Variability in responsiveness to interventions in people with spinal cord injury: do some respond better than others?

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***Abstract*—Spinal cord injury (SCI) results in significant impairments in function and ankle joint spasticity is a common secondary complication. Various interventions have been trialed to improve function and reduce spasticity after SCI, with variable results. We investigated the effects of a pharmacological (an anti-spastic medication – tizanidine) and a physical intervention (robotic-assisted locomotor training – Lokomat) on function in people with incomplete SCI over 4-week of training. The outcome measures were walking speed, endurance and mobility. Subjects were randomized into one of three groups; no intervention (control), Lokomat (Lok) and tizanidine (Tiz). To account for variability, we used growth mixture modelling (GMM) to class subjects based on their recovery patterns. GMM identified two classes of recovery: high and low function. Significant improvements were seen in walking speed and mobility in high and low functioning subjects in the Lok group, and in walking endurance in high functioning subjects in the Tiz group. However, changes with training were clinically important only for approximately 10% of subjects, who achieved a minimal important difference (MID) in functional outcomes as a result of the training. We used mixed model ANOVAs to compare the group effects. Improvements with training were seen in both classes, however no differences between interventions were found. The GMM had classed all subjects that achieved the MID as high functioning. GMM can be used to successfully class subjects; however larger subject numbers and longer interventions are required to fully utilize this technique. Our results demonstrate that both interventions have potential to improve walking capacity, but more intense training for a longer period may need to achieve MID.**

I. Introduction

A Spinal cord injury (SCI) is a devastating condition that can significantly impair the affected individual's ability to perform functional tasks. Therefore finding ways to optimize function after SCI has been the focus of SCI rehabilitation research for many years.

One secondary consequence of SCI is neuromuscular abnormalities, resulting in hypertonia or spasticity of muscle groups, and has been noted as the main self-reported secondary complication after SCI [1]. Spasticity commonly affects the muscles surrounding the ankle joint, which have important roles during functional tasks [2]. Some studies have demonstrated that increased hypertonia relates to impaired function [3-6]. Others however, demonstrated no functional improvements with reduced hypertonia, based on clinical observations [7, 8]. Tizanidine, an antispasticity medication, has been shown to reduce hypertonia in SCI individuals [9-12]. Tizanadine has been shown to substantially reduce reflex mechanical responses in SCI individuals [13], and facilitate locomotor capacity in spinalized cats [14]. One study however reported that it had no effect on activities of daily living in SCI individuals [9].

An alternative intervention that became popular in SCI rehabilitation to improve function is Locomotor treadmill training (LTT). LTT, incorporating body-weight supported training and robotic-assistive step training [15]. In people with chronic SCI, studies have reported that LTT training improves overground walking speed [16-20] and endurance [18]. It has also been reported to reduce abnormal neuromuscular activity, measured by clinical scores [21] or electromyographic activity [22], although these changes did not correlate with functional improvements [21]. Some authors however believe that the evidence for LTT is limited [23] since these studies often omit alternative intervention groups, or do not find LTT training superior when compared with other interventions [19, 20, 24].

Overall, the observed extents and rates of improvement in functional performance after incomplete SCI are variable, and the group averaging techniques commonly used in longitudinal intervention studies, may mask important data. Recently, growth mixture modelling (GMM), widely used in psychological and educational research, has been applied to recovery patterns in rehabilitation research. The technique attempts to classify subjects into latent classes according to their baseline scores and recovery patterns. Subsequently, a patient's baseline data can be used as a predictor for their class membership, prior to treatment. This technique has successfully classed stroke survivors based on their recovery patterns, and their Fugl-Meyer Assessment score was a strong predictor for class membership [25].

Given that functional improvements in response to interventions tend to be small in these subjects [23], it is also important to consider which subjects achieve an improvement considered greater than the minimal important difference (MID). That is, the minimum difference required for each of the outcome measures to detect real (clinical) change [26]. One study noted that a greater proportion of more impaired SCI subjects, classified by Lower Extremity Motor Scores (LEMS), attained the MID for walking speed after locomotor training, when compared with less impaired subjects [20].

We therefore investigated whether two different interventions, LTT and tizanidine, improved function in

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people with chronic SCI, and categorized the results using GMM, as well as the proportion of subjects that attained the MID.

II. Methodology

A. Subjects

Subjects with incomplete spinal cord injury, as a result of trauma, were recruited from the outpatient service at the Rehabilitation Institute of Chicago. All subjects provided written informed consent and the study had ethical approval from the Northwestern University Institutional Review Board. Subjects were randomized into one of three intervention groups; no intervention (control; n=29), LTT (Lok; n=23) and Tizanidine (Tiz; n=26).

B. Interventions

Interventions were provided for 4 weeks in the Lok and Tiz groups. Control subjects received no intervention. For the Tiz group, .03 mg/kg of Tizanidine was administered four times a day for four weeks.

For the Lok group, locomotor training was provided using a robot-assisted locomotor training device (Lokomat, Hocoma AG, Switzerland). The individual is suspended in a harness over a motorized treadmill while the frame of the robot, attached by straps to the outside of the lower limbs, moves the limbs in a natural walking pattern (Fig 1). Training was provided three times per week; each session lasted $\leq$1 hour, with 30-45 minutes of training. Treadmill speed, body-weight support and robotic guidance force was determined by the physical therapist, based on tolerance and comfort of the subject. A mirror placed in front of the subjects provided visual feedback.

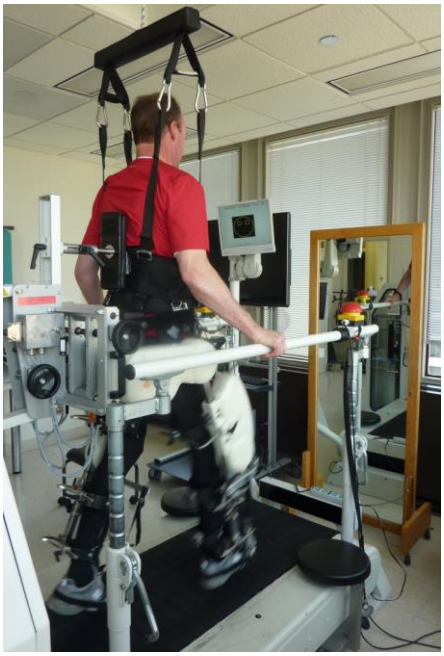

Figure 1. Robotic-assisted Locomotor (LOKOMAT) Training Apparatus

C. Outcome Measures

Outcomes were measured at baseline and 1, 2 and 4 weeks into the intervention.

Functional measures included; i) the Timed up and go (TUG) whereby subjects are instructed to stand up from an armed chair, walk 3 meters, turn, return to the chair and sit down [27]; ii) the 10-meter walk test (10MWT) whereby subjects are instructed to walk 10 meters as quickly and safely as possible [28] and; iii) the 6-minute walk test (6MWT) whereby subjects are instructed to walk for 6 minutes, and the distance covered is measured [29].

III. Data Analysis

Data were classified for each task using growth mixture modelling (GMM) and Random Coefficient Regression (RCR) analysis to classify subjects by baseline data and slope trends using R software.

Data collected at the final time-point were presented as change from baseline, and subjects that achieved MID's for each test (0.13m/s for 10MWT; 45.8 for 6MWT; 10.8s for TUG; [26] were summed.

Two way mixed design analysis of variance (ANOVA) was then used to identify significant changes due to time-point (within-subject) and group (between-subject) for each class using SPSS.

IV. Results

GMM categorized subjects for each outcome measure into two classes: high and low functioning. For the 10MWT, RCR revealed significant improvements with time for the Lok group in both the higher (slope=0.03m/s/week; p=0.003) and lower (slope=0.01m/s/week; p<0.05) functioning subjects, with no significant changes for Tiz or control subjects (Fig 2). For the 6MWT, significant improvements with time were found for the Tiz group in the higher functioning subjects only (7.1m/week; p=0.02). For the TUG, significant improvements with time were found for the Lok group in the lower functioning subjects only (-0.39s/week; p=0.002).

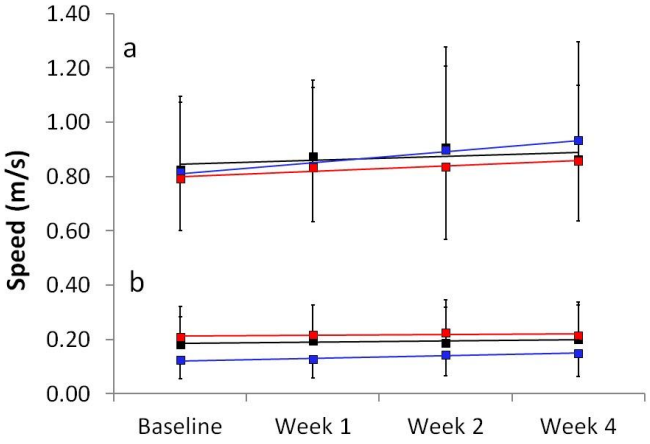

Figure 2. Mean (SD) speed during the 10 meter walk test at each time-point for the control (black), Lok (blue) and Tiz (red) groups for the higher (a) and lower (b) functioning classes, determined by GMM.

The number of subjects that achieved the MID for the 10MWT, after 4 weeks of training, was 8, 13 and 12% for the control, Lok and Tiz groups respectively (Fig 3). Similar values were obtained for the other two measures. The GMM

classed all subjects that achieved the MID for the 10MWT and the 6MWT as higher functioning; however only approximately 10% of subjects in the higher functioning class achieved the MID (Fig. 3).

Mixed model ANOVAs revealed significant improvements with time for the 10MWT in both classes ($p<0.05$), with no group effects or interactions. For the 6MWT there was no effect of time-point for the lower functioning class, but a significant improvement with time in the higher functioning class ($p<0.05$), with no group effects or interactions. For TUG, there were significant effects of both time-point ($p<0.05$) and group ($p<0.05$) for the higher functioning class with no interaction. There was no significant effect of time-point or group for the lower functioning class in the TUG test.

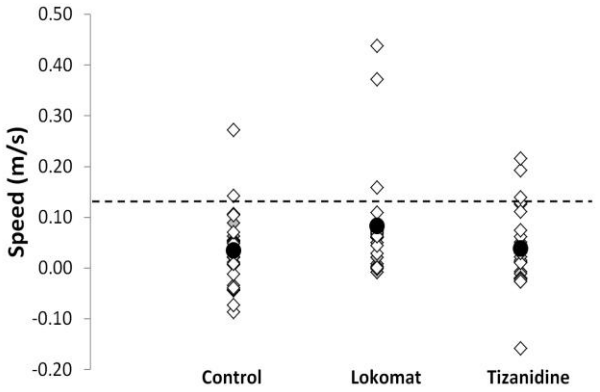

Figure 3. Mean (black circles) and individual (diamonds) change in speed during the 10 meter walk test for subjects classed as low (grey diamonds) or high (open diamonds) functioning by the GMM, within each group (dashed line illustrates the MID [26].

V. Discussion

This study used GMM to class the recovery patterns of subjects with incomplete SCI for different interventions; subjects were classed as high or low functioning. RCR revealed significant improvements in speed for the Lok group and in endurance for the Tiz group. However, these changes were observed only in a small proportion of subjects who attained the MID for each clinical test, and in contrast to the RCR model, ANOVAS could not detect significant differences between intervention groups (Lok vs. Tiz vs. Control).

RCR analysis revealed significant improvements in walking speed for both classes in the Lok group only. This is in agreement with previous work that reported improvements in walking speed after body-weight supported locomotor training [16-20]. Endurance did not improve in the Lok group but TUG time was improved in higher functioning subjects only. There is some debate in the literature regarding the effectiveness of bodyweight supported locomotor training [24], which concludes that small functional changes do occur with this training, however these changes are similar compared with other physical interventions. Our findings similarly show small functional changes with this intervention, with an indication that higher functioning subjects may benefit more. The effects of anti-spasticity medications on functional measures have seldom been reported. Studies that have reported the effects of other pharmacological interventions, reported small to negative effects on walking speed [30], and concluded that locomotor training resulted in better outcomes than any of the pharmacological interventions studied [30]. In agreement, Tizanidine had no effect on walking speed or TUG time in our study, but improved endurance in the higher functioning class only. The ability for subjects to walk for a longer duration may have been due to reduced spasticity in the gastrocnemius muscle, which allowed improved (more coordinated) functioning of the tibialis anterior muscle, which is particularly important in the swing phase of gait. Further research is required to corroborate this speculation.

We additionally considered the MID for the functional measures taken, in order to classify subjects as 'responders' or 'non-responders' to the intervention, based on the minimum change in performance required to detect real (clinical) change [26]. As shown in Fig. 3, there was no observable difference between the intervention groups in terms of the number of responders vs. non-responders. However, all subjects that were classified as responders had been classed by the GMM as higher functioning, irrespective of the intervention provided. Thus the GMM technique holds potential to correctly class subjects based on their response to treatment. However, it should be acknowledged that only a minority of the higher functioning class were classified as responders. This may have been due to lack of sufficient training/medication dose or the length of therapy, or the small effects of the interventions. More intense training (provided over a longer time-frame), or more effective interventions may improve the efficacy of this technique. It should also be acknowledged that GMM techniques may require a larger number of data-points than used here, which may also have affected the outcome.

While significant improvements in clinical outcomes were noted, there were no significant differences between the different interventions provided, when assessed using ANOVA's. This is in agreement with previous studies, which have noted similar improvements from different interventions in this population [19, 20, 24]. We did however note a trend in the Lok group, indicating that improvement would continue beyond the 4-week training period provided. Indeed previous studies that showed improved outcomes from locomotor training incorporated training lasting between 8 and 14 weeks [30]. Thus providing longer-term interventions may have revealed differences between groups in the higher functioning class.

VI. Conclusion

GMM was used to classify the subjects into high and low functioning classes, and the model classified all subjects that attained the MID for walking speed and endurance as higher functioning. Overall, the higher functioning classes showed greater potential for responding to interventions. Based on

RCR analysis, both high and low functioning classes in the Lok group showed significant improvements in walking speed; and only the high functioning class showed improvement in TUG time. Also the high functioning class of the Tiz group showed improvements in endurance. However, a relatively small percentage of these subjects showed clinically important improvements and ANOVAs could not detect significant differences between groups. Future work should employ these techniques in similar studies, incorporating higher subject numbers and longer duration interventions.

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