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Lessons learned from the pilot study of an orthostatic hypotension intervention in the subacute phase following spinal cord injury

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Abstract

Context: Following spinal cord injury (SCI) at the cervical or upper-thoracic level, orthostatic hypotension (OH) is observed in 13 to 100% of patients. This study aimed to test the feasibility of conducting a randomized controlled trial combining a dynamic tilt-table (Erigo®) and functional electrical stimulation (FES) to mitigate OH symptoms in the subacute phase after SCI.

Design: Pilot study.

Setting: A tertiary rehabilitation hospital.

Participants: Inpatients who had a C4-T6 SCI (AIS A-D) less than 12 weeks before recruitment, and reported symptoms of OH in their medical chart.

Interventions: Screening sit-up test to determine eligibility, then 1 assessment session and 3 intervention sessions with Erigo® and FES for eligible participants.

Outcome Measures: Recruitment rate, duration of assessment and interventions, resources used, blood pressure, and Calgary Presyncope Form (OH symptoms).

Results: Amongst the 232 admissions, 148 inpatient charts were reviewed, 11 inpatients met all inclusion criteria, 7 participated in a screening sit-up test, and 2 exhibited OH. Neither of the 2 participants recruited in the pilot study were able to fully complete the assessment and intervention sessions due to scheduling issues (i.e. limited available time).

Conclusion: This pilot study evidenced the non-feasibility of the clinical trial as originally designed, due to the low recruitment rate and the lack of available time for research in participant's weekday schedule. OH in the subacute phase after SCI was less prevalent and less incapacitating than expected. Conventional management and spontaneous resolution of symptoms appeared sufficient to mitigate OH in most patients with subacute SCI.

Key-words:

feasibility; spinal cord injury; orthostatic hypotension; tilt-table; electrical stimulation

Lay summary (not part of the accepted peer-reviewed publication):

After an injury of the spinal cord (such as breaking the neck or the back during a car accident), some persons are not only paralyzed but also have trouble with low blood pressure during certain movements (similar to being lightheaded when standing up quickly). Therapists can use a "tilt-table" (a table that tilts from horizontal towards the vertical), to measure and train these people's body to tolerate a more vertical position. The more vertical the table, the harder it is for these persons who have low blood pressure, and it needs to be done slowly or else they may get dizzy, sick, or even faint.

A possible technique to reduce this problem is to put electrodes on the legs to make the muscles contracts with electricity (stimulation), while making the legs move with a type of robotic tilt-table called Erigo. Some research done before suggested it could help people with spinal cord injury to have improved blood pressure when moving with a tilt table. This is why researchers wanted to answer the following question:

Does repeated training with the stimulation and the robotic tilt-table allow these patients to tolerate a more vertical position without having low blood pressure? *(meaning, standing up without being lightheaded).*

To answer this question, a big study was necessary, with a total of 32 participants. So before starting this big study, a small study was organized to see if it was even possible to find enough participants, and if these participants had enough time to take part in the study activities.

In 10 months, while 232 persons arrived in our rehabilitation hospital (typically a few days or a few weeks after being injured), only 2 of them met all the conditions to participate in the study, while 230 didn't participate for the following reasons:

- *34 persons were not seen by researchers because nurses and doctors decided it wasn't a good idea;*
- *50 persons didn't want to hear about research or didn't want researcher to read their medical files;*
- *123 persons did not have this problem of dizziness due to low blood pressure during movements;*
- *14 persons did not have the good type of injury and/or were younger than 18 years old;*
- *4 persons could have participated in the study but preferred not to;*
- *5 persons did the first part of the study, early in the morning, before taking their medicine, and didn't show any or enough problem with low blood pressure, even though they were being quickly seated in their bed after a night lying down (technique used to provoke the same type of light-headedness or dizziness that non-paralyzed people can have when standing up too quickly).*

The 2 persons who did have problem of low blood pressure when moving did a part of the activities of the study, but it was very difficult to find time for the research because they had little time available between their care with the nurses, the physiotherapists, their medical appointment, etc.

Because it was so difficult to do the small study, it was decided that we shouldn't do the big study. Indeed, it isn't a good use of time and money to try to do a study if there are not enough participants at the end. That is because researchers cannot answer their scientific or medical question if there is a small number of participants (they wouldn't know if their results were due to chance or not).

This was however a learning experience that could help other researchers make better studies in the future and better understand the problems of low blood pressure in the first weeks after an injury of the spinal cord.

Introduction

Spinal cord injury (SCI) above the T6 level may result in damage to the autonomic nervous system[1] and subsequently result in compromised blood pressure control. Orthostatic hypotension (OH) is defined as a decrease in systolic blood pressure of more than 20 mmHg or in diastolic blood pressure of more than 10 mmHg when moved from a supine to upright posture, regardless of whether symptoms occur.[1] Symptoms may include dizziness, nausea, pallor, sweating, light-headedness, or faintness. Incidence of OH after SCI has been reported to be 13 to 100% depending on the methodology used, the severity considered, the time since injury, and the level of the injury; albeit the frequency and severity being higher in the earlier phases, higher level of SCI, and in motor complete injuries.[2–5] OH can severely impact quality of life due to the fatigue and/or syncope interfering with daily activities (e.g. required interruption to recover), and the risk of fall.[6] OH can also prevent some patients from actively participating in their rehabilitation.[3] However, intensive rehabilitation is critical in the early phase after SCI to reduce secondary consequences such as muscle atrophy and to improve physiological abilities.[7,8] In the long run, hypotension and reduced cerebral blood flow are related to reduce cognitive functions in individuals with SCI.[9]

Among the various approaches to mitigate OH, midodrine and functional electrical stimulation (FES) of the lower-limbs muscles (quadriceps, triceps surae, hamstrings, and tibialis anterior) have the highest level of evidence.[10] Midodrine[11] is an alpha-1-adrenergic agonist drug, now commonly used in clinical practice, that increases peripheral vascular resistance.[12,13] FES can be used to activate the physiologic muscle pump via intermittent muscle contractions; however, it is not routinely used. Another intervention clinically recommended to treat OH is incremental exposure to orthostatic stress using tilt table.[14,15]

FES can upregulate blood pressure during exposure to orthostatic stress with a tilt table in individuals with acute or chronic SCI.[16–19] The Erigo, a tilt-table executing passive stepping movements (Figure 1) showed promising results to increase blood pressure during head-up tilt in individuals with chronic SCI, isolated or associated with FES.[20] However, it is still not known if the combination of tilt table and FES has a superior training effect on OH, compared to tilt-table training alone.

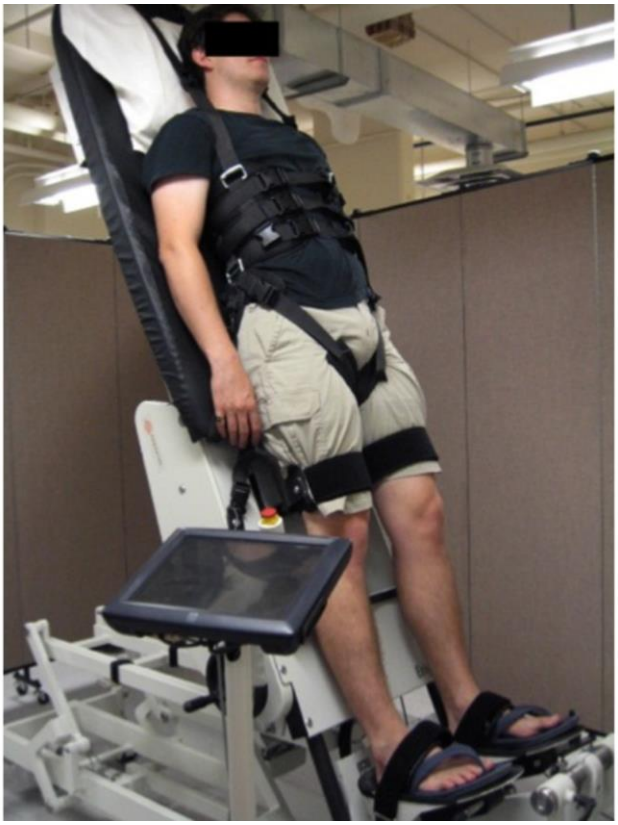

Figure 1: Erigo tilt-table (Hocoma, Switzerland)

Context of the Pilot Study

We designed a randomized controlled clinical trial to test the training effect of FES+Erigo tilt-table therapy (intervention) as compared to the tilt-table alone (control) on the control of blood pressure in patients with SCI suffering from OH. The interventions were to be conducted 3 to 5 times per week for 4 weeks, with 1 weekly sit-up test, 1 final evaluation, and a follow-up 1 month after the last intervention.

Based on a planned effect size of 8mmHg of improvement on diastolic blood pressure change during a sit-up test,[21] a standard deviation of 8 mmHg,[15,21,22] alpha and beta risks of 0.05 and 0.2, respectively, a sample size of 16 participants in each group[23] (32 total) was necessary to power the clinical trial (Microsoft Excel):

$$n = \frac{(Z_{\frac{\alpha}{2}} + Z_{\beta})^2 \ * 2\ standard\ deviation^2}{effect\ size^2} = \frac{2 * (1.96 + 0.8416)^2 * 8^2}{8^2} = 16$$

Before initiating this randomized controlled trial, it was decided to conduct a pilot study in 3 participants to test the feasibility of recruitment[24,25] and identify barriers to trial execution.

Methods

This pilot study was approved by the Research Ethics Board of the University Health Network (Toronto, ON, Canada). The study was conducted in a tertiary hospital specialized in subacute SCI rehabilitation (Lyndhurst Centre, Toronto Rehabilitation Institute, Canada).

Recruitment

Recruitment occurred over 45 weeks between June 2017 and May 2018. The inclusion criteria were: Hospitalization as inpatient in this tertiary hospital; First SCI less than 12 weeks prior to joining the study; AIS Impairment Scale A to D; Neurological level of injury C4-T6; reported OH (see below); and age ≥ 18. The exclusion criteria were conditions precluding safe participation, such as non-consolidated lower-limb fracture, dementia, chronic renal failure, pregnancy, or implanted electronic devices.

Recruitment was led by a central recruiter, as follow:

(1) The patient's clinical circle of care team evaluated the patient's cognitive and language capacity for engaging in a conversation and participating in research.

(2) If deemed suitable, the patient was given a Research Interest Form, which has three Yes-or-No questions: having their health chart reviewed for eligibility, meeting with a research representative, and being contacted after discharge about future research studies.

(3) If the patient indicated 'Yes' to chart review and meeting the representative, then the health chart was reviewed.

(4) If the patient met inclusion/exclusion criteria, the central recruiter introduced this pilot study to the patient.

(5) If the patient expressed interest, they were introduced to the study coordinator to conduct the informed consent process.

(6) Once signed consent was obtained, the study coordinator organized the screening test to verify eligibility.

During chart review, if midodrine was prescribed to the patient, "reported OH" was noted. If there was no prescribed midodrine but OH was indicated in the Pharmacist's notes, the central recruiter asked the clinical team whether the symptoms persisted (i.e. hypotension managed without midodrine) or had resolved already.

Screening test

To validate the presence of OH, patients who signed consent (pilot participant, PP) completed a screening test, a short version of the sit-up test[21], performed in their bed early in the morning before medication, mobilization, and breakfast, to increase the chance to detect OH. Before the sit-up test, participants were asked to describe the number, context, and intensity of hypotension events, in the preceding 24h, using a visual version of the Calgary Presyncope Form (Figure 2).[26] The function of the form and the meaning of each number were extensively explained.

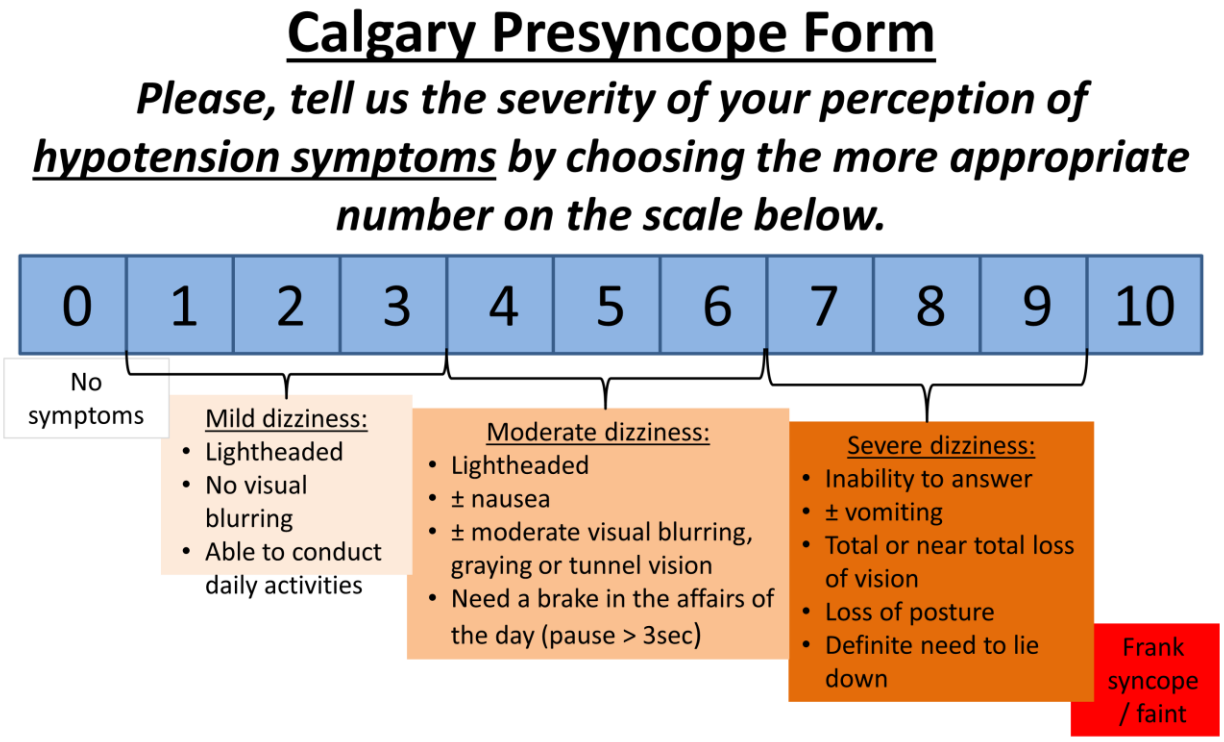

Figure 2: Visual numeric scale version of the Calgary Presyncope Form used to measure orthostatic hypotension symptoms.

Before and during the sit-up test, participants were asked to quantify their symptoms in real-time with this form. Blood pressure was measured at baseline, in a lying position, with an automated blood pressure arm cuff (CARESCAPE V100 Monitor, EG Health Care, USA) and OH symptoms were recorded with the Calgary Presyncope Form. Then the participant was passively positioned in a seated position and blood pressure and OH symptoms were recorded each minute for up to 5 minutes until OH was measured, or until the participant's symptom required them to lie down.

Pilot study

Participants who qualified for the study participated in 1 assessment and 3 intervention sessions. To test for feasibility, the assessment and intervention sessions were conducted in the same manner as planned for the randomized controlled trial.

The assessment session was comprised of a Spinal Cord Independence Measure questionnaire[27], a 25-minute sit-up test[21], and bilateral measure of quadriceps thickness (ultrasound imagery[28]) and strength (hand held dynamometer[29]). For the quadriceps thickness, images of the anterior thighs (rectus femoris and vastus lateralis muscles) were obtained using real-time B-mode ultrasound imaging (ACUSON S2000, Siemens Medical Systems, Germany). Muscle thickness and strength assessments were included to determine whether changes in orthostatic symptoms were related to muscle size and/or function changes, and to identify secondary benefits from the intervention.

The intervention sessions consisted of 30 minutes of incremental orthostatic stress using the Erigo® (Hocoma AG, Switzerland), a tilt-table with motors that mobilize the lower-limbs in a walking-like pattern, in combination with FES of the knee and ankle muscles[20]. FES was delivered at 40Hz (pulse duration 400μs) using Compex Motion stimulator (Compex SA, Switzerland) and Axelgaard surface electrodes (5×5cm or 5×9cm) to the quadriceps, hamstrings, ankle dorsi-flexors, and ankle plantar flexors.

During the complete sit-up test and the interventions, participant's blood pressure was monitored intermittently with an automated arm cuff and continuously with an automated finger cuff (Finometer MIDI, Finapres Medical Systems, The Netherlands).

To test the feasibility of the designed clinical trial schedule, the research coordinator tried to book 1 assessment (1.5 hour, once), and 5 interventions per week (1 hour each, 1/day, Monday-Friday) in the participants' schedule (although only 3 sessions were necessary for the pilot study).

Results

Over 45 weeks, 148 inpatients had their charts reviewed to determine eligibility (64% of 232 new patients admitted, Figure 3), 11 met inclusion criteria, 7 consented to participate in the screening test (Table 1), and only 2 were eligible to take part in the pilot study (measured OH, Figure 4).

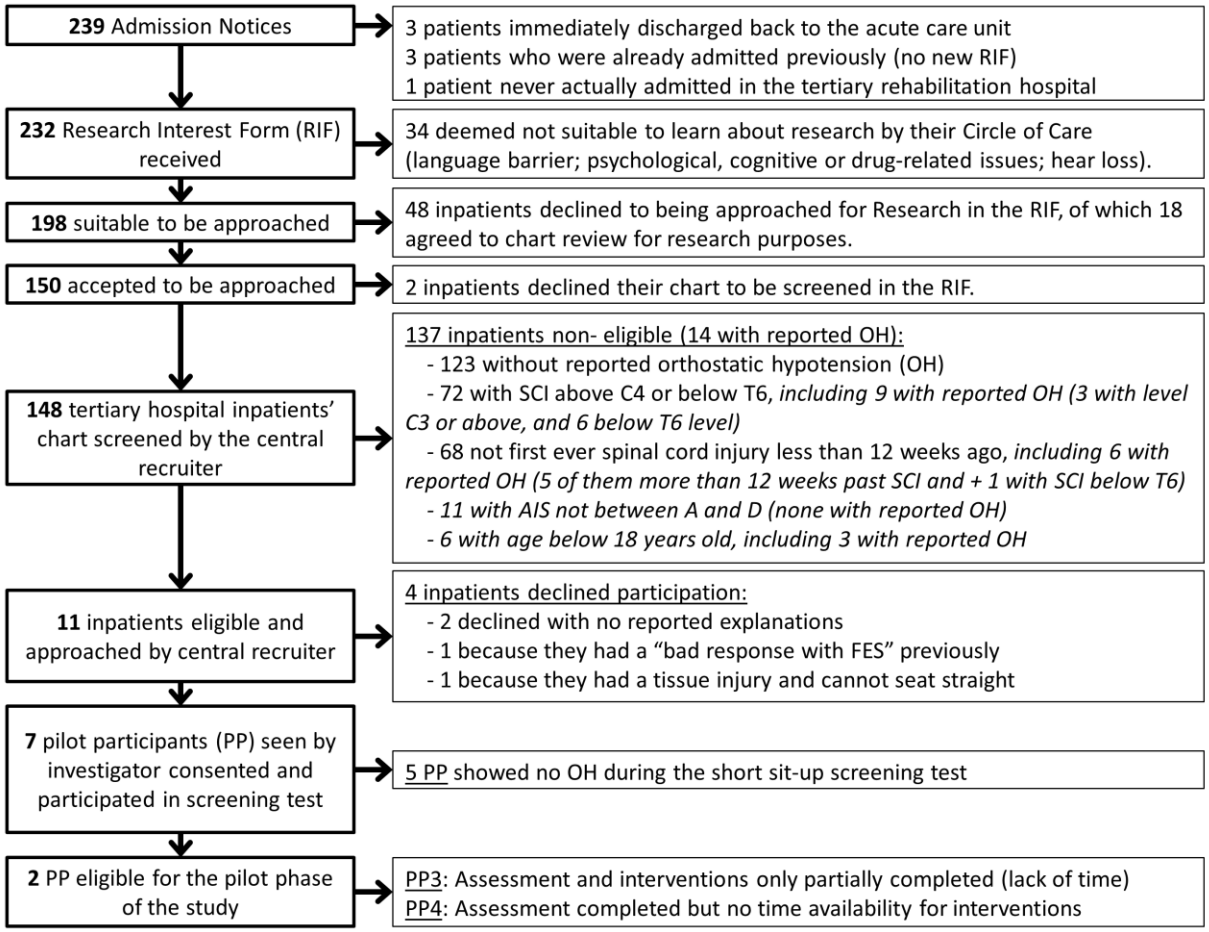

Figure 3: Flow chart of patient recruitment. AIS: American Spinal Injury Association Impairment Scale

Orthostatic hypotension analysis

OH was reported in 25 inpatients (17% of reviewed charts), but only 11 were eligible; meaning that 14 inpatients with reported OH were ineligible, due to the following criteria:

- SCI under the T6 level: n=6;
- SCI more than 12 weeks prior (2.9 to 11 months prior): n=4
- SCI above the C4 level: n=3
- Age below 18: n=1

ID	Age	Sex	Injury	Cause	Delay (days)	# past OH	CPF past OH (0-10)	Description of past Orthostatic Hypotension context	OH during short sit-up screening test
PP1	34	F	C5 AIS-D	Non-trauma	20	1	1	*"I need to move slow with the physio"*	*NO*
PP2	57	F	T6 AIS-A	Trauma	68	0	0	-	*NO*
PP3	56	F	T3 AIS-A	Trauma	78	0	0	-	*YES*
PP4	69	F	C4 AIS-C	Trauma	51	2	4	*"When transferring in wheelchair, until tilting it backward. And when lifting the back rest of the bed 40 deg."*	*YES*
PP5	57	M	C6 AIS-D	Trauma	68	2	4	*"When I get out of bed"*	*NO*
PP6	69	F	C4 AIS-C	Trauma	41	4	4	*"I get cramps after being in wheelchair for long time."*	*NO*
PP7	54	M	C4 AIS-C	Trauma	34	3	2 to 3	*"When turning on right side in my bed"*	*NO*

ID: patient identifier; PP: pilot participant;F: female; M: male; Delay: time since injury. # past OH: number of Orthostatic Hypotension event in the past 24 hours. CPF past OH: Severity of the presyncope symptoms during the Orthostatic Hypotension events in the last 24 hours (from 0 – no dizziness – to 10 – syncope).

Table 1: Participant's information

Among the seven participants who did the screening sit-up test, questioning with the Calgary Presyncope Form revealed inconsistent attitudes toward their symptoms (Table 1, Figure 4):

- three described context inconsistent with OH definition (i.e. not related to a change in position, for PP1, PP6, and PP7; Table 1),
- two reported no OH in the preceding 24 hours (PP2 and PP3; although PP3 had OH during the test),
- and two described OH context consistent with OH definition (i.e. related to a change in position PP4 and PP5, although PP5 had no measured OH during the test).

Despite the absence of measured OH, PP2, PP5, and PP7 expressed a transitory increase of presyncope symptoms (mild presyncope) just after the sit-up movement (Figure 4).

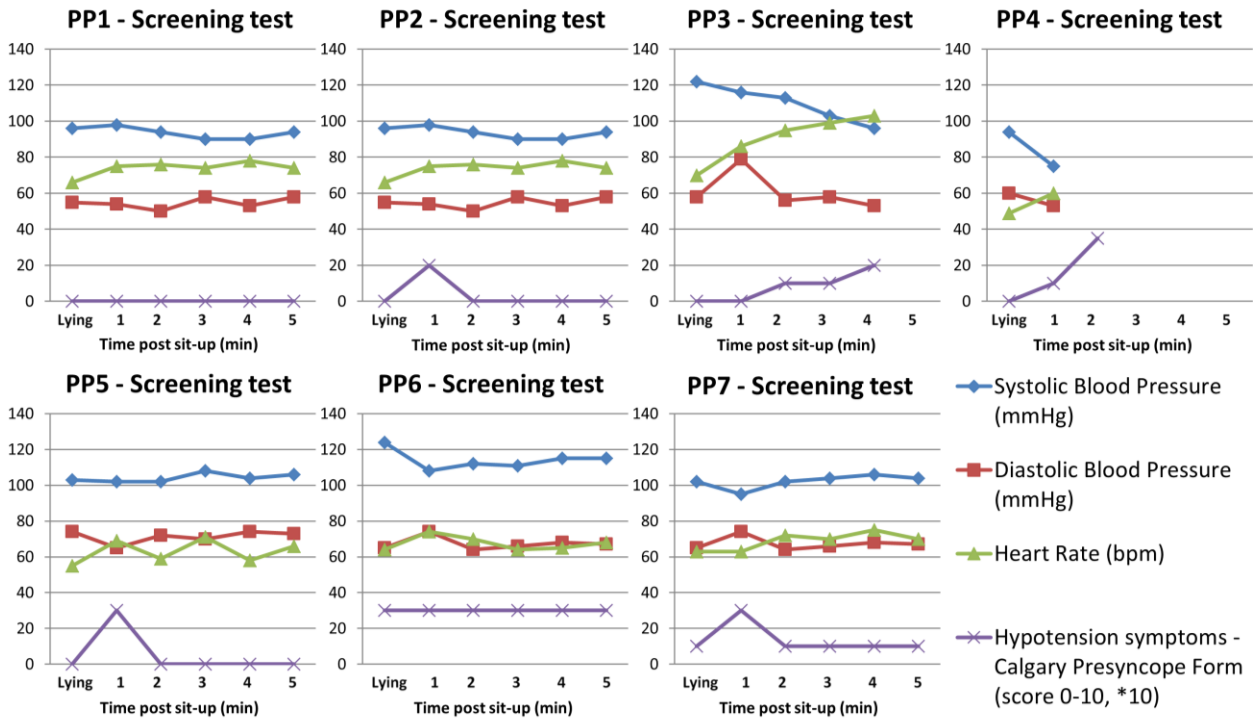

Figure 4: Blood pressure, heart rate, and presyncope symptoms severity during the screening sit-up test. The X-axis is the time in minute, starting once the participant is seated in the bed. The lying measurement is the baseline measurement from which orthostatic hypotension is defined.

During the screening sit-up test PP3 reported only mild dizziness (Figure 4), although she had difficulty paying attention and focusing her eyes at the end of the test. PP4 exhibited a quick decrease in blood pressure but the second measurement after sit-up failed due to lack of

measurable signal (typical when blood pressure is low), while she simultaneous asked to lie down due to OH symptoms.

During the full sit-up test, with medication, PP3 and PP4 experienced OH, after 8 and 9 minutes, respectively. They described none or minimal OH symptoms and their blood pressure recovered before the end of the test (Figure 5).

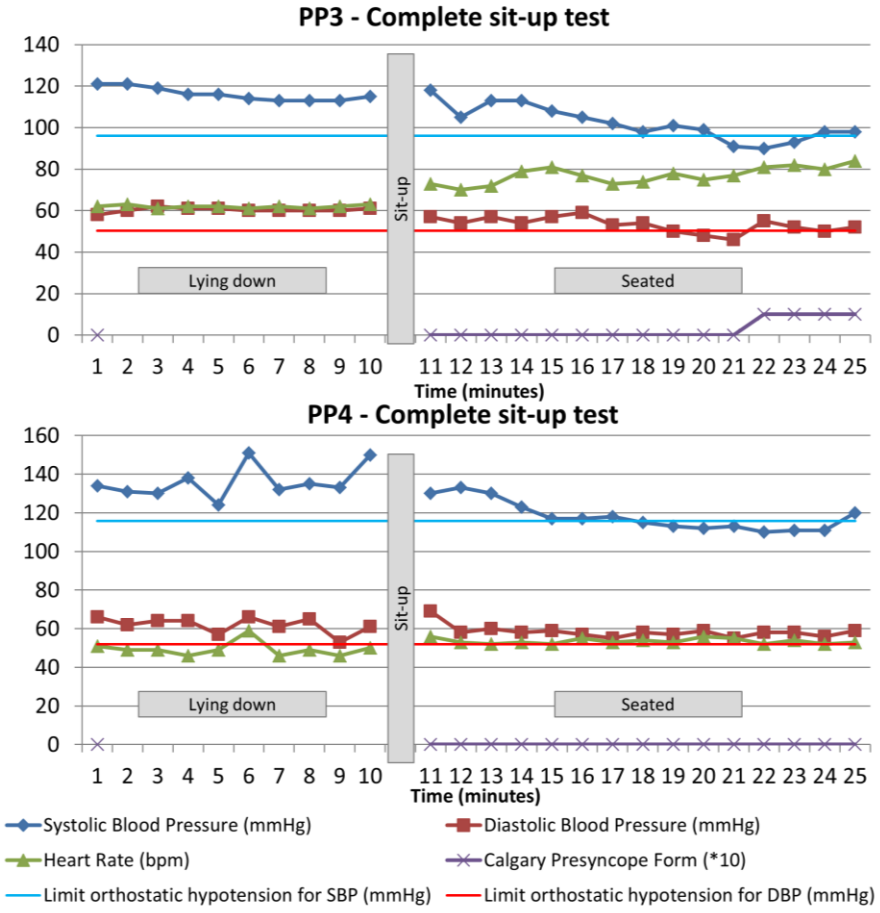

Figure 5: Blood pressure, heart rate, and presyncope symptoms severity during the complete sit-up test. The X-axis is the time in minute. The blank between 10 and 11 minutes marks represents the transition from lying to sitting position. Orthostatic hypotension threshold is defined based on the average of blood pressure values during the 10 minutes in lying position.

During intervention, PP3 exhibited transient OH and recovery as the tilt table angle increased and decreased, respectively (Figure 6). PP3 did not report OH events during the 24

hours before any of the 3 intervention sessions, except 1 event rated at 1/10 on the Calgary Presyncope Form.

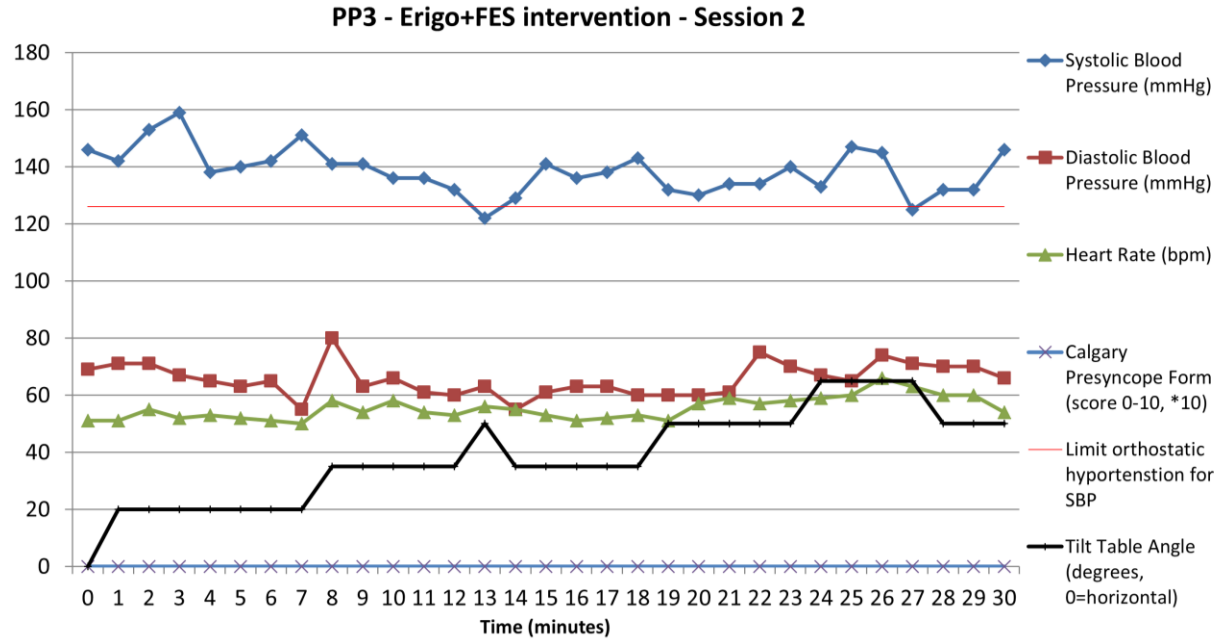

Figure 6: Blood pressure, heart rate, and presyncope symptoms severity during the second intervention session with the Erigo® and functional electrical stimulation. Orthostatic hypotension threshold is defined based on the baseline blood pressure values, in lying position, at t=0.

Feasibility analysis

The screening sit-up test in bed took 15 to 20 minutes, did not interfere with the usual care (nurses were informed ahead of time), and presented no technical or organizational difficulties. Two research personnel were required for the screening test: one for executing the sit-up and one to take notes and help as needed. The passive supine-to-sit transfer can be executed by one person, if they are properly trained.

The assessment and intervention sessions, 1.5 hours and 1 hour respectively, were difficult to plan due to the lack of availability in participants' weekday clinical schedule (e.g. dependent upon nurses to get ready in the morning, concentrated rehabilitation sessions in the afternoon, additional medical exams in remaining time slots, etc.). For PP3, it took 5 weeks to complete 1 assessment session and 3 intervention sessions. For PP4, the assessment session was

done 6 days after the screening test, but it was not possible to schedule the intervention sessions in the three weeks following. The assessment session was completed in 1h 50 minutes without difficulty with PP4, but could not be completed within the assigned time for PP3 due to an initial delay and difficulty with the finger blood pressure cuff during the sit-up test (lack of signal due to reduced blood circulation in hands).

For PP3, the first intervention session could not be fully completed (due to time required to define the appropriate Erigo set-up), the second session was completed (Figure 6), and the third session was not fully completed due to a baseline high blood pressure (166/87mmHg, without clinical signs of autonomic dysreflexia). The necessity to transfer participants using an overhead lift (from bed to wheelchair and then from wheelchair to the Erigo) and to have their bladder voided by a nurse before participation created additional delays in all research sessions. Three persons were required to ensure safety throughout the assessment and intervention sessions (e.g. position the head and legs properly during transfer, monitor the participant, take notes, etc.).

Due to these poor recruitment and feasibility results, the pilot study was interrupted before recruiting the 3rd participant.

Discussion

This pilot feasibility study, conducted in preparation of a randomized controlled clinical trial, evidenced that: 1) the number of inpatients admitted to this tertiary rehabilitation hospital, who met inclusion criteria and consented to participate was insufficient to meet the required sample size, and 2) eligible inpatients in this hospital did not have sufficient time available

outside of their rehabilitation schedule, during their rehabilitation stay, to take part in a trial requiring multiple evaluations and 3 to 5 interventions per week.

The previously reported high prevalence of OH (up to 100% if including the entire acute phase,[3] and up to 74% at 1 month following complete cervical SCI[5]) involved patients tested 1 to 45 days post-injury (mostly 1 to 20 days post injury[3,5]), while the participants in our screening test were 20 to 78 days post-injury. It is consistent with typical description of reduced OH prevalence over time[10]. The other study showing high prevalence of OH (57%) used a tilt-table test (60 deg head-up) to detect OH in patients that were 4 to 211 weeks post-injury and had their autonomic medication suspended the day prior to the study.[4] Using a tilt-table, considered the gold standard to detect OH,[21] may have allowed a more passive transition from supine to erect posture, resulting in a higher prevalence of OH. Our lower prevalence (17%) is consistent with a previous study using a similar identification method[2] (13% OH prevalence, identified through the prescription of ephedrine, their standard OH-management drug then).

There were few participants' complaints related to OH in our study, compared to previous reports.[3,5] This might be because midodrine was not typically prescribed at the time these studies were conducted. Indeed, use of midodrine in patients who sustained a SCI was documented as case reports from the 1990's[30,31] up to 2001.[12] One study specified that midodrine was not prescribed for patients in their study during the time they were monitored, i.e. the first month following SCI.[5]

The recruitment may have been higher without exclusions of: time post-injury greater than 12 weeks (although OH prevalence reduces as time from injury increases); age less than 18 (although a different consent process is required), and level of injury higher than C4 (although there are additional safety concerns with patients having limited neck control). Inclusion could

have been expanded to SCI below the T6 level, although the pathophysiological mechanism would be different because the autonomic system is typically not impacted below T6. Also, a third of inpatients could not be approached for research due to patient decision or clinician judgment (Figure 3).

Relying on the OH reported in medical charts as an inclusion criteria may have resulted in under-recruitment, i.e. limited to the symptomatic OH. However, patients with asymptomatic OH are unlikely in need of more interventions to upregulate blood pressure.

Midodrine was typically given to patients during breakfast and lunch so that peak concentration coincided with their time in an upright posture (wheelchair and rehabilitation). It was thus hypothesized that testing participants after lying down for an entire night (19-20 hours after last drug intake, with metabolite reaching peak blood concentrations 1-2 hours after midodrine intake and having a half-life of about 3 to 4 hours[11]), before taking medication, and before engaging in physical activity, would allow a high sensitivity for the detection of OH. The screening test used in this study (i.e. sit up test) seemed to be a feasible method (for researcher trained in supine-to-sit transfer technique) to exclude individuals not actually exhibiting OH, but may have been less sensitive than a tilt table. The specificity of this screening test was confirmed by the long version of the sit-up test where both study participants exhibited OH, despite their medication.

Overall, our criteria may have been too strict to allow sufficient inclusion. However, even eligible patients were unable to fully participate in the pilot study due to lack of time (insufficient time slots per week and available time slots being too short). Even though they were compromised by OH, the therapists scheduled activity that would not trigger hypotension (e.g. stretching in the wheelchair). The availability of a sufficient number of target population for

receiving additional treatments should be explored before developing said treatments. A different research approach seems necessary; otherwise no new rehabilitation technique can be developed for individuals at such early stage of rehabilitation.

Interventions occurring in the acute or subacute phase following a neurological injury, where the spontaneous evolution of patient's abilities introduces more variability, typically require a bigger group and/or a higher effect size to demonstrate efficacy[32];

Engaging inpatients in an interventional clinical trial, particularly those dependent upon caregivers for fundamental aspects of care (feeding and toileting), is challenging due to their limited time availability. Possible solution to these barriers could be: 1) interventions that do not require a lot of time per delivery and/or few repetitions (e.g. medication, information, equipment); 2) interventions that are conducted during scheduled therapy (i.e. coordination with clinicians); and 3) interventions that can be delivered during off-hours (e.g. after dinner, during the weekends).

This pilot study answered the feasibility question at a minimum cost (before engaging specific personnel), and without impacting the normal course of daily care. A lesson learned from this pilot study is that this condition might be too rare at the subacute stage to conduct a proper randomized controlled clinical trial: 32 participants were needed for the sample size and only 2 participants were recruited in 11 months At such a rate it would take about 15 years to complete the study.

The recruitment challenges identified in the present study are part of a trend described in an ongoing review of SCI clinical trial recruitment[33]. Possible solutions to these challenges include attention to organizational practice patterns, and improvements in clinical trial design, sensitive outcome measures and additional surrogate markers. To improve recruitment in SCI

clinical trials, several initiatives are currently underway. Five STUDI CRCs (Spinal Trials, Understanding, Design and Implementation Critical Review Committees) have organized guidance documents intended for publication and dissemination. Specifically, manuscripts focusing on recruitment, protocol design and outcome assessments (Bio-markers, Electro-physiology and Neuro-imaging) are in progress. Specifically, the SCITT CRC (Spinal Cord Injury Trials Toolbox Critical Review Committee) conceptualized an online platform (SciTrials.org) that directly connects willing participants to clinical trial investigators (though this initiative would not help trials targeting the acute or subacute stages). These initiatives aim to improve the quality, accessibility, feasibility and efficiency of clinical trials involving individuals living with spinal cord injury.

Limits

Despite the study coordinator explaining extensively what the Calgary Pre-Syncope Form was measuring, it seemed that not all participants understood it correctly. The reason may have been the participants' lack of familiarity with sensations resulting from their recent injury: some rated symptoms not related to OH (e.g. cramps), while others down-rated symptoms that were clearly related to OH (e.g. loss of focus following changing position). As a consequence, researcher should be aware that research participants might not be knowledgeable about their condition, particularly early after injury.

This Calgary Pre-Syncope Form was selected because it expressed the overall symptomatic state of the person with a single number and verbally (as opposed to a Visual Analog Scale[34]). Another tool, such as the OH Questionnaire[35] may have captured more accurately the symptom during the preceding 24 hours, but it would not have worked for the real-time quantification of symptoms during the sit-up test and interventions.

Measuring blood pressure only once per minute with the automated blood pressure cuff may have resulted in missing transient OH. However, there would be little justification for engaging patients in a time intensive rehabilitation procedure aiming to mitigate OH lasting less than 1 minute and producing few symptoms.

Conclusion

This pilot study evidenced the non-feasibility of the clinical trial as designed, due to the time constraints and very high screening-to-recruitment ratio. It provides two recommendations: doing a realistic estimate of the target condition frequency at the study site, and tailoring the interventions to fit within an inpatient's busy schedule. An alternative method to run the proposed clinical trial, if clinically and institutionally acceptable, would be to execute the trial's intervention during their regular rehabilitation session, in order to not take away any therapeutic time. A multi-centric design and/or broader inclusion criteria could also facilitate recruitment.

OH in the subacute phase after SCI was less prevalent and incapacitating than expected, making the recruitment challenging. Conventional management (e.g. medication, binders, and adapted rehabilitation exercises) and symptoms' spontaneous resolution may be sufficient to mitigate OH during inpatient subacute rehabilitation in a majority of patients who sustain an SCI. New OH intervention might be more warranted in the acute phase.

Conflict of Interest:

Milos R Popovic is CTO, co-founder and Director of MyndTec Inc., a company manufacturing stimulators for functional electrical stimulation.

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