Author’s response to reviews

Title: Exoskeleton-assisted Gait Training to Improve Gait in Individuals with Spinal Cord Injury: A Pilot Randomized Study

Authors:

Shuo-Hsiu Chang (shuo-hsiu.chang@uth.tmc.edu)

Taimoor Afzal (Taimoor.afzal@uth.tmc.edu)

TIRR SCI Clinical Exoskeleton Group TIRR SCI Clinical Exoskeleton Group (marcie.kern@memorialhermann.org)

Jeffreý Berliner (Jeffreý.Berlíner@memorialhermann.org)

Gerard Francisco (Gerard.E.Francisco@uth.tmc.edu)

Version: 1 Date: 14 Sep 2017

Author’s response to reviews:

Dear Editor,

We would like to thank the reviewers for their thoughtful review of the manuscript. They raise important issues and their inputs are very helpful for improving the manuscript. We are very excited to have been given the opportunity to revise our manuscript. We agree with almost all their comments and we have revised our manuscript accordingly. We are confident that the new version of the manuscript will be greatly improved.

We respond below to each of the reviewer’s comments. We hope that the reviewers will find our responses to their comments satisfactory, and we are willing to finish the revised version of the manuscript including any further suggestion that the reviewers may have.

Please, find below the reviewers’ comments repeated in italics and our responses inserted after each comment. To facilitate the work of the reviewers, we refer to the revised manuscript indicating the page and line number.
Looking forward hearing from you soon.

Sincerely,

Shuo-Hsiu (James) Chang

Response to comments from Anonymous Reviewer #1

1. "Exoskeleton-assisted Gait Training to Improve Gait in Individuals with Spinal Cord Injury: A Pilot Randomized Study" is a welcome study in the emerging new technology based rehabilitation for spinal injury

The report of this Pilot study is consistent with the Standards of CONSORT Extension 2010 Statement regarding Pilot & Feasibility studies, Table 2

https://urldefense.proofpoint.com/v2/url?u=https-3A__pilotfeasibilitystudies.biomedcentral.com_articles_10.1186-s40814-2D016-2D0105-2D8&d=DwIGaQ&c=6vgNTiRn9_pqCD9hKx9JgXN1VapJQ8JVoF8oWH1AgfQ&r=alxEtV2y yqDOAEC-HNbi1aYAfvE2HajLqKQ1neTvmH8&m=qKQ9z6xRgnfzgHOhofALJoIA4ZtBJILDpD73Vaz7F M8&s=tZ9XAg0BV6lWuYfMD6ZFo0cxS7zy7rWpoPVfQRkCxQ&e=

However, the authors did not mention the rationale of the number of patients included in this study. I accept it's not possible to demonstrate any statistical calculation of the sample size.

Scientific background and explanation of rationale for future definitive trial was well established by the authors. However, they could have articulated the reasons for a randomised pilot trial preceding a definitive RCT.

Response: As indicated by reviewer, we have included the rationale of the number of patients included in this study. The purpose of conducting this randomized pilot trial was to ascertain if
the complete procedure i.e. assessing patient eligibility, baseline assessment, randomization process, treatment reliability and post assessments could be conducted in a well-defined manner and estimate sample size (page 5, line 7). The initial target of the number of patients in the pilot study was 5 for each group. However, due to a number of reasons mentioned in the CONSORT diagram, only 7 participants completed the study. We wanted to look at the willingness of participants to be randomly assigned to different groups and whether or not they would be more inclined to be randomly assigned to the exoskeleton training group.

2. The entire cohort of patients was incomplete spinal injury. They could have explained the reason for excluding complete spinal injury since other exoskeleton trials in spinal injury included people with complete spinal injury. Reference: "Results of the first interim analysis of the RAPPER II trial in patients with spinal cord injury: ambulation and functional exercise programs in the REX powered walking aid". Journal of NeuroEngineering and Rehabilitation (2017)

DOI 10.1186/s12984-017-0274-6

https://urldefense.proofpoint.com/v2/url?u=http-3A__jneuroengrehab.biomedcentral.com_articles_10.1186_s12984-2D017-2D0274-2D6&d=DwIGaQ&c=6vgNTiRn9_pqCD9hKx9JgXN1VapJQ8JVoF8oWH1AgfQ&r=alxEtV2yyqDOAEC-HNbl1aYAfve2HajLqKQlnetvmH8&m=qKQ9z6xRgnfzgHOhofALJoIA4ZtBJILDPD73Vaz7FM8&s=L_W9tCktRGvIKeMejr1d0_gA1p_swxxFfWFBVhP6fmE&e=

Response: As mentioned by reviewer, we excluded complete spinal cord injury patients from our study. We have added the reasoning in the background section of the paper (page 4 line 49). Two major reasons to include only chronic incomplete spinal cord injury are:

i. Chronic individuals particularly >6 months post injury reach a stable level of recovery and any observed improvement from any intervention could be attributed to the intervention itself, unlike acute and subacute stage where the observed improvements could also be a result of spontaneous recovery.
ii. The focus of previous studies has been on examining the safety and clinical effectiveness of exoskeletons, therefore both incomplete and complete spinal cord injury population were included. However, the focus of our study is to examine the efficacy of training with exoskeleton on gait, therefore we have included only patients with incomplete spinal cord injury that have some preserved levels of gait and mobility.

3. Outcome Measures: The authors have used appropriate measures. However, there is an inaccuracy in reference 23 for Timed Up & Go test (TUG). Reference 23 is the study by Rossier P (2001) where they compared 4 outcome measures of mobility which did not include TUG. This needs to be corrected. Also, TUG is described as an indicator of risk of falls which is not accurate. TUG represents functional mobility and the authors’ choice of TUG is correct but not for the reason expressed by them. The risk of falls can be assessed by Berg Balance Score (BBS) or Modified Falls Efficacy Score. BBS has cut off values which reflect hierarchy risk of falls.

Response: The reference error regarding the TUG has been corrected. We have included the article (Podsiadlo D, Richardson S. The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. Journal of the American geriatrics Society 1991; 39: 142-8) as a reference. The reviewer’s suggestion that TUG represents functional mobility and not risk of falls has been corrected. We have removed the sentence relating TUG and risk of falls (reference 27).

4. Statistical analysis: Due to modest sample size of 9, no inter-group comparisons were attempted. However, it would be interesting to see any differences even if statistically insignificant. The stated hypothesis was exoskeleton group (EGT) will perform better than the Conventional group CPT.

Response: The inter-group comparisons have been included in the results section (abstract line 27, page 9 line 12, 30, page 10 line 32, 50, page 11, line 7).
5. The authors correctly identified the weakness of the study for having dissimilar baseline characteristics of the two randomised groups. The CPT group has better baseline functions as measured by the outcome scales used in this study. For example, the EGT group's endurance average score 50 m vis a vis CPT group's average 6 MWT of 147 m. No wonder, the CPT group couldn't improve much, relative to EGT group. Hence, statistical significance of the difference need to be considered with less enthusiasm. This could explain in Table 1 and Table 2 of the result section. By the way, There is another Table 1 describing "Participant Characteristics " - page 8. To avoid confusion, there needs to be accurate numbering of the Tables. The problem of this biased grouping despite randomisation weakened the study. The authors described the randomisation procedure as through" drawing lots". Perhaps, in the definitive trial, a different randomisation procedure will be employed. The major flaw/ bad luck is reflected in fig 1, the CONSORT Diagram. From 44 eligible patients, only 9 patients met inclusion criteria. This practical challenge has to be addressed before the future definitive RCT is planned. This may reflect the design characteristics of the device that they used. Unless, this issue is resolved, generalizability of future RCT or translation into clinical practice will be difficult regardless of the statistical findings. Perhaps, multi-centre will be needed to address this problem. This screen failure issue needs some reflections by the authors.

Response: The reviewer has correctly pointed out the baseline differences between the two groups. We have further elaborated on this in the study limitations and we understand that the results should be interpreted with caution (page 13, 14). We have also suggested a different randomization procedure. We suggest stratified randomization procedure to be used for unbiased allocation of individuals to various interventions, thus reducing the risk of unbalanced groups based on functional level (page 13, 14).

The table numbering has been corrected as pointed by the reviewer (page 11 Table 3).

The screen failure, as pointed by the reviewer, was partly due to size range of exoskeleton used in this study. Apart from that, few patients (4 in total) passed the screening but lived too far from the study site and therefore they withdrew to participate. We have addressed this challenge in the discussion section (page 14).

6. Comments on written English language: Well written. However, on page 3 para 2, line 3, "deliberate observance of task" is difficult to understand. Do the authors mean performance of
Response: The wording on page 3 line 30 has been changed from “deliberate observance of task” to “systematic execution of task”.

As suggested by reviewer, the compound sentence has been broken down to multiple sentences for clarity.

Response to comments from Anonymous Reviewer #2

Reviewer #2: This paper reports on findings from 7 participants with incomplete spinal cord injury who completed 3 weeks of either exoskeleton or conventional physical therapy to improve gait. The findings may inform the design of future larger clinical trials. However, the presentation and the discussion of the findings should be re-written to focus on the usefulness of this study’s findings for future research. Overall this paper needs to be edited for readability and grammatical errors, of which there are many throughout.

Background:

1. The background should discuss chronic SCI specifically, given that the participants recruited were 2-34 years post-injury. Exoskeleton gait training may benefit acute iSCI differently than in chronic iSCI (more atrophy, deconditioning perhaps in chronic iSCI).

Response: As suggested by the reviewer we have included discussion on this in the background section (page 4 line 50).
2. In the background, the authors state that "effectiveness of exoskeleton-assisted gait training for individuals with SCI remains unclear"; however, the purpose of this pilot study or its results do not relate to "effectiveness", which is determined through a Phase III clinical trial. This should be reworded to efficacy.

Response: We have reworded the sentence and replaced effectiveness with efficacy (page 4 line 40).

3. The within-group differences are analysed and reported, however no between-group comparisons were made; therefore the authors should not be hypothesizing greater improvements in the EGT group COMPARED to the CPT group.

Response: We have included the inter-group differences in the results section of the study (abstract line 27, page 9 line 12, 30, page 10 line 32, 50, page 11, line 7).

Methods:

4. The number of subjects screened, enrolled, and completed the study should not be reported in the methods, and should be included in the results section instead.

Response: As suggested by reviewer, we have moved the information regarding subject screening to the results section (page 8 line 13).
5. Please elaborate on the randomization process of drawing lots, was this done manually or via a software? Was it a 50/50 allocation ratio?

Response: The randomization process was done manually by drawing an envelope from 10 sealed envelope with group assignment inside (50/50 allocation ratio).

6. The EGT group received 60 minutes of therapy and 30 minutes of set-up, while the CPT group received up to 60 minutes; please clarify if all CPT participants received a full 60 minutes for each session and perhaps comment on the extra time spent with researchers in the EGT group

Response: The CPT group also received 60 minutes of therapy. The extra time in the EGT group was required for donning and doffing the exoskeleton. We have mentioned this in the training protocol and slightly reworded it (page 6 line 23).

7. Validity of measures chosen for iSCI should be provided.

Response: According to the article (Lam, Tania, Vanessa K. Noonan, Janice J. Eng, and SCIRE Research Team. "A systematic review of functional ambulation outcome measures in spinal cord injury." Spinal cord 46, no. 4 (2008): 246) on the functional ambulation outcome measures in spinal cord injury, it was found that 10MWT, 6MWT and TUG were consistent in terms of test-retest, inter-observer reliability, constrict validity in ambulatory SCI patients. As the focus of our research was on ambulatory SCI patient therefore we used 10MWT, 6MWT and TUG as the assessment measures. As suggested by reviewer 2 we have included this information in the Methods section under assessment protocol (page 7 line 47).
8. Why was balance not measured?

Response: The original design of this pilot study was to look at the changes in gait and mobility after exoskeleton assisted gait training and conventional physical therapy, therefore, we did not consider measuring balance in this pilot study. We realize that balance is a very critical function in patients with SCI, therefore, we plan to include balance as a measure using the Berg Balance Scale in future definitive RCT.

9. The statistical analysis should be determined a priori, and so the comment that between group differences were not analysed because of small sample size should be removed or reworded.

Response: We have removed the sentence and included the statistical analysis of inter-group differences (abstract line 27, page 9 line 12, 30, page 10 line 32, 50, page 11, line 7).

Results:

10. Do not need to include the exercises the CPT group underwent (should be in methods instead).

Response: As suggested by reviewer, we have moved the information regarding exercises by CPT group to the methods section (page 6 line 24).

11. "As expected, subjects in EGT group spent significant more time on walking … compared to subjects in CPT Group" - this should be reworded to substantially, as no between group comparisons were made and so significance is misleading.
Response: As suggested by the reviewer, the word significant has been reworded to substantially (page 8 line 27).

12. At times, stride length and step length are used interchangeably but conceptually are different. Please re-word appropriately throughout the gait characteristics. There are also mistakes in reporting results, e.g. reporting on the right side but then commenting on left side.

Response: The reviewer has correctly pointed out the incorrect use of stride and step length. We have corrected this error. Also, we have corrected the mentioning of left step length and changed it to right step length (page 9 line 33).

Discussion:

13. There is too much focus on potential mechanisms (not measured in this study) for the observation of non-significant, minor, or sparse improvements in the EGT group; there were improvements noted in the CPT group as well, and so excessive focusing on the mechanisms for improvement does not seem appropriate given the lack of findings of superiority. Instead, please comment on how findings might inform future larger scale studies, how it might determine sample size, inclusion/exclusion criteria, intervention duration, etc.

Response: The reviewer has indicated the lack of superiority of findings and therefore we have mentioned in the discussion that the results should be interpreted with caution. As suggested by the reviewer we have revised the discussion and included the practical issues of patient recruitment, randomization that would be important for future large scale studies in the discussion (page 14).

14. Paraplegic vs quadriplegic - please comment on how the exoskeleton training may be different or have different effects based on impairment
Response: The design and control of wearable exoskeleton (Ekso) requires the user to be able to use and control assistive device such as walker or canes and perform lateral and forward trunk sways for movement initiation of the exoskeleton. Therefore, strategy of exoskeleton assisted training is different between training with paraplegia and quadriplegia. One of the significant differences is the ability to maintain balance and trigger stepping movement when using wearable exoskeleton, however, this can be compensated by body weight supported harness and assistance from the trainer (i.e. assist the user to perform trunk sway). Depending on the impairment and patient goals, potential therapeutic effects, if any, of exoskeleton assisted gait training could mainly focus on gait and balance for paraplegia and bowel and bladder function for quadriplegia. We have included this in the discussion section (page 13 line 3).

15. The participants in the CPT group scored much better than the EGT group at baseline on various measures; please comment on how this affects findings or may bias findings. It is more difficult to make changes in stride length, strength, or functional tasks if they are already closer to normal (less room for improvement).

Response: The reviewer 2 has correctly pointed out the baseline differences between the EGT and CPT individuals and the inter-group differences as a result of the baseline differences should be interpreted with caution. The reviewer has also mentioned that it is difficult to make changes in stride length, strength or functional tasks if they are closer to the normal, however, though the gait characteristics of individuals in the CPT were much better placed that EGT group at baseline but we cannot assume that they are closer to normal. E.g. the average walking speed of a healthy individual without neurological disorder is around 1.3 to 1.4 m/s. Two individuals in the CPT group have speeds less than 1/3 the normal walking speed. We consider that the CPT group also had room for improvement. Due to small sample size and the fact that distribution of participants resulted in baseline differences, the results from this study may not be a realistic representation of the effect of the training. We have included some discussion on baseline differences between the two groups (page 13).

16. Though mentioned briefly in the limitations, greater discussion regarding impairment/injury/functional level and how they might have impacted results should be provided.
Response: We have included further discussion on the effect of injury/functional level under study limitations in the Discussion section (page 13 and 14).