flexion or extension). Joint angle data from the encoders will be collected using custom software written in LabView (National Instruments, Austin, Texas, USA). For JPS, the absolute average difference between the actual and target position across six trials will be calculated; smaller differences correspond to better static position sense. MDS for each joint will be calculated by the sum of (1) joint excursion before the button was pressed normalised to maximum absolute joint excursion (10 degrees); and (2) the verbal response to the direction of movement. The maximum normalised joint excursion score for each trial is 1, and a score of 0 will be given if the verbal response is correct and 1 if the response is incorrect. Thus, the maximum possible score (worst MDS) for a given trial totals 2, and the minimum is 0 (best MDS).

Blood pressure regulation

BP regulation will be monitored using 24-hour ambulatory BP monitoring (ABPM, 24 hours). Twenty-four hours ABPM will be performed using the Meditech Card(X)plore (Meditech, Budapest, Hungary), using a well-established clinical protocol.[61] Participants will be affixed with an appropriately sized brachial cuff on their non-dominant arm and a mercury sphygmomanometer attached to the monitor will take BP recordings every 15 min during the daytime period (07:00 hours–23:00 hours) and then every hour during the night-time period (23:00 hours–o7:00 hours). All participants will be asked to complete an activity log to indicate the time before and after each bowel movement, transfer, meal, time they transferred into supine position to sleep then seated when they woke-up or any other times they felt a sudden rise in BP occurring. Data will be stored and analysed offline using CardioVisions Software (Meditech, Budapest, Hungary). We will extract the average daily and night-time BP, number of episodes and severity of

autonomic dysreflexia, number of episodes and severity of orthostatic hypotension.

Secondary outcome measures

Sensorimotor function

Corticospinal excitability

We will apply transcranial magnetic stimulation (TMS) over the primary motor cortical area for the lower limb and record Motor evoked potentials (MEPs) via surface EMG from the tibialis anterior and soleus. TMS will be delivered using a Magstim Rapid Pulse^2 system (MagStim Company) with a double cone coil. Stimuli will be delivered in blocks of increasing per cent of the maximum stimulator output (MSO) until 100% MSO is reached or the MEP amplitude reaches a plateau. The peak-to-peak amplitude of the MEPs and the MEP latency will be computed offline. We will construct recruitment curves for each muscle by plotting MEP amplitude against TMS intensity (%MSO), and then fit a Boltzmann function to determine measures of corticospinal excitability and connectivity including slope, peak slope, area under the curve and maximum MEP amplitude.[62–64]

Spinal excitability

H-reflex testing will provide a measure of spinal sensorimotor excitability[65] which may be modulated via stimulation interventions in people with SCI.[66] Motor responses to peripheral nerve stimulation will be measured using surface EMG (Delsys, USA) and analysed offline. To investigate the changes in spinal reflex excitability, we will examine the size of the soleus H-reflex normalised by M max (H–M ratio) and H-reflex recruitment curves at rest.[65]

Seated balance control (static and dynamic)

Participants will sit on an elevated force plate (Bertec, Ohio, USA) with their feet off the floor and arms crossed at their chest. For static balance, participants will sit as still as possible for 60 s first with their eyes open, and then with their eyes closed. Force plate data will be used to calculate the RMS distance, velocity and 95% confidence ellipse area from the centre of pressure trajectory to examine overall seated stability and the amount of postural activity during the task.[67] To test dynamic balance, participants will lean as far as they can in the 8-cardinal directions. Total distance travelled in each direction as calculated by the centre of pressure trajectory from the force plate will be recorded.[53 68]

Cardiovascular parameters

Severity of CV dysfunction

The Autonomic Dysfunction Following SCI (ADFSCI) questionnaire will be used to assess self-reported frequency and severity of BP dysregulation. The participant will complete 18 items from the third and fourth part of the ADFSCI only, which evaluates autonomic dysreflexia and orthostatic hypotension. The autonomic dysreflexia and hypotension parts of the questionnaire include 10 and 8 items, respectively, each using a 5-point scale to score the frequency and severity of hypertensive or hypotensive symptoms, such as headache, goose bumps, confusion and so on, under different circumstances.[69]

Orthostatic hypotension

The presence or absence of orthostatic hypotension (OH) will be determined using a 60° Head-Up-Tilt Test. Beat-to-beat systolic and diastolic BP, mean arterial pressure and heart rate will be recorded continuously via finger photoplethysmography and electrocardiogram (Finapres Nova; Finapres Medical Systems BV, Arnhem, Netherlands), while discrete BPs will be taken every minute from the right brachial artery (Carescape V100; GE Healthcare, Milwaukee, Wisconsin, USA). Following instrumentation, baseline recordings will be made during a 10 min supine rest period. Participants will then be passively moved to the 60° upright position using an automated tilt table.[70] This position will be maintained for 10 min, during which recordings of heart rate and BP will be continued. A further 5 min of measurements will be recorded on return to the horizontal supine position. Data will be monitored via LabChart (ADInstruments, Colorado, USA) and analysed offline to detect postural changes in systolic BP.

Cardiac structure and function

Echocardiography will be used to determine cardiac structure and function. Participants will be placed in a left lateral decubitus position. Following 5 min of quiet rest, images will be collected using a 2.5 MHz phased-array transducer on a commercially available ultrasound (Vivid 7/q; GE Medical, Horton, Norway) and stored for offline analysis using specialised computer software (EchoPAC; GE Healthcare, Horton, Norway) according to the recommendations of the American Society of Echocardiography.[71] Images will be collected using parasternal long and short axis, apical 4, 2 and 3 chamber and subcostal views and will be recorded at the end of a tidal expiration. Indices will be determined from the mean of three cardiac cycles and will include measures of left ventricular structure, global systolic and diastolic function, and cardiac mechanics. The research team has considerable expertise with assessing these indices in people with SCI.[72]

Pelvic organ function

Lower urinary tract, bowel and sexual function

Neurogenic Bladder Symptom Score (NBSS): comprises 23 questions covering three domains, including incontinence, storage and voiding and specific consequences, as well as one question on QoL.[73] *The Incontinence-QoL (I-QoL)*: comprises 10 questions covering three domains, including avoidance and limiting behaviour, psychosocial impacts and social embarrassment, which will be summarised as a total score. All scores, for each domain and a total, will be transformed into a continuous scale value.[74] *Neurogenic Bowel Dysfunction Score (NBDS)*: the NBDS is a measure of both constipation and faecal incontinence in the SCI population.[75] This questionnaire comprises 10

questions focusing on defecation (ie, frequency, duration and clinical symptoms), constipation (ie, use of aiding medication and digital stimulation) and faecal incontinence (ie, frequency, aiding medication and flatus; and peri-anal skin problems. The consequential NBDS relates to four different neurogenic bowel dysfunction severity levels. *The International Index of Erectile Function (IIEF-15) (male participants)*: comprises of 15 questions covering five domains, including erectile function, orgasmic function, intercourse satisfaction and overall satisfaction.[76] The Female Sexual Function Index (FSFI) (female participants) is comprised of 19 questions covering six domains, including desire, arousal, lubrication, orgasm, satisfaction and pain.[77] A sexual health clinician, with experience providing clinical care to individuals with SCI, will also conduct a semistructured one-on-one interview, to capture the nuances of the subjective experiences of how their sexual functioning has changed over the course of the intervention. This interview will only be conducted on trial completion.

Health-related quality of life

Fatigue, spasticity, pain and quality of life

The Fatigue Severity Scale is a 9-item questionnaire, which captures how fatigue interferes with certain activities of daily living and is accompanied by a global fatigue visual analogue scale.[78] The Spinal Cord Injury-Spasticity Evaluation Tool consists of 35 questions regarding both the problematic and useful effects of spasticity on daily life in the past 7 days.[79] The International SCI Pain Basic Data Set V.2 determines the intensity and location of pain, and the subsequent impact of that pain interference on different domains of life.[80] The Short Form (36) Health Survey is a validated questionnaire to assess HRQoL. Precoded numeric values for each item were transformed into a score, ranging from 0 to 100, while also accounting for items that were negatively scored. Items in the same scale were then averaged together to create eight subscales: four represent physical quality of life (Physical Component Summary) and four represent emotional quality of life (Mental Component Summary).[81]

Statistical analysis

We will use an intention-to-treat analysis to draw accurate and unbiased conclusions regarding the effectiveness of our intervention. All assumptions for statistical tests are evaluated before use of the test and corrected if necessary and possible. Outcome measures will be assessed by a two-way repeated measures ANOVA with the aim to determine the effect of time (ie, baseline vs 12 weeks vs open-label 12 weeks), group (ie, LT+TSCS vs LT+Sham stimulation) and the time × group interaction. Should any tests for normality fail, non-parametric testing (ie, Kruskal-Wallis) will be used to compare preintervention to postintervention changes. Where an interaction effect is apparent, post hoc analyses will be performed (eg, Tukey HSD test or Wilcoxon signed-rank test). Standardised effect sizes (Cohen's *d*) will also be determined to quantify the difference in response magnitudes between groups. All comparisons will be conducted at the 0.05 significance level. All quantitative data from the semistructured interviews will be imported into NVivo V.11 software (QSR International, 2021) and analysed using thematic analysis.

Data management and safety

The investigators will take all appropriate measures to ensure that the anonymity of each participant is maintained by using deidentified data. The identification key linking participants to their study identifiers will be kept in strict confidence, with access restricted to appropriate study personnel. The data will be monitored by the Institute of Safety and Effectiveness Evaluation for the University. All versions of signed informed consent forms will be kept for the Health Canada regulated period of 25 years. Any adverse events reported during the intervention will immediately be reported to the Data and Safety Monitoring Committee (DSMC), which is comprised of three external, independent physician scientists with no involvement in the study, as well as the appropriate ethics board. The DSMC is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring the overall conduct of the clinical trial.

Patient and public involvement

Patient surveys have revealed higher priorities given to the recovery of sexual function, BP, bowel and bladder when compared with the restored ability to walk.[5] Furthermore, the conceptualisation of this study was driven by a collaboration with community-dwelling individuals living with SCI. Moreover, the research team for this project has a well-established track record of collaboration with the SCI community, evidenced by the completion of numerous research studies and engagement events. Therefore, we have included extensive autonomic function testing and patient-reported HRQoL measures as exploratory outcomes in this study. Extensive, individualised feedback will be provided to each participant on completing the trial. The future sustainability and potential expansion of this proof-of-principle trial will be ensured by applications to national and international funding agencies to run a larger, multicentre clinical trial. We will seek patient and public involvement in the development of an appropriate method of dissemination.

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki and is consistent with the International Conference on Harmonisation Good Clinical Practice Guidelines, as well as applicable regulatory requirements. Version 10.0 of this protocol was approved by the UBC Clinical Research Ethics Board on 13 October 2022 (UBC CREB H20-01307). Each protocol revision requires ethics approval. The results of this trial will be presented at national and international conferences and will be published in peer-reviewed journals. Written

informed consent will be obtained from all participants prior to publication of data from this study. All subsequent manuscripts will be reported in conjunction with the Consolidated Standards of Reporting Trials.[66] Additionally, a summary of the trials findings will be posted on the ICORD website and in magazines published by service organisations for people with SCI in the BC province where participants were recruited (ie, SCI BC magazine).

Study status

Protocol V.11.0, 6 December 2022. Trial recruitment was initiated on 22 July 2022 with an approximate recruitment completion date in June 2024.

Author affiliations
[1]International Collaboration on Repair Discoveries, Department of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada
[2]Department of Medicine, Division of Physical Medicine and Rehabilitation, The University of British Columbia, Vancouver, British Columbia, Canada
[3]School of Kinesiology, The University of British Columbia, Vancouver, British Columbia, Canada
[4]Division of Cardiology, The University of British Columbia, Vancouver, British Columbia, Canada
[5]Department of Physical Therapy, King Fahad Medical City, Riyadh, Saudi Arabia
[6]GF Strong Rehabilitation Centre, Vancouver Coastal Health Authority, Vancouver, British Columbia, Canada
[7]Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia, Canada
[8]Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada
[9]School of Sport, Exercise and Rehabilitation Sciences and Centre for Trauma Science Research, University of Birmingham, Birmingham, UK
[10]Centre for Trauma Science Research, University of Birmingham, Birmingham, UK

Twitter Shane JT Balthazaar @ShaneBalthazaar and Thomas E Nightingale @Tnightingale10

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Contributors AK conceived the study and is the principal investigator who will oversee data collection. CS is responsible for running the study, collecting, and managing data. The study is conceived with expert support and input from SE, TN, TL, RS, MB, SJTB, AA and AK. CS, SS, TM, RM, SJTB and AMMW are responsible for data collection. All authors will be involved in data analysis and preparation of various outcome measures manuscripts. CS and AK wrote this protocol manuscript, the final version of which all authors have reviewed and approved.

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ORCID iDs
Claire Shackleton http://orcid.org/0000-0002-5042-1490
Soshi Samejima http://orcid.org/0000-0003-3796-8085
Tania Lam http://orcid.org/0000-0002-5782-2537
Andrei V Krassioukov http://orcid.org/0000-0002-0022-7972

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