LITERATURE REVIEW: APPLICATIONS FOR

Traumatic brain injury

F. Marsili

2. PERIPHERAL RECOVERY

ALGIAMED

Author's choice

Traumatic brain injury (TBI) is a lesion of the brain which occurs as a consequence of trauma following falls (40.5%) or car/motor accidents (14.3%) [1]. Birth brain injuries are a sub-category of TBI with a yearly prevalence of 26.46 per 1000 hospital births [2]. Generally, TBI is associated with older individuals, aged 75 or above. Though children with birth brain damage (birth related or otherwise) cover a relatively small percentage of the total TBI population, the significant impact of TBI on the quality of life of children, of their parents and their extended families, makes the research on the improvement of TBI symptomatology especially relevant [2], [3].

The first few weeks or months of an infant are the most critical: children are born with around 100 billion neurons, which are yet to be connected. Neuroplastic events occur continuously during the first developing phases of a newborn, where connections are build and wired experientially [4]. This fact makes early detection and intervention on newborns with TBI essential.

Electrical stimulation therapies have been demonstrated to have significant effects on recovery from brain injuries, such as stroke, ischaemic events, brain and spinal cord trauma, and TBI [5], [6], [7]. Even though the exact underlying mechanisms of electrical stimulation are yet to be understood, clinical evidence shows its efficacy on neurophysiological reorganisation of cortical areas as well as functional recovery including facilitation of movements and pain relief [8], [9]. It can be concluded that electrical stimulation takes advantage of the neuroplastic ability of peripheral nerves and central neurons to trigger adaptive cascades to counteract the maladaptation occurring as a consequence of injuries or disease.

In this collection of papers, we first explore the concept of neuroplasticity, with particular focus on the significance of cortical organisation in developing brains and the role that electrical stimulation plays in triggering reorganisation of cortical areas in developing as well as adult brains. Following, we focus on the clinical evidence of electrical stimulation in enhancing both functional peripheral recovery (e.g., motor and sensory functions) and cortical adjustments (e.g., plastic changes on sensorimotor cortex).

In summary, TBI is a condition significantly affecting the quality of life of the individuals affected by it. In the case of birth brain injuries, children and their families experience significant and long-term impact on their daily lives. Being able to leverage on the brain's ability to reorganise after maladaptation using neuroplastic processes could have an essential role in the treatment of TBI in infants and children. The following papers explore the role that electrical stimulation could have in enhancing adaptive, neuroplastic responses in TBI: a potential therapeutic application for children with brain injuries.

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[7] Bao, Shi-chun et al. (2020) Rewiring the lesioned brain: electrical stimulation for post-stroke motor restoration. *Journal of Stroke,* 22(1): p47-p63. doi: 10.5853/jos.2019.03027

[8] Deer, Timothy R. et al. (2021) Peripherally induced reconditioning of the central nervous system: a proposed mechanistic theory for sustained relief of chronic pain with percutaneous peripheral nerve stimulation. *Journal of Pain Research,* 14: p721-p736. doi: 10.2147/JPR.S297091

[9] Ebrahimzadeh, Masoome et al. (2021) Effect of functional electrical stimulation combined with stationary cycling and sit to stand training on mobility and balance performance in a patient with traumatic brain injury: a case report. *Anaals of Medicine and Surgery,* 72(103122), doi: 10.1016/j.amsu.2021.103122

2. Peripheral recovery

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Journal of NeuroEngineering and Rehabilitation

RESEARCH Open Access

Effects of somatosensory electrical stimulation on motor function and cortical oscillations

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Abstract

Background: Few patients recover full hand dexterity after an acquired brain injury such as stroke. Repetitive somatosensory electrical stimulation (SES) is a promising method to promote recovery of hand function. However, studies using SES have largely focused on gross motor function; it remains unclear if it can modulate distal hand functions such as finger individuation.

Objective: The specific goal of this study was to monitor the effects of SES on individuation as well as on cortical oscillations measured using EEG, with the additional goal of identifying neurophysiological biomarkers.

Methods: Eight participants with a history of acquired brain injury and distal upper limb motor impairments received a single two-hour session of SES using transcutaneous electrical nerve stimulation. Pre- and post-intervention assessments consisted of the Action Research Arm Test (ARAT), finger fractionation, pinch force, and the modified Ashworth scale (MAS), along with resting-state EEG monitoring.

Results: SES was associated with significant improvements in ARAT, MAS and finger fractionation. Moreover, SES was associated with a decrease in low frequency (0.9-4 Hz delta) ipsilesional parietomotor EEG power. Interestingly, changes in ipsilesional motor theta (4.8–7.9 Hz) and alpha (8.8–11.7 Hz) power were significantly correlated with finger fractionation improvements when using a multivariate model.

Conclusions: We show the positive effects of SES on finger individuation and identify cortical oscillations that may be important electrophysiological biomarkers of individual responsiveness to SES. These biomarkers can be potential targets when customizing SES parameters to individuals with hand dexterity deficits. Trial registration: NCT03176550; retrospectively registered.

Keywords: Transcutaneous electric nerve stimulation, Stroke, Rehabilitation, Brain injury, Electroencephalography, Upper extremity

Background

Despite recent advances in rehabilitation, a substantial fraction of stroke patients continue to experience persistent upper-limb deficits [1]. At best, up to 1 out of 5 patients will recover full arm function, while 50% will not recover any functional use of the affected arm. [2] Improvement in upper limb function specifically depends on sensorimotor recovery of the paretic hand [3]. Yet, there remains a lack of effective therapies readily available to the patient with acquired brain injury for recovery of hand and finger function; a systematic review found that conventional repetitive task training may not be consistently effective for the upper extremity [4]. It is thus critical to explore inexpensive and scalable approaches to restore hand and finger dexterity, reduce disability and increase participation after stroke and other acquired brain injuries.

Sensory threshold somatosensory electrical stimulation (SES) is a promising therapeutic modality for targeting hand motor recovery [5]. It is known to be a powerful tool to focally modulate sensorimotor cortices in both healthy and chronic stroke participants [5–8]. Devices such as transcutaneous nerve stimulation (TENS) units can

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deliver SES and are commercially available, inexpensive, low risk, and easily applied in the home setting [9]. Previous studies have demonstrated short-term and long-term improvements in hand function after SES [5, 10–15]. However, the effect of SES on regaining the ability to selectively move a given digit independently from other digits (i.e. finger fractionation) has not been investigated. Poor finger individualization is an important therapeutic target because it is commonly present even after substantial recovery and may account for chronic hand dysfunction [16]. Further, it is unclear if SES is associated with compensatory or restorative mechanisms. Prior studies have largely relied on relatively subjective clinical evaluations of impairment, such as the Fugl-Meyer Assessment, or timed and task-based assessments, such as the Jebson-Taylor Hand Function Test. Biomechanical analyses, on the other hand, can provide important objective and quantitative evidence of improvement in neurologic function and normative motor control [17, 18]. Therefore, we aimed to determine not only the functional effects, but also the kinematic effects, of SES on chronic hand dysfunction.

Simultaneously, it should be noted that although SES can potentially be an effective therapy, not all individuals who are administered SES experience positive effects. While improvement levels as high as 31–36% compared to baseline function have been reported, [11, 19] about half of one cohort demonstrated minimal or no motor performance improvement after a single session of SES [15]. One method to shed more light on this discrepancy is to identify neurophysiological biomarkers associated with motor responses to SES. Neurophysiological biomarkers are increasingly used to predict treatment effects [20, 21]. Although some studies have examined biomarkers associated with treatment-induced motor recovery, to our knowledge none have been performed for SES [22, 23]. A recent study using electroencephalography (EEG) found that changes in patterns of connectivity predicted motor recovery after stroke [24]. At present, little is known about the effect of peripheral neuromodulation on EEG activity, how existing neural dynamics interacts with peripheral stimulation, and whether this interaction is associated with improvements in motor function. Associating EEG activity with treatment response may also provide mechanistic insight regarding the effects of SES on neural plasticity. EEG activity can also potentially be used as a cost-effective real-time metric of the time-varying efficacy of SES. This novel application of EEG information may help tailor treatment efforts while reducing the variability in outcome.

The main goal of this pilot study was to evaluate both changes in finger fractionation in response to SES and identify the associated neural biomarkers through analyses of EEG dynamics. Outcomes from this study have potential in designing targeted SES therapy based on neural biomarkers to modulate and improve hand function after acquired brain injury such as stroke (e.g. enrollment in long-term studies of the efficacy of SES).

Methods

Ethics, consent and permissions

This research was conducted in accordance with and approval of the University of California San Francisco Institutional Review Board (IRB). All research participants provided informed consent to participate in the study.

Inclusion/exclusion criteria

Inclusion criteria included participants between 18 and 80 years old, with a history of an acquired brain injury resulting in residual hemiparesis or other motor deficits of the arm/hand equal to or more than 6 months prior to enrollment; and capacity to adhere with the schedule of interventions and evaluations determined in the protocol. Subjects were excluded if they met any of the following criteria: currently pregnant; uncontrolled medical conditions; significant cognitive impairment on the Montreal Cognitive Assessment (MoCA ≤23); ≤ 10 degrees of active index finger range of motion; significant hand joint deformity; severe active alcohol or drug abuse; significant depression (PHQ-9 ≥ 15); baseline spasticity score (MAS) >3 for any joint tested (wrist and metacarpophalangeal joint flexion and extension); apraxia screen of Tulia (AST) <5; absent light touch, proprioception, pinprick and vibration sensation on the modified Nottingham Sensory Assessment; no upper limb strength against gravity; severe aphasia; or had an implanted pacemaker. The NSA was used for both exclusionary purposes as well as for reporting the presence of baseline sensory deficits.

Participant baseline characteristics and clinical assessments are shown in Table 1. Fourteen individuals were screened, 9 were enrolled and received the intended intervention, and 8 completed the study protocol, on which the final outcome analyses were performed. Reasons for exclusion of 5 individuals were significant cognitive impairment (MoCA <23), less than 10 degrees of active finger range of motion (two people), lack of residual motor deficits, and active treatment for brain tumor. One participant was unable to complete the study protocol due to fatigue.

Clinical and kinematic assessments

The primary outcome measurements consisted of the standardized Action Research Arm Test (ARAT) and a kinematic measurement of finger individuation, the finger coupling index (FCI). Participants performed

Table 1 Summary of patient characteristics

Patient	Age	Gender	Years since injury	Affected UE	Type of Brain Injury	Lesion location	Baseline ARAT[a]	Sensory impairment	Baseline MAS	Baseline FCI[a]
1	45	F	6	Right[b]	hemorrhage	Left frontotemporal and insular lobes	49	Yes	0	0.61
2	32	M	7	Right[b]	Stroke	Left posterior frontal lobe	34	No	4	0.45
3	36	M	16	Left	hemorrhage	Right internal capsule	24	No	5	0.71
4	64	M	3	Left	Stroke	Right parietal precentral gyrus	33	Yes	1	0.86
5	72	M	1	Left[b]	Stroke	Right frontal lobe	52.67	Yes	0	0.50
6	41	M	14	Left	tumor	Left frontal lobe	33	No	5	1.51
7	66	M	6	Left	Stroke	Right posterior internal capsule and thalamus	55	Yes	0	0.42
8	28	F	2	Right[b]	TBI	Right frontal and bilateral temporal lobes, left cerrebellum	37	No	0	0.40

TBI traumatic brain injury, *UE* upper extremity, *ARAT* Action Research Arm Test, *MAS* Modified Ashworth Scale, *FCI*, finger coupling index
[a]Mean performance
[b]Dominant hand

multiple repetitions of the ARAT and finger individuation measurements during one familiarization session prior to the beginning of the study to address potential practice effects. The ARAT has been previously validated and was selected for its ability to measure defined domains of distal hand function (i.e. proximal, grasp, grip, and pinch tasks) [25]. Digital video recordings were obtained for kinematic motion analysis using a 30 Hz video capture system. Videos files were analyzed using a custom Matlab script to record beginning positions and end positions of the required tasks. Virtual markers were superimposed on top of recorded visual markers adhered to the participant's hand. The beginning and end positions of each task were validated visually by video replay frame by frame. FCI was measured from frames exhibiting the maximum difference between the angle traversed by the passive middle finger divided by the angle traversed by the active index finger. (Fig. 1a-b). Three trials were averaged to obtain the mean finger coupling index. Given frequent rest breaks, participants did not have any difficulty completing the required number of trials per task. Trials that were interrupted or failed due to technical errors were discarded, and an additional set of trials would be repeated from the beginning. Secondary outcome measurements included finger pinch force (standardized dynamometer), and the Modified Ashworth Scale (MAS) to assess spasticity affecting wrist and finger flexion and extension. Outcome assessments were measured immediately before and after the intervention. Participants wore an EEG cap (Enobio, Neuroelectrics Corp., Barcelona, Spain) consisting of pre-determined electrode positions located anatomically according to the International 10–20 EEG System. Resting state EEG data with eyes open was acquired (Enobio, Neuroelectrics Corp., Barcelona, Spain) for a duration of 10 min before and after stimulation, using 8 electrodes over the Fp1, Fp2, C3, C4, P3, P4, O1, O2 at 500 Hz with a mastoid reference. Kinematic and functional outcome measurements were performed without blinding. Participants were aware of the research question regarding whether somatosensory electrical stimulation had any effect on hand motor function.

Intervention

TENS was performed using a commercially available device (ProStim, Alimed Inc., Dedham, Massachusetts, USA). One pair of 2 × 3.5 in. rectangular electrodes

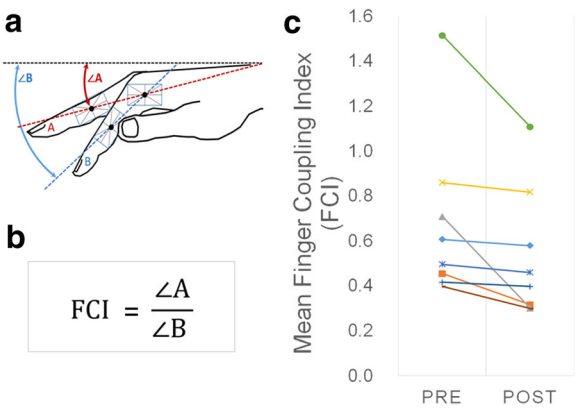

Fig. 1 **a** Schematic representation of the method used for calculating the FCI. The participant is instructed to flex only the index finger as much as possible without flexing the other digits. **b** FCI is defined mathematically as the angle traversed by the middle finger (digit A) divided by the angle tranversed by the index finger (digit B) relative to the horizontal starting position. **c** Statistically significant change in mean fractionation from baseline to immediately after peripheral nerve stimulation. Fractionation improvement is indicated by a decrease in finger coupling index (FCI)

(Vermed ChroniCare TENS Electrodes, Vermed, Buffalo, NY, USA) were placed on one aspect of the forearm to simultaneously stimulate both median and ulnar nerves, while a second pair of round 2 in. diameter electrodes were placed on the lateral aspect of the forearm to stimulate the radial nerve. (Additional file 1: Figure S2) Optimal positions to stimulate the ulnar, median and radial nerves of the paretic hand were determined by using standard localization technique [26, 25]. Sensory thresholds (minimum intensity of stimulation) at which subjects report paresthesias in each nerve territory were determined. Stimulus intensity was further increased and adjusted until subjects reported strong paresthesias in the absence of pain and visible muscle contractions. The mean stimulation intensity was 5.3 mA (19% above mean sensory threshold) for the radial nerve and 5.8 mA (29% above mean sensory threshold) for the median/ulnar nerves. Bursts of electrical stimulation at 10 Hz (100 microsecond pulse width duration) were delivered to all nerves simultaneously for 2 h [5, 10, 12–15, 18]. During the stimulation period, the affected hand was at rest while participants read or viewed a film.

Statistical analyses

Experimental data were collected immediately before and after the intervention. Intervention effects were determined using non-parametric bootstrap tests to assess the difference between the pre- and post-intervention means [26]. Statistical significance was set at $p < 0.05$. Continuous 10 min EEG resting state data were epoched into non-overlapping 1000 ms time-voltage data segments and mean-baselined, with the "right hemisphere" as the common lesion hemisphere. In essence, this involved flipping hemispheric cortical activity for left hemispheric patients. Artifact correction on the epoched data was performed using a combination of principle component analysis (PCA) and the 3 S.D. voltage metric [27] to reject epochs that had abnormally large voltage values due to eye blinks, head-motion or extraneous noise. Bilateral sensorimotor electrodes (C3-C4 and P3-P4) formed the regions of interest. Resting state power was computed within each epoch across four frequency bins (delta 0.9–3.9 Hz, theta 4.8–7.9 Hz, alpha 8.8–11.7 Hz, beta 12.7–30.27 Hz) via averaging the absolute values of short time Fourier transforms (STFT) on non-overlapping 256 ms snippets within each epoch. Subsequently, the percentage change in mean resting state power, pre to post intervention, was computed for each subject at each frequency bin and electrode. A bootstrap test was used to assess the null hypothesis of group-level changes in mean resting state power being similar to a distribution with mean zero. The percentage change in mean FCI was regressed onto the percentage change in mean resting state power across all 4 bins and 4 electrodes via multivariate regression. Given that there were more predictors (changes across 4 channels X 4 frequency bins = 16 predictors) than measurements (changes in 8 subjects' FCI), penalized regression was performed to counter effects of multicollinearity. Specifically, we used ridge regression and the ridge parameter was identified via leave-one-out cross validation [28]. It should be noted that both simple and penalized regression is susceptible to outliers given that the objective functional to be minimized is quadratic (least squares error minimization). Given the low sample size of 8 subjects, rather than reject data we used robust multivariate regression that automatically corrects for outliers based on a function of the least squares error. Specifically, robustness was implemented via an iterative re-weighted least squares algorithm based on Huber's weighting function [29]. A permutation test was used to determine significance of the ridge coefficients that are associated with changes in mean resting state power with changes in mean FCI [30]. Bonferroni corrections for multiple comparisons were performed wherever appropriate.

Results

Results of kinematic and clinical outcome measurements are presented in Table 2. Mean scores were significantly improved after peripheral nerve stimulation for measures including ARAT total score, overall ARAT completion time, ARAT pinch tasks subset completion time, finger coupling index, and MAS. The mean change in ARAT score was 1.5 points change (or 3.75% improvement) after one session of SES ($p < 0.05$). ARAT domain subsets were further analyzed to determine whether one specific domain improved or a generalized effect in distal upper limb function could be observed. Significant improvement was noted for speed (overall time to complete all tasks decreased by 1.72 s (13.31% change; $p < 0.05$) and pinch tasks time which reduced by 7.26 s (29% change; $p < 0.05$). Changes in proximal tasks time, grasp tasks time, and grip tasks time were not significant. Finger fractionation significantly improved; FCI decreased from 0.68 to 0.53 (22% change). Of the secondary outcome measurements, MAS decreased significantly by 1.13 points (60% change) amongst those who had baseline spasticity ($p < 0.05$), while mean pinch force increased by 1.22 pounds of force (11.3% change).

Results of resting state EEG analyses are shown in Fig. 2. At the group level, stimulation caused significant decreases primarily in mean ipsilesional resting state power at low frequencies (delta 0.9–3.9 Hz and theta 4.8–7.9 Hz bands, $p < 0.05$, Bonferroni corrected, Fig. 2a-b). In contrast, no significant changes were found for alpha and beta frequencies (Additional file 2: Figure S1A, B). In addition, combined theta and alpha power changes over the ipsilesional motor cortex were

Table 2 Results of kinematic and functional outcome measures (Mean)

	Pre	Post	Absolute change	% Change	*P*-value
ARAT					
Total Score (57 points max)	40	41.5	1.5	3.75	0.008
Overall Time (sec)	12.92	11.2	−1.72	−13.31	0.004
Proximal Task Time (sec)	1.29	1.25	−0.04	−3.9	0.823
Grasp Tasks Time (sec)	6.28	6.75	0.47	7.46	0.361
Grip Tasks Time (sec)	8.3	11.3	3.03	36.4	0.058
Pinch Tasks Time (sec)	25.04	17.78	−7.26	−29	0.002
Pinch Force (lb)	10.8	12.03	1.22	11.3	0.048
MAS (16 points max)	1.88	0.75	−1.13	−60	0.010
Finger Coupling Index	0.68	0.53	−0.15	−21.63	0.006
Active Range of Motion (degrees)	68.5	75.3	6.84	9.98	0.001

ARAT Action Research Arm Test, *MAS* Modified Ashworth Scale, *Pre* pre-intervention performance, *Post* post-intervention performance

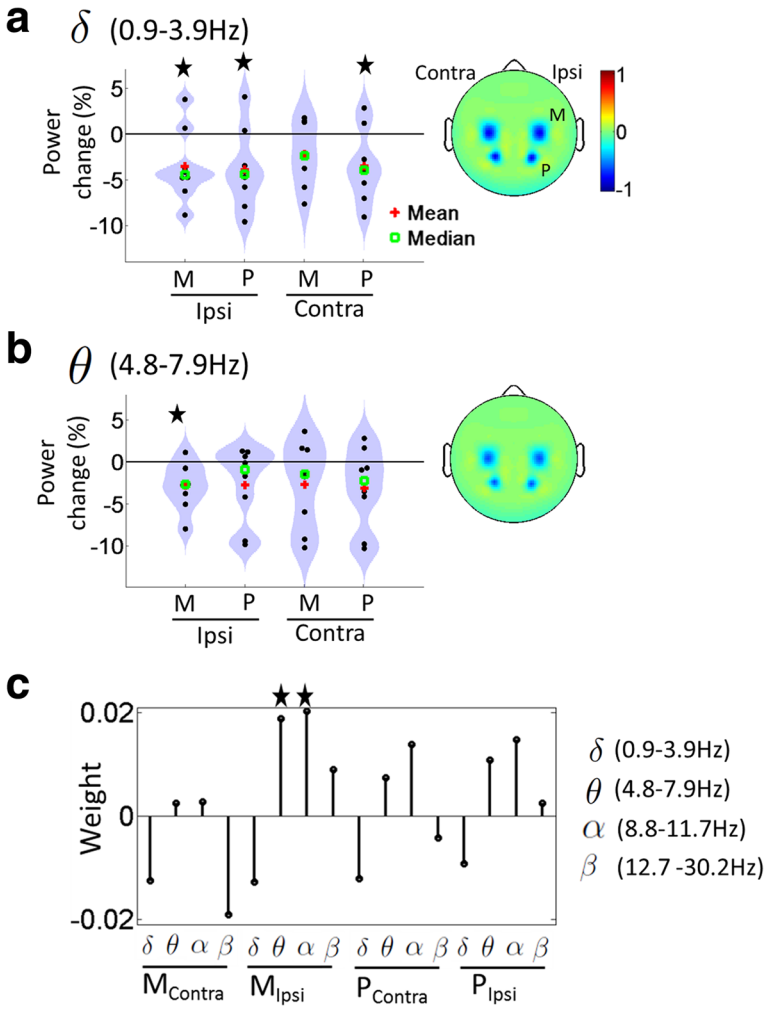

Fig. 2 Distribution of percentage change in mean resting state EEG power across the eight subjects, pre to post intervention, within the (**a**) delta frequency band and (**b**) theta frequency band with head plots depicting 1/coefficient of variation (mean/standard deviation) of group level percentage changes. Star sign represents a significant change in group level resting state EEG power from zero. **c** Magnitude of the coefficients of the multivariate robust ridge model from regressing mean FCI changes to mean power changes, pre to post intervention, with the star sign depicting coefficients whose absolute magnitude were greater than 95% of those produced by random data permutation. M: electrodes over Motor cortex; P: electrodes over Parietal cortex

significantly correlated with fractionation changes ($p < 0.05$) when controlling for all other predictors in the multivariate robust ridge regression model (Fig. 2c). The ridge parameter value of 12.13 was obtained via leave one out cross-validation (Additional file 2: Figure S1C, D) and visual assessment of the quantile-quantile plot from the regression showed normally distributed residuals (Additional file 2: Fig. S1E). It should be noted that ridge regression shares coefficient values amongst correlated predictors (theta and alpha are closely related frequencies) while shrinking coefficients of predictors not correlated with the response variable.

Discussion

Our primary results showed that a single two-hour session of SES resulted in statistically significant improvements in functional measurements as well as finger kinematics in individuals with chronic acquired brain injury. Improvements were found in the domains of activity (i.e. ARAT) and impairment (i.e. pinch strength, spasticity, and finger fractionation). A statistically significant improvement was detected in the mean ARAT score after only one session of SES. This finding is broadly consistent with similar studies of the effects of SES on hand function in stroke patients [3, 5, 15, 19, 31]. One particular study using the ARAT, however, did not find any change after SES. It was determined to be largely due to a ceiling effect [12]. For example, their participants averaged a higher baseline ARAT score than the participants in the present study. While the change in ARAT score was small in magnitude, it may be of clinical relevance; larger or additive effects have been demonstrated with multiple stimulation sessions and in combination with motor training [32, 33].

The relationship between SES and recovery of individuated finger movements has not been investigated in previous studies. Past studies mainly focused on functional measurements as outcomes, such as the Jebson-Taylor Hand Function Test, or on relatively subjective evaluations of impairment, such as the Fugl-Meyer Assessment, to determine the efficacy of SES [5, 10, 15, 19, 31]. Combining functional clinical evaluations with kinematic measurements of finger fractionation is one strategy we implemented to distinguish between functional improvements solely related to compensatory changes versus recovery of impairments. For the purpose of this study, we defined treatment-induced motor recovery as a relative improvement in finger fractionation ability after peripheral nerve stimulation. Our finding here of normalized finger fractionation kinematics suggests that SES can modulate the neural control of finger dexterity. This observation is consistent with a prior study demonstrating immediate improvement in index finger and hand tapping frequency after a single 2-h session of SES. [13] Interestingly, the ARAT total score improvement was specifically attributable to improved performance in pinch tasks rather than performance of grip, grasp, or proximal tasks. This indicates that SES may have a highly specific or greater effect on tasks that require relatively more finger individuation. However, findings of improvements in peak velocity of the wrist during reach-to-grasp tasks after SES have also been reported. [13] Although the differential effect of SES on the various aspects of upper limb function needs further evaluation, the findings taken together underline the importance of emphasizing recovery of finger dexterity to facilitate meaningful and measurable functional improvements.

The specific mechanism for increased fractionation ability after SES is unclear. Prior research suggests that SES affects complex motor skill performance by reorganization and altered excitability of the sensorimotor cortex. Neuroanatomical, electrophysiological, and imaging data revealed that unilateral electrical stimulation, including SES, can activate the contralateral S1 and S2 bilaterally [34–38]. Direct connections between Brodmann areas 1 and 2 of S1 and M1, and S2 and M1 could provide a neuroanatomical basis for the observed effects [39–43]. Furthermore, when patients with pure motor lacunar strokes have interrupted corticospinal projections at a subcortical location, the remaining descending pathways mediating voluntary movement are unable to produce selective patterns of muscle activation required for finger individuation tasks. [16] This underlines the importance of motor cortex output for the orchestration of individuated finger movements. Studies have shown no effects on peripheral nerve M-wave and spinal cord excitability (H waves) with SES, further suggesting that the changes in excitability most likely occur at the level of the cortex. [44, 45]

It has been proposed that finger individuation is a result of not only the voluntary movement of one digit but also the inhibition of digits intended to remain stationary [16]. One study using high frequency SES found a reduction in motor evoked potential (MEP) from the muscle stimulated and an increased MEP from the antagonist muscle [45]. A more recent study found increased MEP with supramotor threshold stimulation and reduced MEPs with SES [44]. Although these results cannot be directly compared to our findings because the stimulation parameters and conditions were dissimilar, they illustrate the complexity of the parameter-dependent effects of SES that can be both facilitatory as well as inhibitory. Therefore, it is plausible that SES improves motor control during finger individuation tasks by modulating cortical excitability and inhibiting inappropriate antagonist and agonist muscle co-contractions, a hypothesis in need of further exploration. The plausible neural correlates underlying the proposed

corticomotor excitability changes are addressed in the following paragraph based on our EEG results.

The EEG results suggest that the observed improvements in motor kinematics and function after SES may be primarily related to changes to ipsilesional cortical oscillations. There were two results detailing the neural plasticity induced by SES that are suggestive of the aforementioned link. First, we observed a relative decrease in ipsilesional resting state low frequency power primarily in the delta band (and ipsilesional motor theta band) immediately after SES when compared to the baseline resting period. Secondarily, a decrease in ipsilesional motor theta and alpha power (two closely coupled frequency bands that were pooled together in the multivariate ridge regression model) were significantly correlated with fractionation changes with SES. Together, our results highlight the importance of reductions in low-frequency, ipsilesional cortical oscillations in association with improved behavioral responses to SES. It is thought that the loss of functional outputs from injured or damaged neurons in affected brain regions [46, 47] can result in an increased synchronous 'idling' state [48] of the cortical pathways as a whole. The increased idling is recorded at the surface EEG as a pathological increase in low frequency power [49]. A potential reason as to why lower frequency oscillations in particular are affected could be due to the slow oscillatory nature of blood flow and metabolism in neuronal tissue. [46, 50] In any case, an increase in low frequency ipsilesional oscillations can be thought to correspond to increased inhibitory activity in the underlying neural tissue [49]. Indeed, a recent study suggested that the reduction of resting-state low-frequency cortical oscillations are a predictor of spontaneous recovery [51]. Here, we show that SES lowers the aforementioned ipsilesional low-frequency oscillations with correlated improvements in behavioral outcomes. Mechanistically, SES could therefore serve to induce cortical plasticity in ipsilesional neural tissue by transitioning the affected region from a synchronous idling state to motor-function related activation. [48, 52]. While the low frequency power changes observed here resulted in better motor behavior, further work (e.g. corticomuscular coherence) is necessary to understand how these power changes relate to individual components of agonist and antagonist muscle activity underlying finger fractionation. Overall, our data provide evidence that neuromodulatory approaches that further reduce low frequency oscillations may be critical to improving motor function. This finding is broadly in line with changes observed in low frequency dynamics during recovery from stroke in a rodent model [53].

Our study also demonstrates how EEG features can be used as biomarkers of SES-induced recovery. In general, EEG has been correlated with motor skill acquisition in healthy individuals and as a biomarker of motor system function and improvements with physical interventions in stroke patients [23]. EEG is a safe, inexpensive, and wearable technology with the potential not only for objectively stratifying candidates, but also for serving as a biomarker of responsiveness to treatment in the outpatient setting. These preliminary findings warrant further exploration to advance our ability to select appropriate candidates for longer-term studies of SES and to customize rehabilitative treatments to individuals.

In summary, we demonstrated the feasibility of using a wearable EEG system with 8 channels to monitor and serve as a biomarker of treatment response. However, using a higher resolution EEG system with a greater number of channels may be more informative, albeit more cumbersome to apply. Given the small sample size, it is unclear whether inhomogeneity of baseline sensory impairments would impact individual responses to SES. Investigations into the impact of sensory deficits and generalizability of findings in a larger patient population is warranted. Future studies will also need to address other potential limitations of this pilot study, including the need for a randomized, controlled study design, monitoring of long-term effects of SES, varying dosing and stimulation parameters to determine their effects on EEG, and explorations into the mechanisms for the effects of SES on complex motor skills.

Conclusions

A single 2-h session of SES can improve finger fractionation and hand function in participants with chronic acquired brain injuries. We also identified cortical oscillations using EEG that may be important electrophysiological biomarkers of individual responsiveness to SES. These biomarkers can be potential targets when customizing SES parameters to optimize its effects on individuals with residual hand dexterity deficits.

Additional files

Additional file 1: Figure S2. (A) Placement of the rectangular electrodes overlapping the stimulation sites of the median and ulnar nerves. (B) Placement of the circular electrodes over the stimulation site of the radial nerve. (TIFF 846 kb)

Additional file 2: Figure S1. Distribution of percentage change in mean resting state EEG power across the eight subjects, pre to post intervention, within the A) alpha frequency band and B) beta frequency band with head plots depicting 1/coefficient of variation (mean/standard deviation) of group level percentage changes. There were no significant differences. C) Result from the leave-one-out cross validation (CV) procedure to find the optimal ridge parameter (lambda) that produced the lowest CV error given by the vertical dotted red line. D) Ridge trace plotting the coefficient weights of the multivariate ridge model for various values of the ridge parameter with the optimal lambda indicated by the dotted red line. E) Quantile plots from the weighted residuals of the Huber robust regression. M: electrodes over Motor cortex; P: electrodes over Parietal cortex. (TIFF 362 kb)

Abbreviations
ARAT: Action research arm test; AST: Apraxia screen of Tulia; EEG: Electroencephalography; FCI: Finger coupling index; MAS: Modified ashworth scale; MoCA: Montreal cognitive assessment; PCA: Principle component analysis; SES: Somatosensory electrical stimulation; STFT: Short time fourier transforms; TENS: Transcutaneous nerve stimulation

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
AT designed the study with KG and GA, collected and analyzed study data, and was a major contributor in writing the manuscript. KG, GA and NN were also major contributors in writing the manuscript. GA, NN and JG contributed to data analysis and interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The University of California San Francisco committee for human research protection approved the study, and all participants provided written consent.

Consent for publication
Not applicable.

Competing interests
KG, NN, and AT have submitted a provisional patent application that is based partially on the results reported here. The authors declare that they have no other competing interests to report.

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Neuromuscular electrical stimulation in critically ill traumatic brain injury patients attenuates muscle atrophy, neurophysiological disorders, and weakness: a randomized controlled trial

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Abstract

Background: Critically ill traumatic brain injury (TBI) patients experience extensive muscle damage during their stay in the intensive care unit. Neuromuscular electrical stimulation (NMES) has been considered a promising treatment to reduce the functional and clinical impacts of this. However, the time needed for NMES to produce effects over the muscles is still unclear. This study primarily aimed to assess the time needed and effects of an NMES protocol on muscle architecture, neuromuscular electrophysiological disorder (NED), and muscle strength, and secondarily, to evaluate the effects on plasma systemic inflammation, catabolic responses, and clinical outcomes.

Methods: We performed a randomized clinical trial in critically ill TBI patients. The control group received only conventional physiotherapy, while the NMES group additionally underwent daily NMES for 14 days in the lower limb muscles. Participants were assessed at baseline and on days 3, 7, and 14 of their stay in the intensive care unit. The primary outcomes were assessed with muscle ultrasound, neuromuscular electrophysiology, and evoked peak force, and the secondary outcomes with plasma cytokines, matrix metalloproteinases, and clinical outcomes.

Results: Sixty participants were randomized, and twenty completed the trial from each group. After 14 days, the control group presented a significant reduction in muscle thickness of tibialis anterior and rectus femoris, mean of − 0.33 mm (− 14%) and − 0.49 mm (− 21%), $p < 0.0001$, respectively, while muscle thickness was preserved in the NMES group. The control group presented a higher incidence of NED: 47% vs. 0% in the NMES group, $p < 0.0001$, risk ratio of 16, and the NMES group demonstrated an increase in the evoked peak force (2.34 kg/f, $p < 0.0001$), in contrast to the control group (− 1.55 kg/f, $p < 0.0001$). The time needed for the NMES protocol to prevent muscle architecture disorders and treat weakness was at least 7 days, and 14 days to treat NED. The secondary outcomes exhibited less precise results, with confidence intervals that spanned worthwhile or trivial effects.

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Conclusions: NMES applied daily for fourteen consecutive days reduced muscle atrophy, the incidence of NED, and muscle weakness in critically ill TBI patients. At least 7 days of NMES were required to elicit the first significant results.

Trial registration: The trial was registered at ensaiosclinicos.gov.br under protocol RBR-8kdrbz on 17 January 2016.

Keywords: Critical care, Electrical stimulation therapy, Muscular atrophy, Muscle weakness, Neuromuscular diseases, Traumatic brain injury

Background

Traumatic brain injury (TBI) is a frequent cause of morbimortality and represents a significant economic burden around the world [1, 2]. Mechanically ventilated critically ill TBI patients present a high risk of poor functional outcomes and often need substantial support after intensive care unit (ICU) discharge [3]. These patients demonstrate extensive muscle wasting, which occurs rapidly at the onset of a stay in the ICU [4]. In addition, patients can develop critical illness neuromyopathy, which is the leading cause of functional disorders [5]. This neuromyopathy alters nerve conduction and muscle excitability, inducing neuromuscular electrophysiological disorder (NED), which in addition to the muscle wasting, generates widespread muscle weakness [5]. The presence of NED is indicative of peripheral nerve disease with a sensitivity ranging from 90 to 100% [6]. The development of widespread muscle weakness among critically ill patients has been referred to as ICU-acquired weakness (ICUAW) [5, 7]. ICUAW patients also display high levels of plasma cytokines such as IL-6, IL-8, and TNF-α, which are associated with inflammatory and catabolic responses [8]. Clinically, ICUAW is associated with prolonged mechanical ventilation, longer ICU stays, and increased morbimortality rates [5]. Therefore, the prompt diagnosis of ICUAW is considered a cornerstone for preventing functional impairments [9].

Early rehabilitation in the ICU seems to be a feasible alternative for the prevention and treatment of ICUAW [10]. Among the treatments available for the early rehabilitation of patients in the ICU, neuromuscular electrical stimulation (NMES) has been considered a promising treatment [11]. Two systematic reviews concluded that NMES added to usual care proved to be more effective than usual care alone for preventing skeletal muscle weakness in critically ill patients [12, 13]. However, these studies found inconclusive evidence of its benefit in the prevention of muscle atrophy [12, 13]. In fact, there are particular gaps in the definition of a more efficient NMES protocol for non-cooperative critically ill patients [14, 15]. For example, the time needed for the NMES protocol to elicit the first countermeasure effects has still not been determined [16]. It appears that stimulation of a larger muscle area, as well as the production of maximum evoked contractions, is crucial for better results [16, 17]. Moreover, the number of stimuli per day and the number of treatment days could also be essential to generate significant results [18, 19]. Therefore, the present study aimed to assess the time needed and effects of an NMES protocol on muscle architecture, NED, and muscle strength, and, secondarily, to evaluate the effects on plasma systemic inflammation, catabolic responses, and clinical outcomes. The hypothesis was that the NMES protocol would counteract muscle atrophy and strength reduction, while preventing NED, and minimizing the presence of plasma inflammatory and catabolic responses.

Methods

Study design

This was a prospective, randomized, controlled, single-blind trial carried out over a period of 14 consecutive days. The study was performed in a neurotrauma ICU at a tertiary public reference hospital in the Federal District of Brazil. It was conducted according to the Declaration of Helsinki, and approval for the project was obtained from the local ethics committee (FEPECS/SES-DF, Brasília, Brazil, protocol 1.107.517). The trial was registered at the Brazilian Clinical Trials Registry (protocol number RBR-8kdrbz). The patient's legal guardians signed an informed consent form since all patients were sedated or non-cooperative. The study is reported according to the Consolidated Standards of Reporting Trials and Statement for Randomized Trials of Nonpharmacologic Treatments and the Template for Intervention Description and Replication [20, 21].

Randomization and allocation concealment

This was a 2-parallel group randomized clinical trial with a 1:1 intervention allocation. Computer-generated randomization lists were prepared using the website www.random.org, which sequentially distributed the patients into the control or NMES group. One researcher (PES) prepared sealed, opaque, and numbered envelopes. When each patient was enrolled in the study, the investigator opened the envelope with the smallest item number, containing the group.

Blinding

A blinded researcher (KLC) completed all functional assessments (ultrasonography, NED, and evoked peak force) and gathered all clinical data on the electronic medical record of each participant. Plasma analyses were performed by another blinded researcher (VCS).

Patients

Patients of both genders, between 18 and 60 years of age, who had undergone mechanical ventilation for up to 24 h, following a severe traumatic brain injury, were included. We excluded patients with a history of alcoholism, HIV, chronic kidney failure, spinal cord injury, pregnancy, skin lesions in the region to be treated, and patients with unstable fractures in the vertebral column and lower limbs.

Study flow

Patients were randomized to the control or NMES group. From this time point, they were followed from the first 24 h of mechanical ventilation up to the 14th day. The assessment of muscle architecture, NED, evoked peak force, and plasma sample analyses were performed in both groups, after the first 24 h and on days 3, 7, and 14. Both groups were submitted to routine physiotherapy for early rehabilitation based on the protocol proposed by Morris et al. [22]. The physiotherapy routine protocol was applied for 10 to 30 min twice every weekday by the staff physiotherapists. In both groups, the level of routine physiotherapy and intensity were adapted to the patient's cardiorespiratory status, level of sedation, cooperation, and functional status [22]. The protocol started with a global passive range of motion exercises in comatose or sedated patients, followed by active and resistive exercises, transfer to the edge of the bed or a chair, standing, and walking. The NMES group, in addition to daily routine physiotherapy, underwent NMES for 14 days bilaterally in the quadriceps femoris, hamstring, tibialis anterior, and gastrocnemius muscles.

NMES protocol

NMES was applied using two identical electrical stimulator devices (Dualpex 071, Quark Medical, Piracicaba, Brazil). The electrodes were positioned according to the motor point, as previously described by Botter et al. [23]. Before initiating the NMES protocol, the criteria for starting and interruptions were followed, as proposed by Kho et al. [24]. The NMES was applied once a day for 25 min, with pulse duration and frequency of 400 μs and 100 Hz, respectively. The time on (T_{ON}) was adjusted to 5 s and the time off (T_{OFF}) to 25 s, thus eliciting a total of 50 contractions per day. The current amplitude was applied as high as possible to evoke maximum contractions in each muscle group (type 5/5, according to Segers et al. classification [25]).

Outcomes

Primary outcomes were the effect of NMES over the muscle architecture, the presence of NED, and the evoked peak force. Secondary outcomes were the plasma level of cytokines and metalloproteinases, mechanical ventilation time, length of stay in the ICU, and length of hospitalization.

Muscle architecture

Muscle architecture was assessed through muscle thickness and echogenicity using B-mode ultrasonography, with an ultrasound device, M-Turbo® (Sonosite, Bothwell, WA, USA). A water-soluble transmission gel was applied to the measurement site. A linear transducer of 7.5 MHz was positioned perpendicular to the tissue interface with the lowest possible skin compression. The muscle thickness was measured in two muscles: rectus femoris (RF) and tibialis anterior (TA). The transducer was positioned according to a previous recommendation by Arts et al. [26]. Evaluation of the RF was conducted at the mean distance between the anterior superior iliac spine and the superior border of the patella. The TA was evaluated at the proximal 1/4 of the distance between the inferior border of the patella and the lateral malleolus. Measurements were performed in the same predefined location during the intervention period. After acquisition of the images, the assessment of thickness was performed [26].

The RF thickness was measured between the upper part of the femur and the lower limit of the superficial fascia of this muscle since we only measured the RF thickness without the vastus intermedius muscle. We used the deep fascia of this muscle to delimitate the vastus intermedius muscle in order to exclude it.

The TA was measured between the interosseous membrane (on the side of the tibia) and the superficial fascia of the TA. Points were marked with a semi-permanent dermographic pen to avoid different positions over the days.

Muscle thickness and echogenicity were analyzed utilizing ImageJ software (http://imagej.nih.gov/ij/) [27]. Muscle echogenicity was measured through a quantitative grayscale analysis, where the most affected muscles had a white presentation (i.e., increased echogenicity). The echogenicity assessment area of analysis was selected in each muscle, including the maximum possible area (trace technique) [4] with an 8-bit image resolution, in values ranging from 0 (black) to 255 (white). The echogenicity and thickness were determined in each muscle, considering the mean value of the three different measures [26].

Neuromuscular electrophysiological disorders

The presence of NED was assessed through the stimulus electrodiagnosis test (SET) in which rheobase and chronaxie were analyzed [4]. NED was recognized when

chronaxie values reached ≥ 1000 μs [6]. Rheobase is the minimal current intensity necessary to reach the neuromuscular excitability threshold applied with a rectangular pulse with an infinite duration (e.g., 1 s). Chronaxie is defined as the shortest pulse duration required to reach the neuromuscular excitability threshold by a current with twice the intensity of the rheobase [4]. The rheobase and chronaxie were measured with a single-phase current and rectangular-shape current. For rheobase assessment, the intensity was increased from 1 to 69 mA with individual 1-mA increments until eliciting a slight and visible muscle contraction. The evaluation was performed with a pulse duration of 1 s and intervals of 2 s between pulses [4]. For the evaluation of chronaxie, the pulse duration was increased from 20 μs to 1 ms in increments of 100 μs. From 1 ms, increments of 1 ms were performed with a current amplitude twice the value of the rheobase until eliciting a slight but visible muscle contraction [4].

The SET was performed in two muscles: RF and TA. A reference electrode (anode), area 100 cm^2, was placed on the patella for all measurements. The active electrode (cathode), in pen shape, approximately 1 cm^2 in area, was used to find the motor points. The same electrode was used to determine the values of rheobase and chronaxie. The scanning area was established based on previous publications [23]. The location of the motor point was also marked with a semi-permanent dermographic pen.

Evoked peak force

To evaluate the evoked peak force, we used a calibrated load cell (CKS model, Kratos Equipamentos, São Paulo, Brazil) attached to a platform and an electrical stimulator (Dualpex 071, Quark Medical, Brazil). Patients were laid down in a supine position with a 30° bed elevation. The platform was adjusted to the hip position at 90° of flexion and knee at 60° of the extension where the highest torque occurs [28]. The electrodes used to evoke muscle contraction were positioned on the RF muscle. The location was the line between the anterior superior iliac spine and the superior border of the patella at the motor points [23]. To find the motor point, we used a single-phase current of rectangular format with a pulse duration of 1 ms and 30 s of stimuli with an intensity of at least 10 mA. The anode electrode (100 cm^2 of area) was placed on the patella and the cathode pen electrode (1 cm^2 area) was used to perform the search for the motor point. Next, two electrocardiogram electrodes (≈ 1-cm^2 area) were positioned on the motor points. The stimuli were performed on twitch contraction with 69 mA, T_{ON} of 3 s, pulse duration, and frequency of 400 μs and 100 Hz respectively. Three stimuli were performed, and the interval between each measurement was 2 min. We used the highest detected value among the measures.

Clinical outcomes

In addition to the functional outcomes, clinical outcomes from medical records were analyzed as secondary outcomes. We evaluated time on mechanical ventilation, ICU mortality rate, length of stay in the ICU, and length of stay in the hospital.

Plasma sample analysis

Approximately 12 mL of blood was collected from the antecubital vein by the standard venipuncture technique using a commercially produced vacuum-sealed kit. Tubes were centrifuged (Centrifugal machine, 3250RPM, Model Centurion, São Paulo, Brazil) at room temperature for 15 min at 2500 rotations per minute (≈ 1000×*g*). Serum was aliquoted (250 μL) and directly stored at − 80 °C until analyses by a blinded examiner. Serum levels of TGF-β and IGF-1 were obtained by regular enzyme-linked immunosorbent assays (ELISA). The circulating assessment of IL-1β, IL-6, IL-8, IL-10, and TNF-*α* was performed by a multiplexed flow cytometry method. The proteolytic activity was measured by analysis of metalloproteinases 2 and 9 activity using the zymographic method. Biological replicate samples of patients containing 1 μL of plasma were added to 1 μL of SDS (8%) (v:v). Metalloproteinases 2 and 9 activity were visualized as clear white bands against a blue background by densitometric scanning (ImageScanner III, LabScan 6.0, Geneva, Switzerland). The analyses were performed in triplicate by a single-blinded examiner using ImageMaster 2D Platinum v7.0 (GeneBio) equipment, and the mean value of peak area was used in the final analysis (further details can be seen in Additional files 1 and 2).

Statistical analysis

Data normality was tested with the Shapiro Wilk test, and parametric variables are described as mean and 95% confidence interval (95% CI). Nonparametric variables are presented as a median and interquartile range [IQR]. In order to measure the statistical differences in the continuous variables (chronaxie, evoked peak force, thickness, echogenicity, and biochemical variables), the two-way ANOVA (time × group) with repeated measurements was used followed by the Bonferroni post hoc test. To evaluate the categorical variables (presence or absence of NED determined by chronaxie ≥ 1000 μs) intergroups, Fisher's exact test and log-Poisson regression to estimate risk ratio were used. The number needed to treat on day 14 of treatment was also computed. For the assessment of intragroup categorical variables, the McNemar test was used. Statistically significant differences were considered when $p < 0.05$. An intention-to-treat analysis was performed for all randomized participants. Missing data were replaced using the expectation-maximization method. For blood sample assessment, we evaluated an average of 10 participants per group due to

an error in biochemical analysis. Thus, we present this outcome as a preliminary result. After each statistically significant comparison between groups, the effect size and power were calculated. Effect sizes were determined using partial eta squared ($\eta\rho^2$). For the muscle architecture, NED, and evoked peak force data, where minimum clinically important differences were not nominated, Cohen's *d* coefficient was calculated to aid interpretation. For this, Cohen provided benchmarks to define small ($\eta\rho^2 = 0.01$), medium ($\eta\rho^2 = 0.06$), and large ($\eta\rho^2 = 0.14$) effects [29]. For statistical analysis, we used Statistica software, version 12 (StatsoftInc, Tulsa OK, USA, 2013).

Sample size was calculated using muscle thickness as the primary outcome. According to the study conducted by Gerovasili et al. [30], we estimated a difference between means and standard deviation of 1 mm ± 0.1 mm in muscle thickness after 14 days of treatment. Considering a study power of 85%, a significance level of 95%, and a sample size ratio of 1:1 (control group or NMES group), we reached the estimated number of 20 subjects per group on the 14th day. Thirty participants per group were recruited, totaling 60 subjects, allowing for possible dropouts during the intervention period [30, 31].

Results

Between June 2016 and July 2017, 278 patients with TBI were admitted to the Neurotrauma ICU, of these 60 were eligible according to the inclusion criteria and were therefore randomized for the study. The recruitment process and follow-up are described in the consort flow diagram

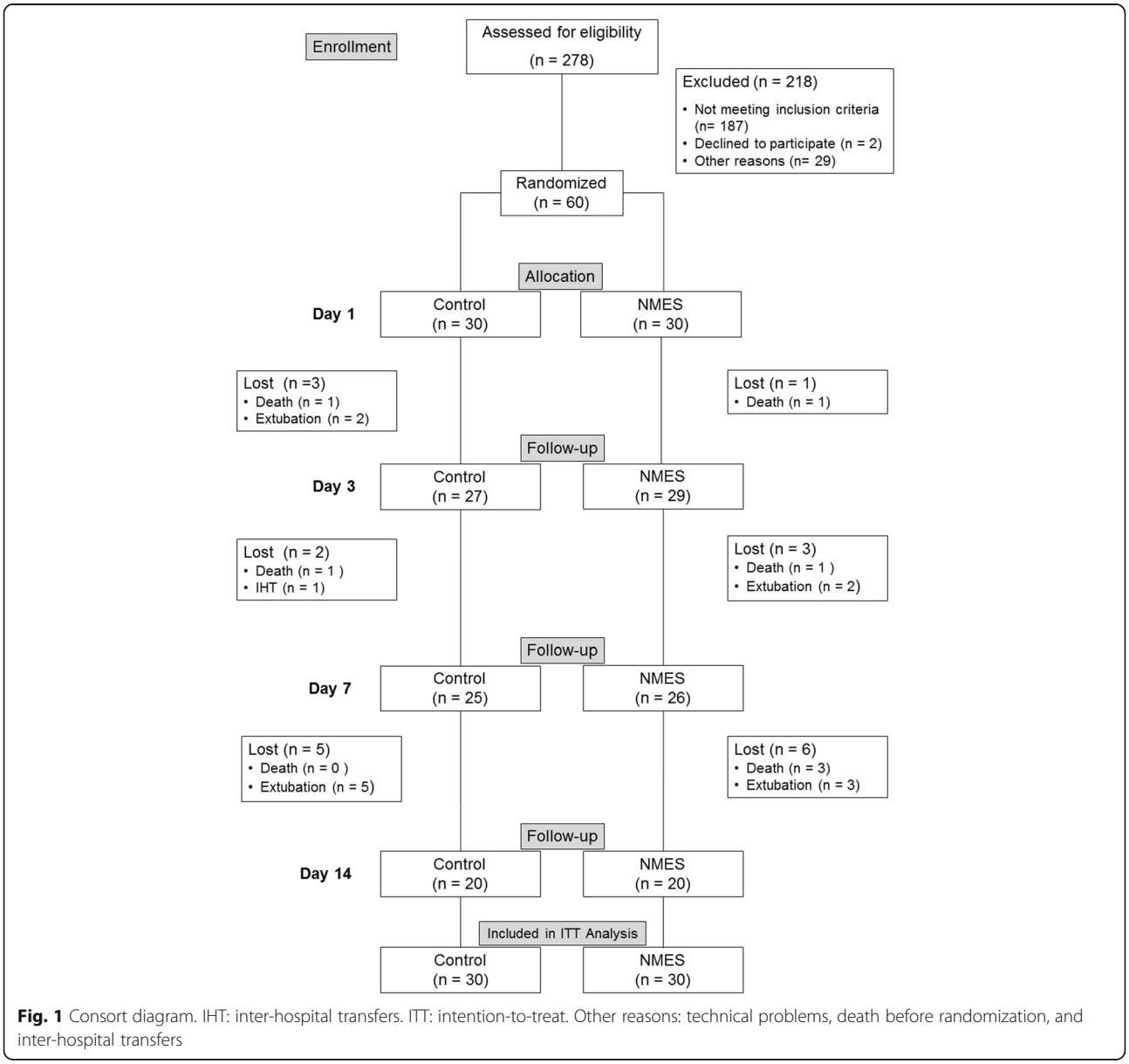

Fig. 1 Consort diagram. IHT: inter-hospital transfers. ITT: intention-to-treat. Other reasons: technical problems, death before randomization, and inter-hospital transfers

(Fig. 1). Patient clinical characteristics are presented in Table 1. Intention-to-treat analysis was applied, and all patients were analyzed on the 14th day.

NMES intervention

The quadriceps femoris, hamstring, tibialis anterior, and triceps sural muscles were stimulated at a mean intensity of 65 mA (95% CI 62 to 67). The general quality of evoked muscle contraction based on the Segers et al.'s [25] scale presented a median and [interquartile range] of 5 [4, 5]. From the initial fourteen expected NMES sessions per patient, eleven (95% CI 10 to 12) were performed on average, achieving a compliance rate of 79% (95% CI 68 to 84). Additionally, the mean intervention time of each session (electrode positioning and NMES protocol in all 4 muscle groups) was 72 min (95% CI 70 to 74). The main reasons for not performing NMES application were as follows: fever, 28 occurrences (46%), followed by hemodynamic instability, 19 occurrences (31%), psychomotor agitation, 9 occurrences (15%), and 5 sessions (8%) did not occur for other reasons.

Complications

No cases of skin burn, or injury caused by NMES, occurred.

Primary outcomes

Muscle architecture

The comparison between groups over days demonstrated a statistically significant interaction in the TA in favor of

Table 1 Patient clinical characteristics

	Group	
Patient characteristics	Control	NMES
n	30	30
Age, years	33 (95% CI 29 to 37)	30 (95% CI 27 to 33)
Male sex, *n* (%)	26 (87%)	26 (87%)
AIS (head)	5 [5–5]	5 [5–5]
AIS (lower extremities)	1 [0–1]	1 [0–1]
Injury severity score	26 [26–30]	27 [26–34]
Cause of injury		
• Motorcycle, *n* (%)	11 (37%)	10 (33%)
• Motor Vehicle, *n* (%)	7 (23%)	2 (7%)
• Beating, *n* (%)	8 (27%)	3 (10%)
• Gunshot, *n* (%)	2 (7%)	6 (20%)
• Pedestrians, *n* (%)	1 (3%)	4 (13%)
• Fall, *n* (%)	1 (3%)	5 (17%)
Penetrating trauma mechanism, *n* (%)	3 (10%)	8 (27%)
Operative intervention, *n* (%)	20 (67%)	20 (67%)
APACHE II at ICU admission	11 [9–14]	11 [8–13]
SOFA at ICU admission	6 [4–9]	5 [5–8]
SAPS 3 at ICU admission	40 [32–47]	40 [30–48]
Diffuse axonal injury grade	2 [2–3]	3 [2–3]
Leucocytes on admission, unit	18.8 (95% CI 8.1 to 29.4)	16.7 (95% CI 14.5 to 18.9)
PaO_2/FiO_2 ratio on admission	296 (95% CI 260 to 331)	276 (95% CI 242 to 311)
Glucose over 14 days, mg/dl	144 (95% CI 130 to 158)	144 (95% CI 133 to 155)
Predicted enteral feeding, (%)	77 (95% CI 74 to 80)	79 (95% CI 75 to 83)
Use of vasopressor drugs, days	7 (95% CI 5.1 to 8.9)	7.7 (95% CI 6 to 9.4)
Use of corticoid drugs, days	0	0
Use of carbapenem antibiotics, n (%)	0	0
Days of sedation on ICU, days	10.8 (95% CI 9 to 12.5)	10.9 (95% CI 9 to 12.7)
Patients sedated on day 14, *n* (%)	19 (63%)	19 (63%)
RASS on day 14	− 3 [− 4 to − 3]	− 3 [− 5 to − 3]

AIS Abbreviated Injury Scale, *APACHE II* Acute Physiologic and Chronic Health Evaluation II, *ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment, *SAPS 3* Simplified Acute Physiology Score 3, PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen, *RASS* Richmond Agitation Sedation Scale. Parametric variables are reported as mean and (95% confidence interval) and nonparametric, as median and [interquartile range]

NMES for preventing muscle loss: [interaction time × group ($F = 30.9$, $p < 0.0001$, power = 0.99, $\eta_\rho^2 = 0.35$)] (Fig. 2a). In the control group, the loss of muscle thickness _in _the _TA_ reached − 14% (95% CI − 17 to − 12) and − 0.33 mm (95% CI − 0.39 to − 0.26) on day 14, $p < 0.0001$. In the NMES group, muscle thickness did not significantly change on day 14 with a gain of 1% (95% CI − 4 to 3) and a mean difference of 0.01 mm (95% CI − 0.069 to 0.08), $p = 0.78$. The intraclass correlation coefficient (ICC) was calculated using three measures and showed excellent reliability (ICC 0.99) over the days. Similar results were found in the RF.

The comparison of muscle thickness between groups over days presented significant results in favor of NMES: interaction time × group [$F = 29.9$, $p < 0.0001$, power = 0.89, $\eta_\rho^2 = 0.34$] (Fig. 2b). The mean loss of RF thickness was − 21% (95% CI − 17 to − 24) and − 0.49 mm (95% CI − 0.58 to − 0.4) in the control group from baseline up to the 14th day, $p < 0.0001$. A non-significant loss was detected in the NMES group comparing the baseline with the 14th day, − 1% (CI 95% − 4 to 3) and − 0.04 mm (95% CI − 0.11 to 0.02), $p = 0.15$. The ICC was calculated using three measures and showed excellent reliability (ICC 0.98) over the days. NMES decreased the echogenicity of the TA and RF from the 7th and 14th days respectively, in the TA [interaction time × group ($F = 17.1$, $p < 0.0001$, power = 0.99, $\eta_\rho^2 = 0.23$)] (Fig. 2c), and the RF [interaction time × group ($F = 18.4$, $p < 0.0001$, power = 0.99, $\eta_\rho^2 = 0.24$)] (Fig. 2d).

Neuromuscular electrophysiological disorders

NMES induced significant reductions in chronaxie values in both the TA and RF. In the TA, significant differences were demonstrated between groups on day 14: [interaction time × group ($F = 16.7$, $p < 0.0001$, power = 0.99, $\eta_\rho^2 = 0.22$)] (Fig. 3a). In the control group, the TA chronaxie presented a significant increase over days: day 1 vs. day 14, $p < 0.0001$. NMES preserved neuromuscular excitability in the TA, maintaining chronaxie values over days: day 1 vs. day 14, $p = 0.99$. A similar significant interaction was observed for RF on day 14: [interaction time × group ($F = 8.8$, $p < 0.0001$, power = 0.99, $\eta_\rho^2 = 0.13$)] (Fig. 3b). In the control group, RF chronaxie values increased significantly over days: day 1 vs. day 14, $p < 0.0001$. In the NMES group, the neuromuscular excitability was preserved, demonstrated by chronaxie value maintenance over days: day 1 vs. day 14, $p = 0.99$.

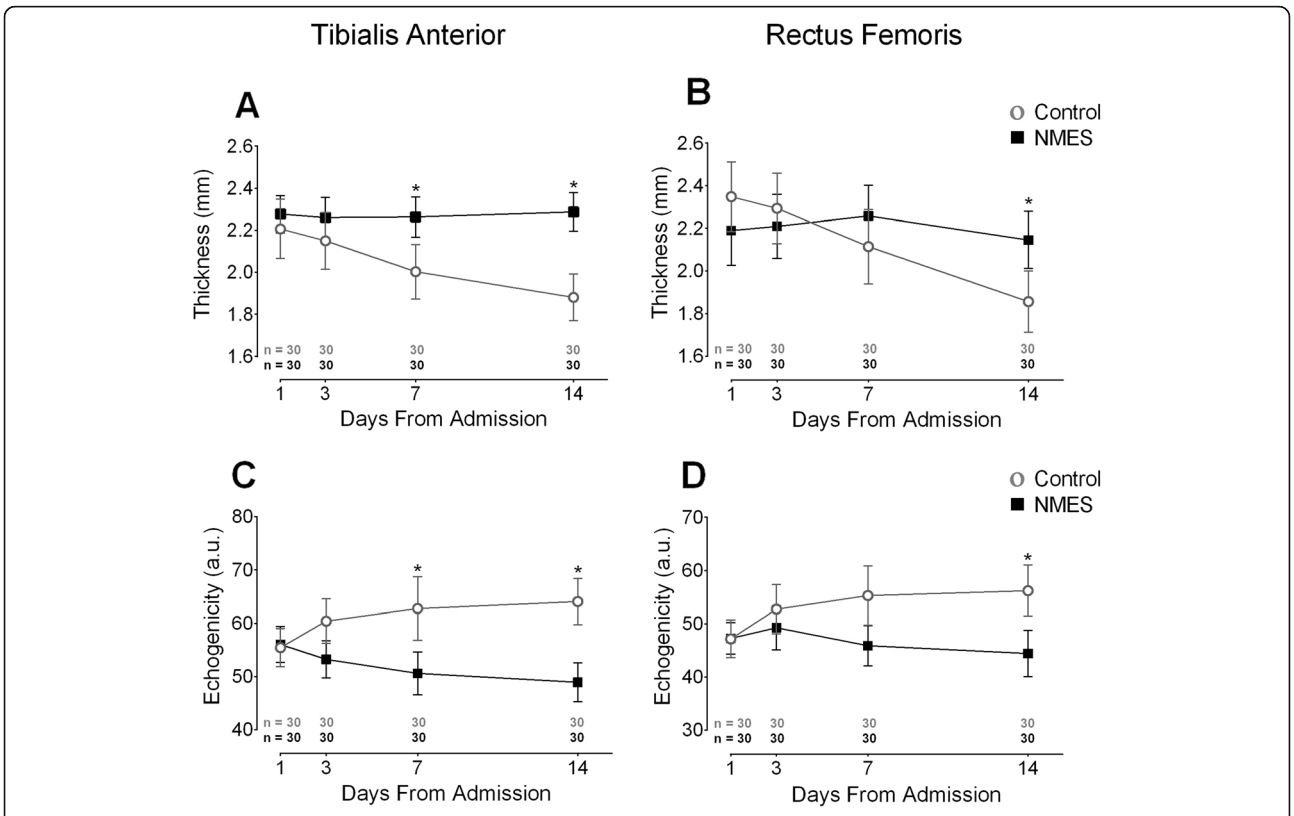

Fig. 2 Effect of bed rest time and NMES on muscle architecture. The left graphs (**a** and **c**) present the tibialis anterior muscle architecture assessed by B-mode ultrasonography. On the right side (**b** and **d**), the rectus femoris muscle architecture assessed by the same test is presented. mm: millimeters; a.u.: arbitrary units. *: statistically significant time x group effect on highlighted day. This effect was analyzed by repeated measures two-way ANOVA. An intention-to-treat analysis was performed for all randomized participants

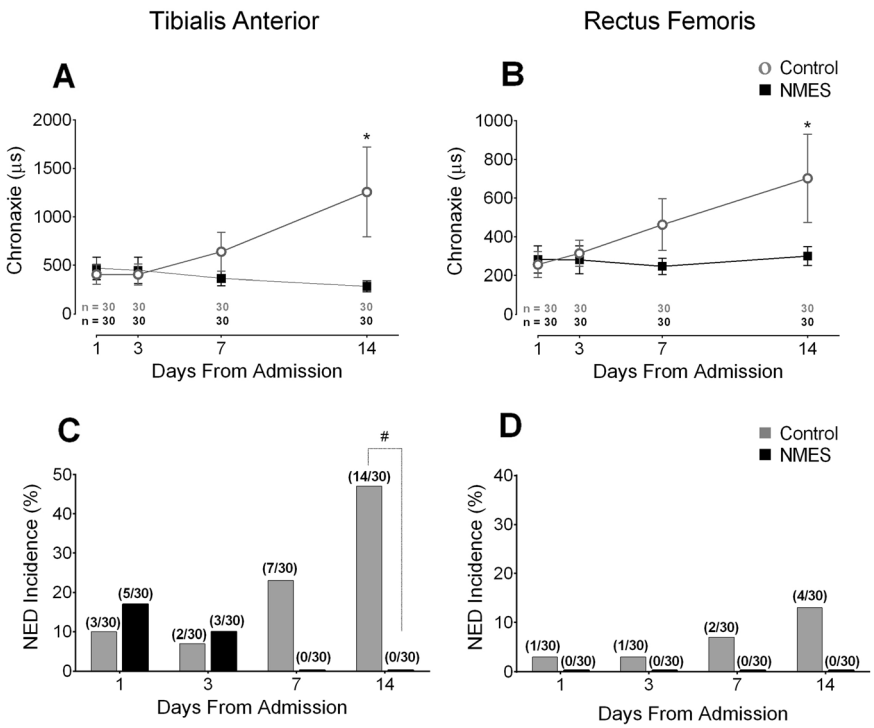

Fig. 3 Effect of bed rest time and NMES on neuromuscular electrophysiology. The left graphs (**a** and **c**) show neuromuscular electrophysiology of the tibialis anterior assessed by the stimulus electrodiagnosis test. On the right side (**b** and **d**), the rectus femoris neuromuscular electrophysiology is presented, assessed with the same test. µs: microseconds; NED: neuromuscular electrophysiological disorder. *: statistically significant time x group effect on highlighted day. This effect was analyzed by repeated measures two-way ANOVA. #: statistically significant differences between groups in the NED incidence analyzed by the Fisher's Exact test. The presence of NED was categorically defined once chronaxie ≥1000 µs. An intention-to-treat analysis was performed for all randomized participants

The control group presented NED incidence in the TA of 10% (3/30) on day 1 that increased to 47% (14/30) on day 14 (Fig. 3c), $p = 0.003$, power = 0.85. The NMES group presented NED incidence in the TA of 17% (5/30) on day 1 that decreased to 0% (0/30) on day 14 (Fig. 3c), $p = 0.06$. The control group presented a significantly higher incidence of NED (14/30) in the TA, compared with the NMES group (0/30) on the 14th day, ($p = 0.0001$, power = 0.99, and risk ratio = 16, (95% CI 2.9 to 88.9) (Fig. 3c). The control group also presented a higher incidence of NED in the RF than the NMES group on the 14th day: 13% (4/30) vs. 0% respectively, but this was not statistically significant $p = 0.12$ (Fig. 3d). Differences between groups were only detected at 14 days in the TA. Taking into consideration the NED incidence in the TA in both groups, the number needed to treat was 2.13 in 14 days of treatment to prevent a NED event.

Evoked peak force

The comparison between groups over days demonstrated a statistically significant interaction in favor of NMES [interaction time × group ($F = 71.9$, $p < 0.0001$, power = 0.99, $\eta_p^2 = 0.55$)] (Fig. 4). Comparing with the baseline, patients in the NMES group presented a significant increase in evoked peak force from the 7th day, $p = 0.001$. In the NMES group, the evoked peak force increased from day 1 to day 14 with a mean difference of 2.34 kg/f (95% CI 1.89 to 2.79), $p < 0.0001$. On the other hand, the control group presented a significant decrement in evoked peak force from the 7th day compared with baseline, $p < 0.0001$. In the control group, the evoked peak force decreased from day 1 to day 14 with a mean difference of − 1.55 kg/f (95% CI − 2.05 to − 1.05), $p < 0.0001$. Differences between groups were detected from the 7th day, $p < 0.0001$.

Secondary outcomes

Plasma sample analysis

The plasma cytokines (IGF-I; IL-1 β; IL-6; TGF-β; TNF-α) and metalloproteinases (MMP-2 and MMP-9) exhibited less precise results, with confidence intervals that spanned worthwhile or trivial effects. The data from these outcomes are presented in the Additional files 1 and 2.

Clinical outcomes

Patients in the control group remained on mechanical ventilation for 15.5 days [8.8–19] vs. 14 days [8–18] in the NMES group: median difference of 1.5 days, $p = 0.65$.

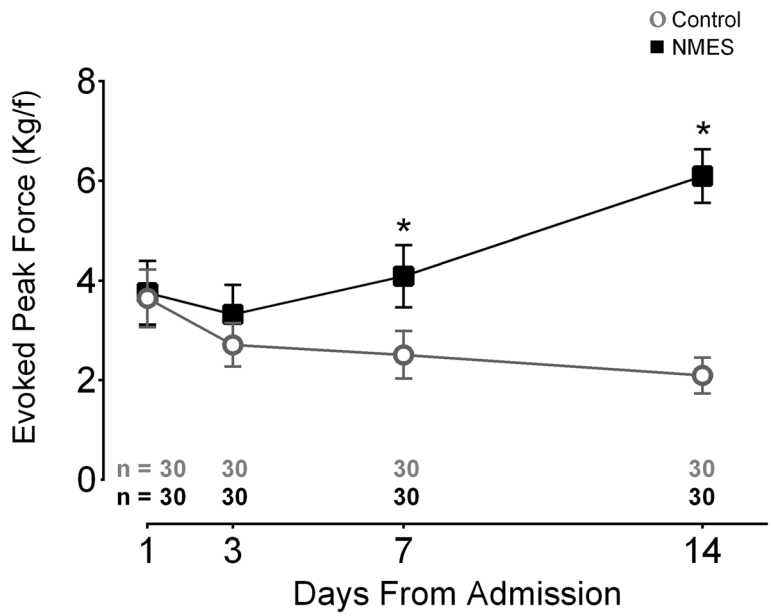

Fig. 4 Effect of bed rest time and NMES on electrically evoked peak force. This graph presents the electrically evoked peak force of the rectus femoris muscle. The highest value after three bouts of electrical stimuli is reported. The contraction was elicited with a pulse duration and frequency of 400 μs and 100 Hz respectively with 69 mA amplitude and 3 seconds of time on. Two electrocardiogram electrodes were placed over the rectus femoris motor points. Kg/f: kilogram force; *: statistically significant time x group effect on highlighted day. This effect was analyzed by repeated measures two-way ANOVA. An intention-to-treat analysis was performed for all randomized participants

The NMES group presented lower median differences in length of stay in the ICU (delta = − 0.5 day, $p = 0.58$) and hospital length of stay (delta = − 8 days, $p = 0.06$) but no significant statistical differences were detected. More details are presented in Table 2. No differences were detected in ICU mortality.

Discussion

The present study demonstrates that a clinical-like NMES protocol is effective to preserve the muscle architecture, increase evoked peak force, and decrease the incidence of NED. Muscle architecture and strength benefits were detected from the 7th day, while the effect

Table 2 Clinical outcomes

Group				
Outcomes	Control	NMES	*p* value	Effect size
N	30	30	–	
Incidence during the first 14 days, *n* (%)				
• Sepsis	13 (43%)	16 (53%)	0.44	–
• Septic shock	9 (30%)	10 (33%)	0.78	–
• Multiple organ failure	4 (13%)	6 (20%)	0.73	–
Time on MV, days	15.5 [8.8–19]	14 [8–18]	0.65	0.1
Time on MV (survivor), days	16 [9–19]	14 [12–18]	0.80	0.09
ICU length of stay, days	19.5 [12–27.3]	19 [10–26]	0.58	0.28
ICU length of stay (survivor), days	20 [15–31]	23 [15–26]	0.98	0.2
Hospital length of stay, days	42 [20–56]	34 [15–41.2]	0.06	0.5
Hospital length of stay (survivor), days	42 [23–53]	35 [23–44]	0.32	0.3
Mortality in ICU, *n* (%)	3 (10%)	5 (17%)	0.71	–

ICU intensive care unit, *MV* mechanical ventilation. Parametric variables are reported as mean and (95% confidence interval) and nonparametric, as median and [interquartile range]. *p* values were calculated by the unpaired *t* test, chi-square test, or Mann-Whitney in accordance with each data distribution and characteristics

of NMES to reduce NED was only observed from the 14th day of treatment. It seems that the time of NMES protocol needed is crucial to guide decision-making concerning treatment effects to counteract skeletal muscle atrophy, weakness, and NED in critically ill TBI patients. The present study was the first clinical trial to evaluate the effect of NMES on evoked peak force and neuromuscular excitability.

Muscle architecture

Our results are supported by several studies that demonstrated the effectiveness of NMES to prevent muscle atrophy in critically ill patients [30, 32–34]. In a study with critically ill patients with similar clinical characteristics, Hirose et al. [33] showed that NMES prevented muscle atrophy in patients with consciousness disorders. These authors applied NMES for 42 days and demonstrated significant results in preventing muscle atrophy starting on the 14th day of treatment, in agreement with our results [33].

It seems that ICU admission etiology and clinical status are strongly related to muscle loss severity [35, 36]. Moreover, according to the study of Strasser et al. [34], the protective effect of NMES over muscle mass is correlated with the quality of evoked muscle contraction [34]. These authors compared the effect of maximum tolerable muscle contraction (~ quality type 5) with visible muscle contraction (~ quality type 3). Their results demonstrated a reduction in muscle atrophy only in the treatment with maximum tolerable muscle contraction.

Some studies [19, 31, 37] were not able to report an effect of NMES on muscle atrophy in the acute phase of critical illness. Gruther et al. [19], Fischer et al. [31], and Poulsen et al. [37] possibly used NMES protocols with lower intensities, since they reported evoking only visible contraction instead of reaching the maximum contraction, as has been recommended to induce muscle hypertrophy [17, 34, 38]. Additionally, Poulsen et al. [37] recruited extremely debilitated patients with septic shock who might not be able to benefit from this treatment [35].

Neuromuscular electrophysiological disorders

We demonstrated that NMES can reduce the incidence of NED. The beneficial effects of NMES to treat NED may have been elicited through improvement in the neuromuscular and systemic circulation [39, 40]. The improvement in blood supply may protect neurons and myofibers against tissue dysoxia, which has been considered an important mechanism to induce axonal degeneration [39, 41]. Evoked contraction can also protect cellular machinery against disuse, mimicking physiological muscle contraction [32, 42].

Routsi et al. [43], in a landmark study, were the first to demonstrate the efficacy of NMES to prevent critical ill polyneuromyopathy, although without reporting therapeutic effects. A protocol for evoking 150 contractions was used with the current amplitude adjusted to elicit visible contraction (quality type from 3 to 4). In their study, the MRC scale was used to diagnose polyneuromyopathy.

In the present study, the presence of NED was used to define a diagnosis of peripheral nerve disease, which is expected in patients with polyneuromyopathy [44]. Paternostro-Sluga et al. [6] showed that the stimulus electrodiagnosis test (SET) is an excellent screening test to detect peripheral nerve disease with a sensitivity ranging from 90 to 100% when compared with needle electroneuromyography. Within the SET evaluation, we demonstrated a NED prevalence of 17% on the 1st day in the NMES group and an incidence of 10% on the 3rd day, though no cases were observed on the 7th and 14th days. Therefore, our results show that the current NMES protocol (fifty maximum evoked contractions) might not only prevent but also treat NED. Thus, the differences in NMES protocols and methods used to detect polyneuromyopathy may explain some discrepancies between the results of Routsi et al. [43] and ours.

Evoked peak force

Muscle strength has been considered an independent factor for ICU mortality, length of stay, readmission to the ICU, and protracted function disability [12, 13, 45]. Therefore, we sought to assess strength through evoked peak force using an accurate and reliable new device as previously described [46]. Evoked peak force seems to be particularly advantageous over the MRC strength scale due to a higher sensitivity to detect change over time and the possibility of being used in unconscious patients [46, 47].

Even though we did not detect any increase in RF muscle thickness, the NMES protocol elicited a significant increase in evoked peak force compared with the control group. These findings are consistent with previous reports confirming that short periods of NMES can increase muscle strength even without hypertrophy [48]. It is now accepted that these strength gains are predominantly associated with neural adaptations [49, 50]. This idea is supported in the present study by lower levels of chronaxie identified in the NMES group. Chronaxie has been used to define the level of neuromuscular excitability, and typical values range from 60 to 200 μs [4]. If neuromuscular excitability decreases, chronaxie values increase [4]. It is important to emphasize that some events (such as sepsis and sedation) may impact muscle strength and should be considered when interpreting the present results [51].

In contrast, Fossat et al. [35] did not find any increments in muscle strength provided by NMES in critically

ill patients. Considering the differences in the treatment protocol, their results could be also associated with the patients' characteristics. In the present study, we controlled some treatment bias, as has been advocated by Reid et al. [52], comparing the effect of NMES solely with passive exercises. Moreover, Fossat et al. assessed muscle strength according to the MRC scale, which can present the ceiling effect bias [35].

Plasma sample analysis and clinical outcomes

The estimates of the effect of the present protocol did not generate any clear implications about whether or not NMES plays a critical role in cytokines and metalloproteinases. Nevertheless, these preliminary data could support future randomized controlled trials. Despite the significant effect of NMES on functional outcomes (muscle architecture, NED, and evoked force), no statistically significant impact was found on the clinical outcomes: time on mechanical ventilation, length of ICU stay, and ICU mortality rate. These results may be associated with an insufficient sample size to detect a statistical difference for these secondary outcomes. Accordingly, a retrospective study with a large sample size (1118 neurocritical patients) demonstrated the significant impact of early rehabilitation for shortening ICU and hospital stays with a mean difference of 0.7 and 2.7 days respectively [53].

Study limitations

Some limitations should be addressed in our study. This was a single-center trial with traumatic brain injury critically ill patients; thus, the findings may not be generalizable to different settings and patients. It was not possible to perform a follow-up of the primary outcomes, as stated in the CONSORT guideline. We did not assess muscle atrophy using the ultrasonography cross-sectional area. It is possible that our results underestimated muscle atrophy and missed statistical correlation with either of the outcomes, as recently described [54]. However, despite the higher sensitivity of the cross-sectional area compared with thickness, we were able to detect significant statistical differences with excellent reliability. In addition, although the appraiser was blinded to the groups, some healthcare providers were aware of the study allocation. Finally, the small simple size did not allow assessment of the effects of NMES on major clinical outcomes.

Future perspectives

Further studies are required to define the optimal NMES prescription (parameters, number of contractions, therapy regularity, and treatment duration).

Furthermore, future multicenter trials should enroll an appropriate number of participants to better understand the effect of NMES on clinical outcomes. These studies should also evaluate the major clinical usefulness of NMES, such as the effect on treatment cost, ICU mortality, ICU length of stay, quality of life, and all domains of the International Classification of Functioning, Disability and Health (ICF) after hospital discharge.

Conclusion

NMES applied daily for fourteen consecutive days reduced muscle atrophy, the incidence of neuromuscular electrophysiological disorders, and muscle weakness in critically ill TBI patients. At least 7 days of NMES were required to elicit the first significant results.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s40560-019-0417-x.

Additional file 1. Supplementary. Results.

Additional file 2: Table S1. Effect of NMES and bed rest on biochemical markers in critically ill patients over 14 days.

Abbreviations

AIS: Abbreviated injure scale; ANOVA: Analysis of variance; CI 95%: 95% confidence interval; ICC: Intraclass correlation coefficient; ICU: Intensive care unit; ICUAW: ICU-acquired weakness; ISS: Injury severity score; NED: Neuromuscular electrophysiological disorder; NMES: Neuromuscular electrical stimulation; RF: Rectus femoris; SET: Stimulus electrodiagnosis test; TA: Tibialis anterior; TBI: Traumatic brain injury; ηp^2: Partial eta squared

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Authors' contributions

All authors contributed substantially to the submitted work, and read and approved the final manuscript. In particular, PES participated in the design of the study, data analysis, data acquisition, and drafting and writing of the manuscript. RMC, GCJr, LV, and VMS participated in the design of the study, analysis, and drafting of the manuscript. KLC, AE, and JLQD participated in data acquisition and drafting of the manuscript. RCM and LOD participated in data analysis and drafting of the manuscript; OTN and VCS critically revised the manuscript and contributed to the design of the study and data analysis. Finally, NB and JLQD conceived of and helped with the coordination of the study, critically revised the manuscript, and provided final approval.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

Ethics approval and consent to participate
The study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards approved the protocol (FEPECS/SES-DF research ethics committee, Brasília, Brazil, protocol number 1107517). The patients' legal guardians signed an informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Research Paper

Pharyngeal electrical stimulation for neurogenic dysphagia following stroke, traumatic brain injury or other causes: Main results from the PHADER cohort study

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ABSTRACT

Background: Neurogenic dysphagia is common and has no definitive treatment. We assessed whether pharyngeal electrical stimulation (PES) is associated with reduced dysphagia.
Methods: The PHAryngeal electrical stimulation for treatment of neurogenic Dysphagia European Registry (PHADER) was a prospective single-arm observational cohort study. Participants were recruited with neurogenic dysphagia (comprising five groups – stroke not needing ventilation; stroke needing ventilation; ventilation acquired; traumatic brain injury; other neurological causes). PES was administered once daily for three days. The primary outcome was the validated dysphagia severity rating scale (DSRS, score best-worst 0–12) at 3 months.
Findings: Of 255 enrolled patients from 14 centres in Austria, Germany and UK, 10 failed screening. At baseline, mean (standard deviation) or median [interquartile range]: age 68 (14) years, male 71%, DSRS 11·4 (1·7), time from onset to treatment 32 [44] days; age, time and DSRS differed between diagnostic groups. Insertion of PES catheters was successfully inserted in 239/245 (98%) participants, and was typically easy taking 11·8 min. 9 participants withdrew before the end of treatment. DSRS improved significantly in all dysphagia

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groups, difference in means (95% confidence intervals, CI) from 0 to 3 months: stroke (n = 79) −6·7 (−7·8, −5·5), ventilated stroke (n = 98) −6·5 (−7·6, −5·5); ventilation acquired (n = 35) −6·6 (−8·4, −4·8); traumatic brain injury (n = 24) -4·5 (−6·6, −2·4). The results for DSRS were mirrored for instrumentally assessed penetration aspiration scale scores. DSRS improved in both supratentorial and infratentorial stroke, with no difference between them (p = 0·32). In previously ventilated participants with tracheotomy, DSRS improved more in participants who could be decannulated (n = 66) −7·5 (−8·6, −6·5) versus not decannulated (n = 33) −2·1 (−3·2, −1·0) (p<0·001). 74 serious adverse events (SAE) occurred in 60 participants with pneumonia (9·2%) the most frequent SAE.

Interpretation: In patients with neurogenic dysphagia, PES was safe and associated with reduced measures of dysphagia and penetration/aspiration.

Funding: Phagenesis Ltd.

Research in context

Evidence before this study

Pharyngeal electrical stimulation (PES) is a potential treatment for neurogenic dysphagia and was associated with less dysphagia (assessed using the dysphagia severity rating scale, DSRS) and instrumentally-assessed penetration/aspiration (penetration aspiration scale, PAS) in an individual-patient data meta-analysis of 3 pilot trials in stroke patients. The phase III STEPS trial of PES for post-stroke dysphagia was neutral on PAS and DSRS, probably because dysphagia was mild at baseline, the active group were undertreated and the sham group received some treatment. In the PHAST-TRAC trial involving a more severe group of patients with post-stroke dysphagia who had required ventilation and could not then have their tracheotomy cannula removed due to persistent dysphagia, PES facilitated decannulation as compared with sham treatment, both in phase II and III trials. A phase II trial in multiple sclerosis showed improvements in PAS score. PES has a CE mark for neurogenic dysphagia.

Added value of this study

This observational cohort study included 245 adults with neurogenic dysphagia related to stroke, traumatic brain injury or following mechanical ventilation and tracheotomy. PES was safe and associated with a significant improvement in oropharyngeal dysphagia and reduced penetration/aspiration risk both overall and in each diagnostic group.

Implications of all the available evidence

In neurogenic dysphagia, pharyngeal electrical stimulation is associated with less dysphagia and penetration/aspiration.

1. Introduction

Neurogenic dysphagia is common in conditions such as stroke and traumatic brain injury (TBI) and is associated with a poor outcome [1]. Although there is no proven treatment, potential efficacious interventions for post-stroke dysphagia (PSD) include acupuncture and behavioural therapies [2]. Pharyngeal electrical stimulation (PES) is a potential treatment for neurogenic dysphagia based on physiological studies [3]. PES has been studied in several phase II trials in patients with PSD [4,5] and was associated with less dysphagia (assessed using the dysphagia severity rating scale, DSRS [4,6]) and instrumentally-assessed penetration/aspiration (penetration aspiration scale, PAS [7]) in an individual-patient data meta-analysis [8]. However, a phase III trial of PES for PSD was neutral on PAS and DSRS, possibly because dysphagia was mild at baseline, the active group were undertreated and the sham group received some treatment [9]. In a more severe group of patients with PSD, specifically those who had required ventilation and could not then have their tracheotomy cannula removed due to persistent dysphagia, PES facilitated decannulation as compared with sham treatment, both in phase II and III trials [10,11]. Moreover, PES has been studied in other neurogenic causes of dysphagia and a phase II trial in multiple sclerosis showed improvements in PAS score [12].

PES has a European *Conformité Européenne* (CE) mark for the treatment of neurogenic dysphagia and US Food & Drug Administration breakthrough designation. Here we report the results of a prospective observational cohort study designed to assess the real-world clinical outcome and safety of PES for reducing neurogenic dysphagia.

2. Methods

2.1. Objectives

Sensorimotor pathways associated with swallowing are susceptible to damage from a variety of neurological insults, broadly categorisable as either non-progressive (e.g. stroke, TBI, critical illness polyneuropathy, Guillain-Barre syndrome) or progressive (e.g. dementia, multiple sclerosis, Parkinson's disease). Since it is the same pathways being damaged, PES targets the resulting dysphagia rather than the initial causative disease. Hence, the primary objective of the study was to assess the real-world effect of PES on dysphagia severity (assessed using the validated dysphagia severity rating scale, DSRS [4,6]) in patients with neurogenic dysphagia. Secondary objectives assessed the effect of PES on penetration/aspiration (PAS [7]) determined using instrumental-testing; feasibility, tolerability and safety of PES; and its ease of use.

2.2. Study design

PHADER was a prospective single-arm observational clinical cohort study. The study was performed in secondary and tertiary hospitals caring for patients with stroke, TBI or other neurological conditions, and who had dysphagia. The study protocol is available at http://www.phagenesis.com/wp-content/uploads/2020/06/AHE02-PHADER_CIP.pdf. This report follows The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

2.3. Setting

Recruitment and follow-up took place between March 2015 and September 2018 at 14 secondary/tertiary care centres in Austria, Germany and UK. Analyses were completed in April 2020.

2.4. Study population

Patients were eligible for the study if they were adults, had oropharyngeal dysphagia with a DSRS score of 6 or higher, and belonged to one of the following diagnostic groups: dysphagia related to (A) stroke not requiring mechanical ventilation; (B) stroke requiring mechanical ventilation and tracheotomy; (C) mechanical ventilation in non-stroke, non-TBI; (D) TBI with or without the need for mechanical ventilation and tracheotomy; and (E) any other neurological cause not needing mechanical ventilation and tracheotomy. Key exclusion criteria were: non-neurogenic dysphagia (e.g. cancer), presence of an implanted cardiac pacemaker or cardioverter defibrillator, pregnancy or a nursing mother. Full inclusion and exclusion criteria are listed in the Supplement 1 (page 4) and given in the uploaded statistical analysis plan.

2.5. Approvals and training

The study was funded and sponsored by Phagenesis Ltd (Manchester UK) and approved by National/Local Research Ethics Committees. Patients signed a standard Research Ethics Committee approved Informed Consent Form explaining the conditions of study participation; where allowed, a legal representative of patients lacking capacity gave proxy consent. All sites received face-to-face training in the study protocol and delivery of PES.

2.6. Intervention

The device used was the CE-marked Phagenyx Base Station® and Phagenyx Catheter® (Phagenesis Ltd, Manchester UK); the CE-mark covers the treatment of neurogenic dysphagia and devices were used as marketed and were not investigational. The treatment catheter is a nasogastric feeding tube with built-in stimulation electrodes, with stimulation provided at 5 Hz for 10 min on each of three consecutive days [4,9,11]. Stimulation was optimised for each treatment by the Base Station software and operator, and intensity set at 75% of the tolerable limit above sensory threshold. The catheter houses a microchip that allows the application of the therapy on three occasions on consecutive days.

2.7. Outcomes

The primary outcome measure was the validated 13-level DSRS score [4,6] at 3 months post-treatment. Secondary outcomes comprised dysphagia severity assessed using the functional oral intake scale (FOIS) [13], and penetration-aspiration assessed with the PAS [7] measured instrumentally (using videofluoroscopy (VFS) or fibreoptic endoscopic evaluation of swallowing (FEES)). Assessments were made at baseline and then at days 5 (range 4–6) and 9 (range 7–21), and 3 months (range 2–4) after catheter insertion. Ease of catheter insertion and time required for insertion was determined after enrolment. Treatment optimisation parameters (threshold, tolerance and stimulation intensity) were recorded on each of the three treatment days. The protocol for decannulation followed that used in the PHAST-TRAC trial [11]; time-to-decannulation was determined during follow-up, and feeding status [14], serious adverse events (SAEs) and deaths measured at month 3.

2.8. Statistical analyses

Sample size was set at 60 participants per diagnostic groups so that the presence of a device deficiency in 5% of the population could be ruled out with confidence of 80%. With 5 groups, the intended total sample size was 300. Group E (other neurogenic dysphagia) was expected to recruit at about half the ideal rate; with redistribution of group E patients the total sample would remain at 300. A statistical analysis plan was developed prior to completion of data collection and lock (Supplement 2; first draft 10 April 2015, updated 12 May 2019, finalised 30 Aug 2019; data lock 30 Oct 2019). Analyses are by intention to treat and results are presented for all participants, for each of the diagnostic groups A-E, by stroke location (supratentorial, infratentorial for groups A, B) and by whether tracheotomised patients were decannulated or not (groups B-D).

A substudy compared the effect of PES on DSRS in non-ventilated stroke patients (PHADER group A) with the control group comprising patients in the STEPS trial [9] who had been randomised to receive sham treatment.

Data are shown as number (%), median [interquartile range, IQR] or mean (standard deviation, SD); difference in means (DIM), mean difference (MD), odds ratio (OR) and 95% confidence intervals (95% CI). Analyses used Fisher's exact test (baseline data), Chi-square test (baseline data, discharge disposition, cannulation status), paired *t*-test (DSRS, FOIS, PAS; to focus on participants not lost to follow-up and so reduce bias), unpaired *t*-test (unpooled, DSRS, FOIS, PAS), Kruskal-Wallis test (baseline data, days), one-way analysis of variance (baseline data, times, ease of use, stimulation levels), analysis of covariance (ANCOVA), ordinal logistic regression (OLR) and multiple linear regression (MLR). The proportional odds assumption was tested using the likelihood ratio test; in each case, the assumption of proportional odds was not violated (all $p>0.05$). MLR assumptions were tested for evidence of linear relationships, multivariate normality and absence of multicollinearity; similarly, these assumptions were not violated. Regression analyses were adjusted for age, sex, NIHSS, mRS, stroke type, time from stroke onset to treatment and baseline value (adjustment variables are all prognostic for recovery after stroke). The primary outcome was examined in the pre-specified diagnostic groups, stroke location (supra/infra-tentorial), and decannulation status. A cumulative plot of time to hospital discharge and/or re-start of oral feeding is given. No imputation was performed for missing data, and no adjustment was made for multiplicity of testing. $P<0{\cdot}05$ is considered significant; analyses were performed using SAS (version 9.4, SAS Institute).

2.9. Role of the funder/sponsor

The funder was involved in the design and conduct of the study and data management, and compensated sites for data collection. A clinical research organisation (FAKKEL, Belgium) performed study management and source data verification. Most analyses were performed by Cytel Corp as specified by Phagenesis Ltd and the Study Steering Committee. The funder reviewed and approved the manuscript. All authors had full access to all data. The corresponding author had final responsibility for the decision to submit for publication.

3. Results

Due to a limited population of patients fulfilling the criteria for Group E (as anticipated above), and to a lesser extent non-stroke ventilator-related and TBI (Groups C, D), the trial was stopped after recruitment of 252 patients. Of these, 7 were excluded from analysis due to lack or withdrawal of consent, spontaneous recovery or unavailability of a catheter or death (Fig. 1). 6 participants had a failed attempt at catheter insertion but are included in the analyses (intention-to-treat). Although recommended in the protocol, not all recruiting sites kept screening logs and so the total number of patients screened for the study is not known. By diagnostic group, 84 had an index stroke not requiring mechanical ventilation (group A); 99 had an index stroke requiring mechanical ventilation and tracheotomy (group B); 35 had dysphagia related to a non-stroke/non-TBI cause (group C) with 15 of these due to critical illness polyneuropathy (Supplement 1, Table I); 24 had a TBI (group D); and 3 had another cause

for their dysphagia (group E, Supplement 1, Table I). Abbreviated results on 15 participants in group C who presented to one centre have been published previously [15]. Due to the limited number of patients in Group E ($N = 3$) it was deemed permissible that these participants should not be included in most analyses. Overall, the average age was 68 (14) years although this varied significantly between groups with TBI patients the youngest (63 years) and non-ventilated stroke the oldest (74 years) (Table 1). The majority of patients were male (71%) and 17% of stroke participants had an infratentorial lesion. Time from onset to treatment averaged 32 [44] days and differed between the groups being shortest in stroke patients 16 [24] days and longest in TBI 73 [154] days. In patients enrolled with a stroke, approximately one-third received thrombolysis; a similar proportion received mechanical thrombectomy (with an overlap in these).

On average it took just under 12 min to insert the catheter (Supplement 1, Table II) and this was reported to be easy with mean scores of >5 out of 7. Overall, 1·1 catheters were used per participant. There were no differences between the diagnostic groups with respect to user experience. Although threshold levels did not differ between the groups, tolerance and therefore stimulation levels were highest in stroke patients who had been ventilated (30·9 mA on day 1) and lowest in non-ventilated stroke patients (23·8 mA) (Supplement 1, Table III). Stimulation levels did not change over the three days of treatment.

3.1. Primary outcome

Participants were severely dysphagic at baseline (mean DSRS 11·4 of total score 12); however, severity varied between the groups and was highest in participants who received mechanical ventilation and lowest in non-ventilated stroke (Table 2). DSRS fell significantly over 3 months of observation (Fig. 2) by more than 6 points, both overall and in three of the four diagnostic groups (A, B and C) over the 3 months of follow-up; less decline (4·5 points), albeit still statistically significant, was seen in TBI (Table 2). In those participants who had DSRS scores at three months as well as at baseline, the reduction in DSRS was 6·3 points. Improvement was seen in all three DSRS categories of fluids, diet and supervision, again both overall and in each diagnostic group (Supplement 1, Table IV). When assessed in pre-defined subgroups, the reduction in DSRS was greater in participants with shorter times from onset to treatment and duration of ventilation than those with longer times (Fig. 3).

3.1.1. By stroke location

Participants with stroke came from Groups A and B. When compared with patients with supratentorial stroke, those with infratentorial stroke were of comparable age, sex, premorbid mRS and conscious level (GCS) at baseline but had less severe stroke (NIHSS) and penetration/aspiration (PAS), and required higher levels of stimulation current (Supplement 1, Table V, VI). Dysphagia severity (DSRS, FOIS) was comparable at baseline and PES was associated with improvements in DSRS and FOIS in both groups; the final DSRS score did not differ between participants with supratentorial and infratentorial stroke (Supplement 1, Table VI). In participants who were cannulated at baseline, decannulation was feasible in both supratentorial and infratentorial stroke, and rates did not differ between the two groups.

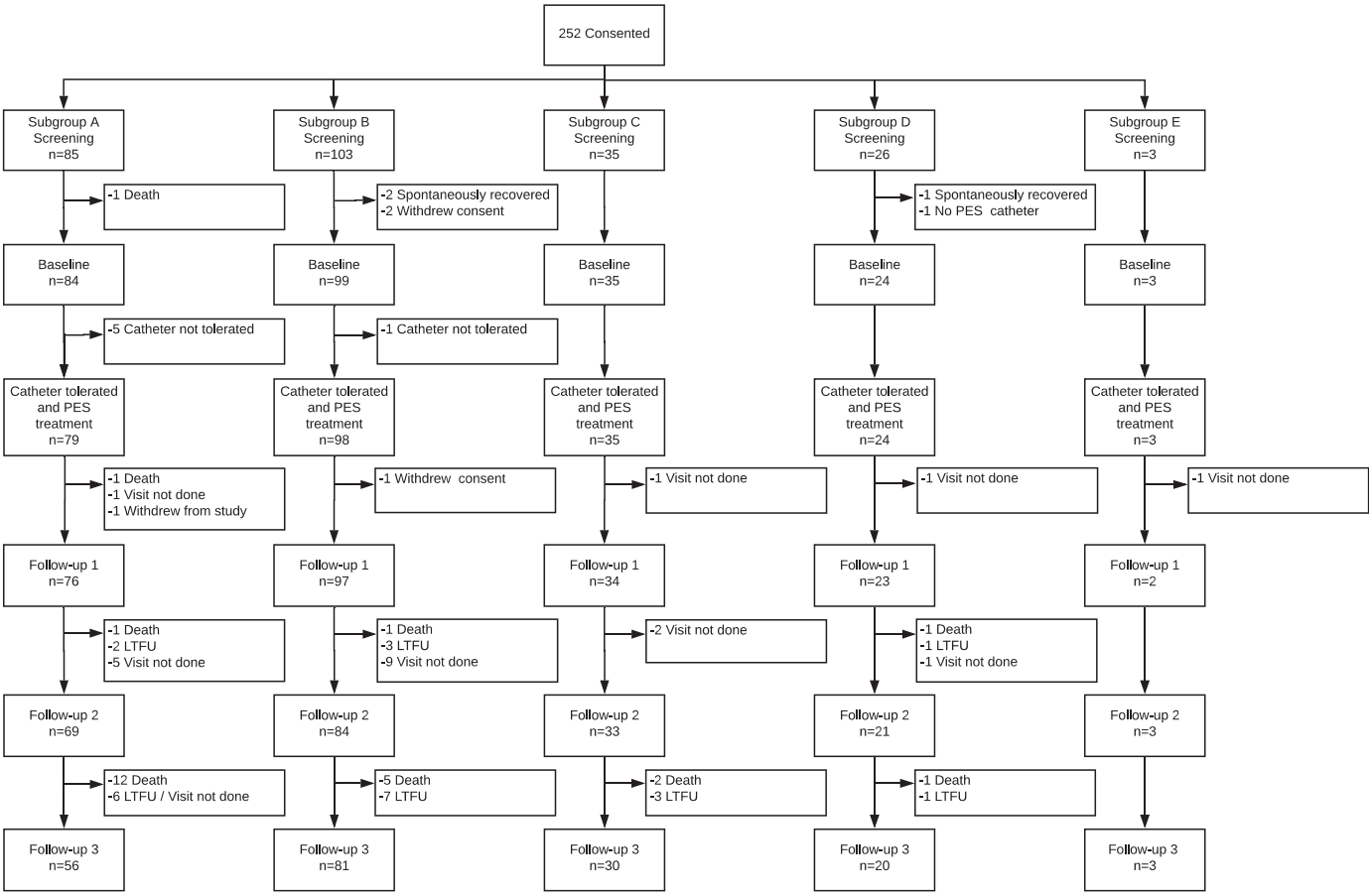

Fig. 1. Study population.

Table 1
Baseline characteristics by diagnostic group in participants where catheterization was attempted or succeeded. Data are number (%), median [interquartile range] or mean (standard deviation); comparison of groups by Chi-square test, Kruskal–Wallis test or one-way analysis of variance.

	N	All	Stroke, not ventilated	Stroke, ventilated	Ventilator-related[a]	TBI	Other	p-value
N		245	84	99	35	24	3	
Age	245	68·2 (14·2)	73·7 (12·7)	66·4 (13·1)	64·7 (14·7)	62·2 (16·4)	61·0 (21·5)	<0·001
Sex, male (%)	245	173 (70·6)	58 (69·0)	73 (73·7)	22 (62·9)	19 (79·2)	1 (33·3)	0.49
OTT (days)	237	32·0 [44·0]	16·0 [24·0]	30·5 [35·0]	43·5 [42·0]	73·0 [153·5]	169·0 [224·0]	<0·001
Feeding status	245							0·004
Oral, normal		0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	
Oral, supervision		5 (2·0)	4 (4·8)	1 (1·0)	0 (0·0)	0 (0·0)	0 (0·0)	
Oral, with support		4 (1·6)	4 (4·8)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	
NGT or NJT		151 (61·6)	50 (59·5)	71 (71·7)	22 (62·9)	8 (33·3)	0 (0·0)	
PEG or RIG		76 (31·0)	21 (25·0)	25 (25·3)	12 (34·3)	15 (62·5)	3 (100·0)	
Other route		9 (3·7)	5 (6·0)	2 (2·0)	1 (2·9)	1 (4·2)	0 (0·0)	
GCS (/15)	164	12·9 (2·7)	14·0 (1·8)	12·8 (2·6)	12·9 (3·1)	10·5 (4·0)	14·0 (-)	<0·001
NIHSS (/42)	151	11·9 (7·4)	10·6 (8·5)	13·3 (5·8)	–	–	–	0·024
mRS (/6)	170	5·0 [1·0]	4·5 [1·0]	5·0 [1·0]	–	–	–	<0·001
Stroke, ischaemic	183	153 (83·6)	78 (92·9)	74 (75·5)	–	–	–	0·002
Lesion location	183							0·44
Right		59 (32·2)	26 (31·0)	33 (33·7)	–	–	–	
Left		75 (41·0)	37 (44·0)	38 (38·8)	–	–	–	
Bilateral		18 (9·8)	5 (6·0)	12 (12·2)	–	–	–	
Infratentorial		31 (16·9)	16 (19·0)	15 (15·3)	–	–	–	
Tracheal cannula	245	99 (40·4)	–	60 (60·6)	23 (65·7)	16 (66·7)	–	0·79
Oxygen use	237	85 (35·9)	15 (18·1)	48 (50·5)	18 (52·9)	4 (18·2)	0 (0·0)	0·016
Dysphagia assessment	244							<0·001
Bedside		46 (18·9)	33 (39·8)	8 (8·1)	3 (8·6)	2 (8·3)	0 (0·0)	
VFS		4 (1·6)	3 (3·6)	0 (0·0)	1 (2·9)	0 (0·0)	0 (0·0)	
FEES		186 (76·2)	41 (49·4)	90 (90·9)	30 (85·7)	22 (91·7)	3 (100·0)	
VFS + FEES		9 (3·3)	6 (7·2)	1 (1·0)	1 (2·9)	0 (0·0)	0 (0·0)	
Ventilation (days)	129	22·0 [18·0]	–	19·0 [18·0]	25·0 [22·0]	30·5 [16·0]	–	0·065

GCS: Glasgow coma scale; mRS: modified Ranking Scale; NGT: nasogastric tube; NIHSS: National Institute Health Stroke Scale; NJT: nasojejunal tube; OTT: onset to treatment; PEG: percutaneous endoscopic gastrostomy tube; RIG: radiographically inserted gastrostomy tube; TBI: traumatic brain injury.
[a] Not stroke or TBI (see Supplement 1, Table I).

3.1.2. By cannulation status in participants with a tracheotomy

Participants who were ventilated and required tracheotomy came from groups B and C and some of D. Participants who could be decannulated had a shorter onset time to treatment and were less likely to have a haemorrhagic stroke (Supplement 1, Table VII). Following treatment (PES stimulation levels did not differ between the groups), two-thirds of participants could be decannulated (Supplement 1, Table VII). Although the DSRS improved in both groups, the magnitude of improvement at three months was greater (7·5 vs 2·1 points) and the final DSRS lower in the decannulated than non-decannulated group (Supplement 1, Table VIII).

3.2. Secondary outcomes

Similar recovery to DSRS was seen for clinical dysphagia when assessed using the FOIS (which increased significantly by 2·9 points across the cohort) and for instrumentally-assessed penetration/aspiration (with the PAS falling significantly by 4·1 units) across all participants (Table 2, Supplement 1, Fig. I). Significant improvements in FOIS and PAS were present across all diagnostic groups although the magnitude of change was smaller for PAS in TBI participants. As with DSRS, FOIS and PAS improved in both supratentorial and infratentorial stroke (Supplement 1, Table VI). Although participants who could not be decannulated showed significant improvements in FOIS and PAS, the magnitude was smaller than that seen in those who could be decannulated (Supplement 1, Table VIII).

Length of stay in hospital did not differ between the diagnostic groups (range 34–49 days across the four groups) (Table 2), supratentorial versus infratentorial stroke (Supplement 1, Table VI) or participants who could or could not be decannulated (Supplement 1, Table VIII). 50% of participants had been discharged from hospital or had at least re-started oral feeding by 30 days (Supplement 1, Fig. III). Discharge disposition, including in-hospital death, varied between the groups (Table 2) with death higher in non-ventilated stroke participants (25·0%) than in the other groups (range 11·8–18·2%). Discharge disposition, including in-hospital death, did not differ between participants with supratentorial and infratentorial stroke (Supplement 1, Table VI) or those who could or could not be decannulated (Supplement 1, Table VIII).

3.3. Serious adverse events (SAEs)

Altogether, 74 SAEs occurred in 60 participants (1·2 SAE per participant, Supplement 1, Table IX) with 29 being fatal. Most SAEs occurred within the first 30 days after start of PES (Supplement 1, Fig. IV). The commonest SAE was pneumonia (27, 11·0%), most of which occurred in participants with a stroke that did not need ventilation (18%, Group A). The next most common SAEs were cardiac arrest (5, 2·0%, Supplement 1, page 5), respiratory failure (4, 1·6%) and recurrent stroke (3, 1·2%). Only one of the 74 SAEs was considered as "possibly" related to catheter insertion which was followed by chest sepsis. There were no differences in the risk of individual SAEs between baseline groups.

3.4. Comparison of PHADER and STEPS (for non-ventilated stroke participants)

Non-ventilated stroke patients who received active treatment in PHADER were compared with those randomised to sham treatment in the STEPS trial [9]. Although participants had similar ages, sex distribution and time from stroke to stimulation, those in PHADER had far more severe dysphagia at baseline (by 3·8 points on the 12 point DSRS scale), were more likely to have an ischaemic stroke, and received a higher treatment stimulation current (by 9·1 mA) than those in STEPS (Supplement 1, Table X). Although the SAP specified a parametric analysis, models were unstable and an ordinal analysis was performed. Following treatment, DSRS fell significantly in both groups but more so with active than sham treatment with a non-

Table 2
Dysphagia severity rating scale score (primary outcome), functional oral intake scale score, penetration aspiration scale score, length of stay in hospital, time from treatment to discharge, discharge destination and death by diagnostic group. Data are number of participants, mean (standard deviation), difference in means and mean difference (95% confidence interval); comparison of groups by analysis of variance, and day 92 versus baseline by paired and unpaired *t*-tests.

	All	Stroke, not ventilated	Stroke, ventilated	Ventilator-related[a]	TBI	*p*
N		79	98	35	24	
DSRS (/12)[b]						
Baseline	236, 11·4 (1·7)	79, 10·9 (2·4)	98, 11·7 (1·2)	35, 11·9 (0·5)	24, 11·3 (1·8)	0·003
Day 5	229, 10·5 (2·6)	74, 9·9 (2·9)	97, 10·8 (2·4)	35, 10·8 (2·5)	23, 11·0 (2·5)	
Day 9	224, 8·6 (3·9)	70, 7·7 (4·1)	97, 8·9 (3·8)	35, 8·5 (4·1)	22, 10·4 (3·1)	
Day 92	174, 5·1 (4·9)	46, 4·2 (4·2)	78, 5·2 (5·0)	30, 5·3 (5·4)	20, 6·8 (4·8)	0·26
DIM (unpaired)	−6·3 (−7·0, −5·6)[c]	−6·7 (−7·8, −5·5)[c]	−6·5 (−7·6, −5·5)[c]	−6·6 (−8·4, −4·8)[c]	−4·5 (−6·6, −2·4)[c]	0·31
MD (paired)	174, −6·3 (−7·0, −5·6)[c]	46, −6·5 (−7·9, −5·2)[c]	78, −6·5 (−7·6, −5·3)[c]	30, −6·6 (−8·5, −4·6)[c]	20, −4·7 (−6·8, −2·5)[c]	0·033
FOIS (/7)						
Baseline	220, 1·4 (0·9)	65, 1·7 (1·3)	97, 1·2 (0·6)	34, 1·1 (0·3)	24, 1·4 (0·7)	<0·001
Day 5	214, 1·8 (1·4)	63, 2·2 (1·5)	96, 1·8 (1·3)	32, 1·8 (1·4)	23, 1·5 (1·0)	
Day 9	213, 2·7 (1·9)	61, 3·2 (1·9)	96, 2·5 (1·9)	34, 3·0 (2·1)	22, 1·9 (1·5)	
Day 92	172, 4·3 (2·5)	42, 4·5 (2·3)	79, 4·3 (2·6)	31, 4·4 (2·7)	20, 3·4 (2·4)	0·38
DIM	2·9 (2·5, 3·3)[c]	2·8 (2·1, 3·5)[c]	3·1 (2·5, 3·6)[c]	3·3 (2·4, 4·3)[c]	2·0 (1·0, 3·0)	0·20
MD (paired)	170, 2·9 (2·5, 3·3)[c]	40, 2·8 (2·0, 3·5)[c]	79, 3·1 (2·5, 3·7)[c]	31, 3·3 (2·3, 4·3)[c]	20, 2·0 (0·9, 3·0)	0·042
PAS (/8)						
Baseline	144, 6·7 (1·7)	42, 6·2 (1·7)	53, 7·2 (1·2)	27, 6·8 (1·6)	22, 6·5 (2·4)	0·031
Day 5	89, 5·2 (2·5)	19, 4·3 (2·5)	39, 5·4 (2·4)	18, 4·9 (2·8)	13, 6·1 (2·4)	
Day 9	100, 4·4 (2·7)	21, 3·8 (2·6)	44, 4·3 (2·7)	20, 3·6 (2·7)	15, 6·7 (1·9)	
Day 92	68, 3·2 (2·6)	10, 2·8 (2·1)	31, 3·0 (2·6)	15, 2·2 (2·0)	12, 5·3 (2·7)	0·011
DIM	−3·5 (−4·1, −2·9)[c]	−3·4 (−4·7, −2·1)[c]	−4·2 (−5·0, −3·3)[c]	−4·6 (−5·8, −3·5)[c]	−1·2 (−3·0, 0·6)	0·003
MD (paired)	68, −4·1 (−4·8, −3·3)[c]	10, −3·8 (−6·3, −1·3)	31, −4·5 (−5·5, −3·4)[c]	15, −5·3 (−6·5, −4·1)[c]	12, −1·7 (−3·6, 0·3)	
Time intervals (days)						
Hospital stay	38·5 [53·0]	34·0 [42·0]	40·5 [62·0]	38·0 [51·0]	49·0 [59·0]	0·38
PES-discharge	36·5 [53·5]	32·0 [42·0]	38·0 [63·0]	36·0 [46·0]	47·0 [59·0]	0·49
Discharge disposition (%)						0·001
Acute care	16 (11·2)	3 (5·0)	10 (18·9)	1 (5·9)	2 (18·2)	
Sub-acute care	40 (28·0)	9 (15·0)	26 (49·1)	4 (23·5)	1 (9·1)	
Assisted care	6 (4·2)	5 (8·3)	0 (0·0)	0 (0·0)	1 (9·1)	
Full-nursing care	11 (7·7)	6 (10·0)	3 (5·7)	1 (5·9)	1 (9·1)	
Home care	44 (30·8)	22 (36·7)	7 (13·2)	9 (52·9)	4 (36·4)	
Death	26 (18·2)	15 (25·0)	7 (13·2)	2 (11·8)	2 (18·2)	

DIM: difference in means between month 3 and 0 (unpaired); DSRS: dysphagia severity rating scale; FOIS: functional oral intake scale; MD: mean difference between month 3 and 0 (paired); NGT: nasogastric tube; NJT: nasojejunal tube; OTT: onset to treatment; PAS; penetration aspiration scale; PEG: percutaneous endoscopic gastrostomy tube; RIG: radiographically inserted gastrostomy tube; TBI: traumatic brain injury.

[a] Not stroke or TBI.

[b] DSRS scored as sum of:

- Fluids: 0 Normal fluids, 1 Syrup consistency, 2 Custard consistency, 3 Pudding consistency, 4 No oral fluids
- Diet: 0 Normal diet, 1 Selected textures, 2 Soft/moist diet, 3 Puree, 4 Non-oral feeding
- Supervision: 0 Eating independently, 1 Eating with supervision, 2 feeding by third party (untrained), 3 therapeutic feeding (trained), 4 no oral feeding.

[c] $p<0.001$.

significant difference at 9−14 days of 1·3 units ($p = 0.46$) and a significant difference at three months of 3·1 units ($p = 0.008$, Supplement 1, Table X). In a *post hoc* analysis, an adjusted ordinal repeated measures analysis showed that PES was associated with improved (lower) DSRS scores, OR 0·22 (95% CI 0·13, 0·38; $p<0.001$).

4. Discussion

We assessed real-world usage of PES in 245 patients with neurogenic dysphagia from 14 hospitals in three European countries. The average age was 68 years and treatment was started at an average of 32 days after ictus. As compared with baseline, DSRS (and its three component subscales), FOIS (another measure of dysphagia severity) and instrumentally-assessed penetration/aspiration (PAS) all improved in each of the diagnostic groups as well as in supratentorial and infratentorial stroke, and in participants who could be decannulated as compared with those who could not following ventilation and tracheotomy. PES appeared to be most effective if started early and with short ventilation periods. Treatment was safe, user experience was positive and an average of only 1·1 catheters were used per participant.

Although PES has been shown to improve dysphagia after stroke [8,10,11], PHADER provides the first evidence that it may work in non-stroke causes of neurogenic dysphagia, including TBI and ventilator-related dysphagia such as critical illness polyneuropathy. Interestingly, the magnitude of improvement in DSRS, FOIS and PAS was less in TBI than other diagnostic groups and there are several possible explanations for this. First, the diffuse brain-damage present in TBI may mean that more of the swallowing circuitry is damaged and so is less amenable to recovery. Second, the same diffusivity of disease may mean that a single cycle of PES treatment is less likely to be effective. In the PHAST-TRAC trial in cannulated stroke patients, a second cycle of PES increased the number of participants who could be decannulated. Therefore, a second cycle with three more daily treatments might be important in TBI. Last, most TBI participants in PHADER were treated well beyond a month (median 73 days) whilst PHAST-TRAC suggested that delayed treatment (>28 days) with PES might be less effective than earlier treatment [11]. Hence, future studies may need to increase the number of PES treatments applied in those with more established dysphagia or with more diffuse neurological injury. A previously published phase II trial found that PES appeared to be beneficial in multiple sclerosis [12]. Treatment of ventilator-associated dysphagia is of relevance in patients with COVID-19 [16] and although patients with SARS-CoV-2 infection were not included in PHADER, PES has been used to treat dysphagia following ventilation for COVID-19 (personal communication: Marianna Traugott, Vienna Austria). Together, these data suggest that PES may be effective across a wide spectrum of causes of neurogenic dysphagia.

Two subgroup analyses were performed and are illuminating. In the first, DSRS fell in stroke patients irrespective of whether the

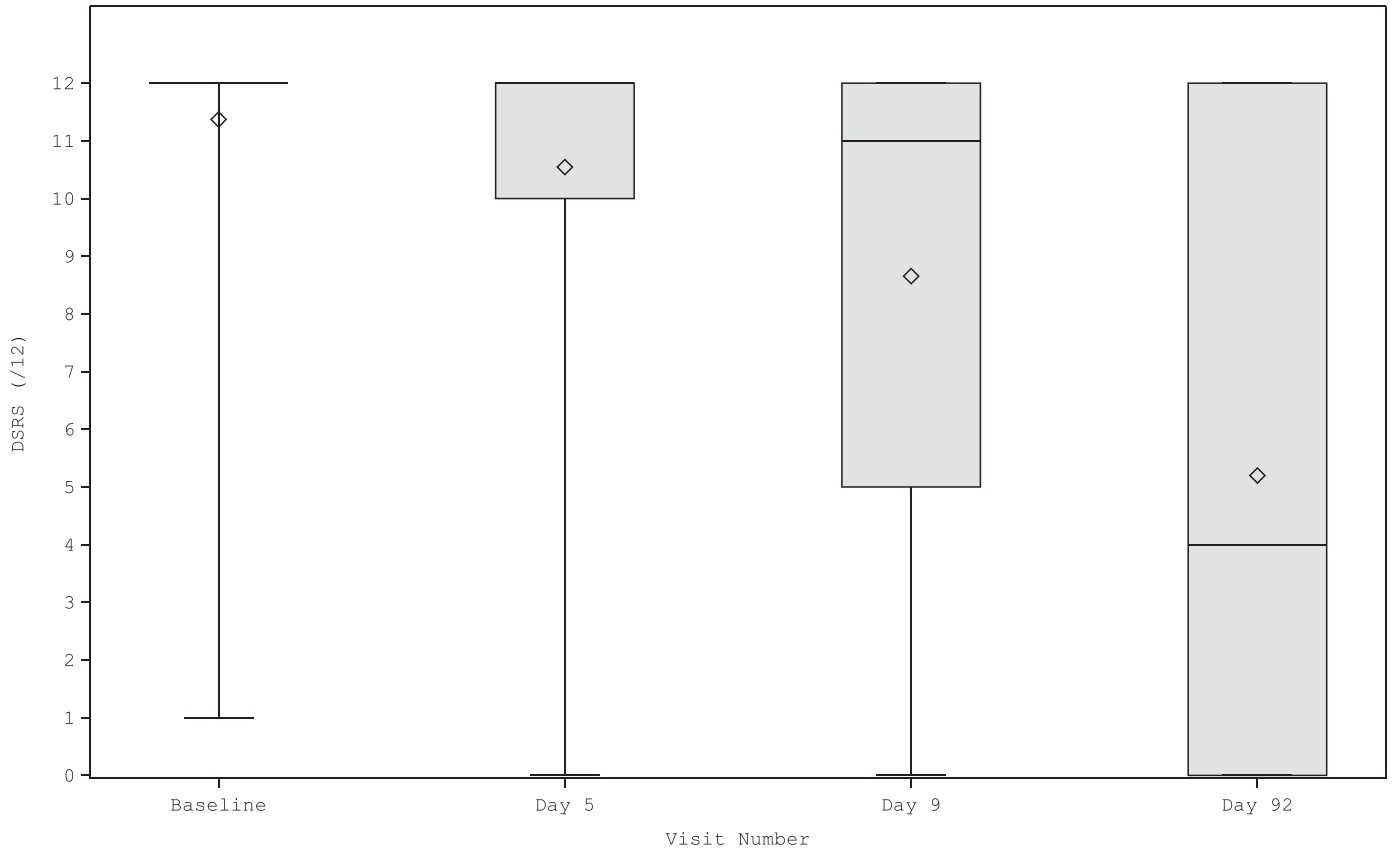

Fig. 2. Box and whisker plot of dysphagia severity rating scale across all patient groups. Figure shows 5th centile, 25th centile, box containing median (horizontal line) and mean (diamond), 75th centile and 95th centile at each timepoint.

lesion was supra- or infra-tentorial. The physiology of swallowing differs by anatomical region and so apparent benefit, irrespective of lesion location, suggests that PES works through multiple mechanisms. Stimulation of sensory afferents in the naso- and oropharyngeal mucosa, which feed the glossopharyngeal and vagus nerves, excite the nucleus tractus solitarius, other brainstem nuclei and onto subcortical and cortical areas [17]. Effects of this may be to increase corticobulbar and swallowing sensorimotor excitability. Additionally, there may be peripheral effects of PES, as seen with increases in salivary substance P in the period immediately after PES in stroke patients [18]. In ventilated patients requiring a tracheotomy, DSRS fell more in those who could be decannulated as compared with those who could not be over the three months of follow-up.

When comparing non-ventilated stroke patients in PHADER with sham-treated patients in the STEPS trial [9], DSRS at three months had improved more with PES than sham by a magnitude of 2·3 points. The difference between PHADER and STEPS appeared to be developing by the second week after treatment with a difference of over 1·0 point. Both differences equal or exceed the minimum clinical important difference for DSRS, which is 1 [6], and so can be considered to be clinically relevant. Two explanations may be relevant; first, clinical measures such as DSRS may lag in detecting improvements in dysphagia (see limitations below for an expanded discussion of this issue) and so assessment within two weeks may be too early. Second, the two studies assessed DSRS at different early timepoints, namely at 9 days in PHADER and 14 days in STEPS; hence, the longer time for natural recovery in STEPS will have benefitted these sham patients. In respect of the STEPS trial itself, patients had milder dysphagia and received a lower treatment current whilst sham patients received partial treatment, so future studies will need to focus on more severe dysphagia and with treatment involving higher treatment currents [9].

Our study has a number of strengths. First, it is the largest study of PES for the treatment of neurogenic dysphagia and is more than twice the size of the earlier STEPS (n = 126 [9]) and PHAST-TRAC (n = 69 [11]) phase III trials. Second, it provides a solid overview of PES treatment in the real-world treatment of patients with neurogenic dysphagia. Although most participants presented with a stroke, TBI or critical illness polyneuropathy, other diagnoses were also represented. Third, dysphagia severity was reduced in all groups suggesting that PES is effective in multiple different causes of neurogenic dysphagia. Last, sufficient patients were recruited to allow subgroups analyses, in particular allowing assessment of the effect of treatment in pre-defined subgroups including supra- and infra-tentorial stroke, and in post-ventilation participants who could, or not, be decannulated.

This study has several limitations. Most importantly, this was a single-arm study with no control/sham group. Following treatment, dysphagia severity improved as compared with baseline and this may have reflected, at least in part, natural recovery. In the STEPS trial, which involved stroke patients without ventilation, the mean DSRS in the sham group fell from 7.0 to 3.9 by 12 weeks, i.e. a total reduction of 3.1 points. This contrasts with a reduction of 6.7 points in the analogous group in PHADER over the same time period; hence, similar amounts of improvement may relate to each of natural improvement and PES. Further, natural recovery is unlikely to be the only explanation since treatment was typically started several weeks (months in the TBI group) after lesion/disease onset suggesting that dysphagia was relatively fixed at baseline; in spite of this, PES treatment was followed by a rapid improvement in DSRS, FOIS and PAS over a matter of days and weeks. Further, the reduction in DSRS seen in non-ventilated stroke participants at three months was greater than that seen in the sham group in STEPS. Comparisons of actively treated patients with a historical control group are difficult since

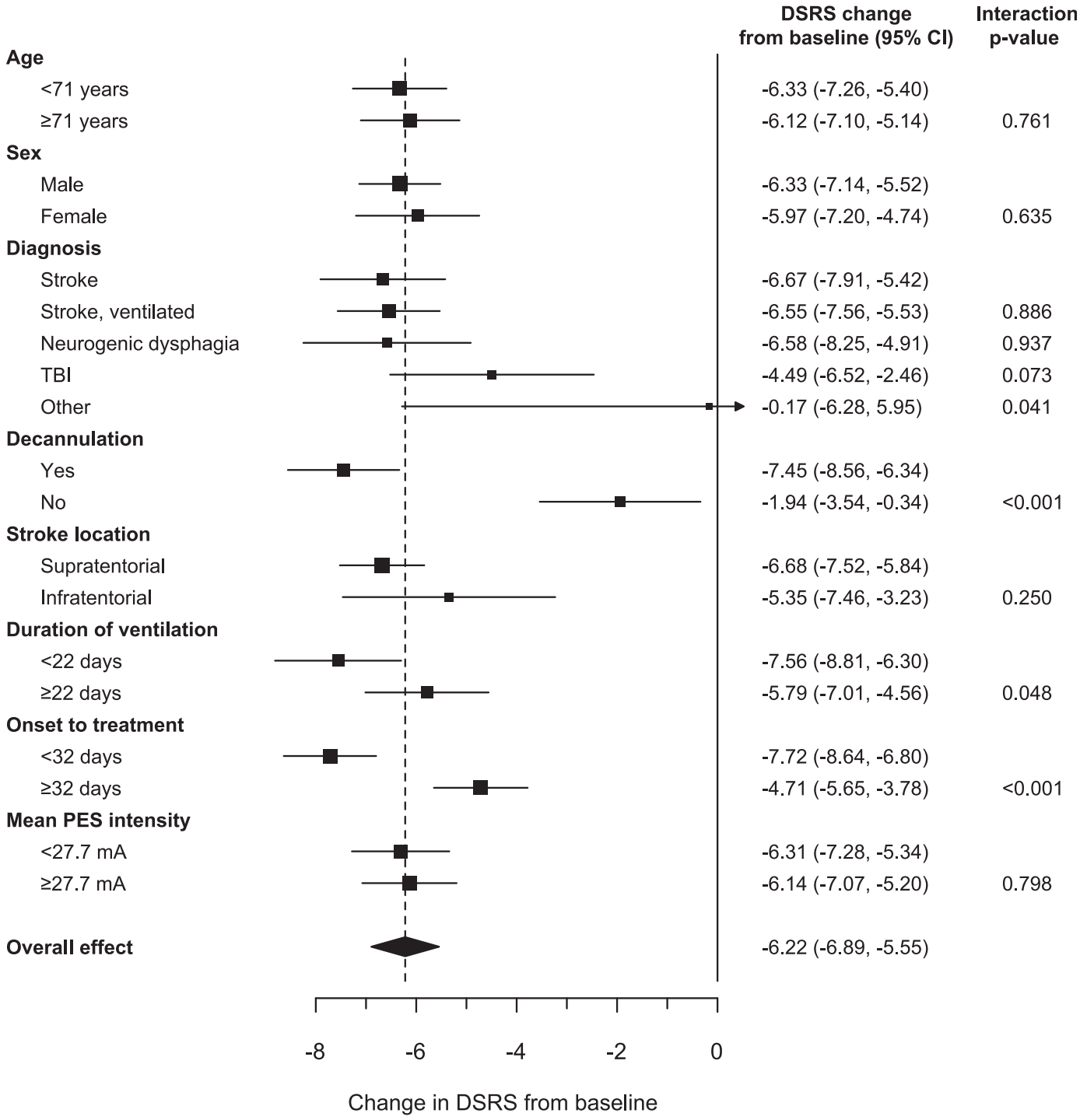

Fig. 3. Forest plot of change in dysphagia severity rating scale (DSRS) from baseline to three months in pre-specified subgroups: age (below/above median 71 years), sex (male/female), diagnosis (groups A-E), decannulation (yes/no), stroke location (supratentorial/infratentorial), duration of ventilation (below/above median 22 days), onset to treatment (below/above median 32 days) and mean stimulation intensity (over 3 days, below/above median 27·7 mA). The dotted line gives the overall effect; if a square and horizontal line do not overlap the dotted line then they differ significantly from the overall effect size.

patient characteristics and background treatment typically differ, as seen here where baseline dysphagia severity differed between PHADER and STEPS by almost 4 points. Nevertheless, regression analysis with adjustment for baseline detected a significant treatment benefit at three months (although baseline adjustment can inflate differences due to regression to the mean).

Second, although DSRS and FOIS are easy to measure, these dysphagia assessments may not be optimal when assessing rapid changes in swallowing performance, i.e. over the first few days. A primary reason is that DSRS is based on feeding routes, dietary and fluid consistency and supervision, and these may not be assessed frequently or changed by healthcare staff immediately on improvement. Hence, it is possible that faster rates of improvement would have been detected if dysphagia had been assessed more frequently, say daily. This potential delay contrasts with other outcome measures such as decannulation which responds rapidly, as seen in PHAST-TRAC [11]. Third, the size of non-stroke groups were relatively small for ventilator-related dysphagia and TBI (groups C and D), and

especially other neurogenic dysphagia (group E); we removed the latter group since only 3 patients were recruited. The small size of this group reflects that the commonest causes of neurogenic dysphagia are stroke, ventilator-related and TBI, hence the predominance of these groups of patients. Fourth, much outcome data were incomplete reflecting the real-world registry design, hence not all secondary end-points could be adequately addressed. This is particularly relevant for the VFS and FEES examinations (and so the measurement of PAS) which were not mandated. Last, the rate of SAEs was relatively low which may be explained by known under-reporting of SAEs in open label studies. Nevertheless, the pattern of SAEs appears reasonable and consistent with previous PES trials and for the populations studied.

In patients with neurogenic dysphagia, PES was safe and associated with reduced dysphagia especially if treatment was started in the first month after ictus. In participants having VFS, PES was associated with less penetration/aspiration. These findings provide empirical support for using PES in patients with neurogenic dysphagia.

Author contributions

Dr Bath had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Bath, Dziewas, Hamdy, Likar, Mistry, Saltuari

Acquisition and interpretation of data: Bath, Bocksrucker, de Broux, Dziewas, Everton, Haase, Hamdy, Herzog, Köstenberger, Ledl, Likar, Pucks-Faes, Ragab, Saltuari, Schüttler,

Suntrup-Krüger, Vosko, Walther, Warusevitane

Drafting of the manuscript: Bath, Dziewas, Hamdy

Critical revision of the manuscript for important intellectual content: Bocksrucker, de Broux, Everton, Haase, Herzog, Köstenberger, Ledl, Likar, Pucks-Faes, Ragab, Saltuari, Schüttler,

Suntrup-Krüger, Vosko, Walther, Warusevitane

Statistical analyses (in addition to Cytel): Woodhouse

Funding: Phagenesis Ltd

Administrative, technical, or material support: Mistry, Raginis-Zborowska

Supervision: Bath, Hamdy, Dziewas

Declaration of Competing Interest

Dr Bath is Stroke Association Professor of Stroke Medicine and is a National Institute for Health Research (NIHR) Senior Investigator; he reports receiving grant funding from the British Heart Foundation and Medical Research Council (MRC), was a co-Chief Investigator of PHADER and reports personal fees from Phagenesis, Diamedica, Moleac, Sanofi and Nestle.

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Dr Dziewas was a co-Chief Investigator of PHADER and reports receiving honoraria/fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Nestle, Olympus, Sanofi and Pfizer.

Dr Hamdy is Chief Scientific Officer of Phagenesis Ltd; he is a board director, holds shares in Phagenesis Ltd; he reports receiving grant funding from the MRC, NIHR and Wellcome Trust, in addition to receiving honoraria from Allergan Pharmaceuticals and Dr Falk; he is also a NICE MTAC committee member and reviews medical technologies for potential guidance for use in the NHS, UK.

Dr. Vosko reports receiving honoraria from Boehringer Ingelheim, Daiichi Sankyo and Ever Pharma.

Dr Raginis-Zborowska and Dr Mistry are employees of Phagenesis Ltd.

The remaining authors have no declarations.

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Data sharing

These data will be used for licensing and so are commercially sensitive and not available for sharing immediately. They be shared with the VISTA Stroke archive in 2023.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100608.

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Case Report

Effect of functional electrical stimulation combined with stationary cycling and sit to stand training on mobility and balance performance in a patient with traumatic brain injury: A case report

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ABSTRACT

Introduction and importance: This case study investigates the effects of functional electrical stimulation, stationary cycling, and sit-to-stand training in a patient with severe chronic traumatic brain injury.
Case presentation: The participant was a 24-year-old man with a traumatic brain injury two years prior to the intervention described in this case report. The accident caused right hemiplegia, right foot drop, aphasia, and poor coordination of movement in both upper and lower limbs. He was using a wheeled walker for functional mobility and was receiving routine rehabilitation before the initiation of treatment. A four week intervention in this study included functional electrical stimulation of the quadriceps and tibialis anterior muscles combined with stationary cycling and sit-to-stand training.
Clinical discussion: Active and passive range of motion of right ankle dorsiflexion, strength of ankle dorsiflexor, balance performance, and mobility were measured before and after the intervention. Active range of motion of right ankle dorsiflexion increased by 8°. In addition, manual muscle test and Brief-BESTest scores increased from 3+ to 5 and from 7 to 9, respectively. Walking speed over the 10-m distance and timed up and go test score improved.
Conclusion: Functional electrical stimulation combined with stationary cycling and sit-to-stand training resulted in increased muscle strength and range of motion, improved balance performance, and improved mobility in an individual with a traumatic brain injury.

1. Introduction

Traumatic brain injury (TBI) is one of the most important causes of death and chronic disability in the world and occurs primarily in adult men [1]. With improvements in medical science and technology, the mortality of these individuals has decreased. However, in severe cases of individuals who sustained a TBI and survived, extensive complications, such as cognitive and motor dysfunctions, psychiatric disorders, seizures, decline in quality of life, and increased economic cost were observed [2,3]. Various treatments have been suggested for reducing the disability and complications of TBI. The World Health Organization (WHO) emphasizes the active and dynamic process of rehabilitation for individuals with TBI [4]. Therefore, developing evidence-based treatment approaches and beneficial rehabilitation programs is necessary.

Functional electrical stimulation (FES) is utilized to improve muscle strength through the application of electric current through healthy peripheral motor nerves [5]. Studies have shown that FES training in the lower extremity can improve muscle strength, joint range of motion (ROM), and gait performance in patients who have had a stroke [6,7]. However, voluntary muscle contraction training (i.e., strength training) resulted in greater gains than FES training alone [8]. Cycling and sit-to-stand or stand-to-sit (STS) are motor tasks that are prerequisite

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exercises for mobility and walking [9–11]. Practicing both voluntary and involuntary muscle strengthening may improve balance control and the ability to walk independently, as these are the most important goals of rehabilitation for people with TBI and require intensive repetitive exercise. We assume that exercise augmented with FES can have beneficial outcomes. Therefore, the aim of this study was to investigate the effects of the simultaneous use of FES and cycling and STS exercise on mobility and balance performance in a patient with TBI.

2. Case presentation

2.1. Participant history

The participant in this study was a 24-year-old man who was in a motor vehicle accident that led to a severe TBI two years ago. According to the report of the spiral brain CT scan, the primary lesion was located in the left frontotemporal area due to contusion, and a few lacunar infarcts were seen in the left basal ganglia. Before the accident, he was an active member of a music band and was involved in bodybuilding activities. He was hospitalized for 48 days after the accident. Following discharge from the hospital, he received regular rehabilitation, including electrical stimulation of the wrist and knee extensors and ankle dorsiflexors, resistance training, and aerobic and endurance conditioning (e.g., walking on treadmill and stationary bike). At the time of the first visit to the research clinic, he could not independently walk or stand up from a chair and was using a wheeled walker for mobility and an ankle foot orthosis to prevent drop foot.

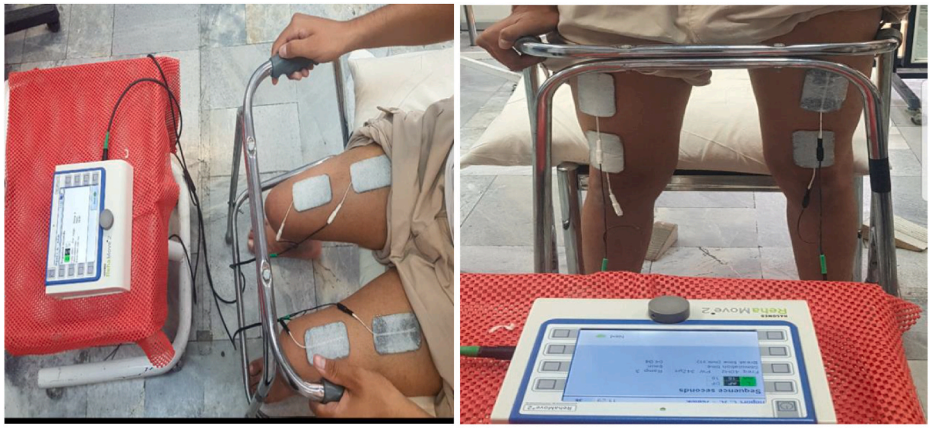
2.2. Clinical examination

The clinical examination was performed by an experienced physical therapist. The participant had right (RT) hemiplegia with full and strong grasping and gripping but without the ability to write. Other impairments were aphasia, bradykinesia, and dyscoordination of movements of RT upper (i.e., finger to nose) and lower (i.e., heel to shin) extremities. Also, deep tendon reflexes were increased with no spasticity in his muscles. He was dependent in some activities of daily living (ADL) (e.g., dressing, toilet use, and feeding).

3. Intervention

Intervention consisted of twelve sessions of stationary cycling combined with FES applied on the quadriceps (QC) and dorsiflexor muscles of the affected leg and STS exercise combined with FES applied on the QC muscles of both legs, three times a week (over a four-week period) (Figs. 1 and 2). The electrical stimulation parameters were progressed by changing the pulse frequency from lower to higher (35–40 HZ), the duration of the wave from shorter to longer (300–450 μs), and the intensity (highest tolerable stimulation) [5,6]. Considering the patient's performance at baseline, three cycles of the stationary cycling program (15 min of actual cycling) and two cycles of the STS program (4 min of actual STS) were established in the first week of treatment. The details of the stationary cycling and STS programs are shown in Table 1; progression over four weeks is shown in Table 2. The stationary bike was set at 25 W for the entirety of the intervention. In the fourth and final week, the patient was able to do 30 min of cycling and 10 min of STS.

Fig. 2. Cycling combined functional electrical stimulation Of right quadriceps and dorsiflexor muscles.



(a) **(b)**

Fig. 1. Standing up from a chair while functional electrical stimulation was applied on quadriceps of both legs.

Table 1
Initial training parameters all performed with FES.

	Warm up	Original	Cool down	Break
SC X 3	1 min pedal	5 min pedal with FES	1 min pedal	2 min
STS X 2	30 sec STS	2 min STS with FES	30 sec STS	2 min

SC = stationary cycling; min = minutes; FES = functional electrical stimulation; STS = sit to stand/stand to sit; sec = second.

Table 2
Progression over the four-week intervention (SC and STS augmented with FES).

	First Week	Second Week	Third Week	Fourth week
SC	3 cycle (27 min)	4 cycle (36 min)	5 cycle (45 min)	6 cycle (52 min)
STS	2 cycle (10 min)	3 cycle (15 min)	4 cycle (20 min)	5 cycle (25 min)

SC = stationary cycling; min = minutes; FES = functional electrical stimulation; STS = sit-to-stand/stand-to-sit.

4. Outcome measures

Active and passive ankle ROMs were measured by goniometer, and the muscle strength of the ankle dorsiflexor in the affected leg was assessed by manual muscle testing (MMT). The Persian version of Brief-BESTest, which has a high inter-rater and intra-rater reliability in patients with stroke (ICC = 0.98 and ICC = 0.99 respectively) [12], was used to assess balance performance. In addition, walking speed over a 10-m distance (WS10 M) was measured prior to (at baseline) and after the intervention. The results of a previous study indicated a very high inter-rater reliability (ICC = 0.999) and an excellent concurrent validity for the WS10 M in patients with TBI [13]. Mobility activity was also evaluated by the timed up and go (TUG) test, which has excellent test-retest reliability in patients with stroke (ICC >0.95) [14]. The participant used his walker to perform the WS10 M and TUG tests. Measures were assessed at baseline and at the end of the sixth and twelfth sessions of intervention. This case report is about the effects of a rehabilitation program and followed the CARE guideline [15,16].

5. Results

At the end of the sixth and twelfth sessions of post-treatment, passive ankle ROM had increased by 2° in comparison with baseline. Active ankle ROM had increased by 5 and 8° at the end of the sixth and twelfth sessions, respectively. The MMT of the affected ankle dorsiflexors improved from 3+ at baseline to 5 at the end of the sixth session. The WS10 M increased from 0.84 m/s at baseline to 0.92 m/s and 1.07 m/s in the sixth and twelfth sessions of treatment, respectively. The TUG time decreased from 46 seconds at baseline to 40 seconds in the sixth session and 28 seconds in the twelfth session. In addition, the Brief-BESTest score increased from 7 at baseline to 9 in the sixth session of treatment. However, it did not change from the sixth to the twelfth session. At the end of the intervention, the participant was able to walk 8 m and sit to stand and stand to sit independently. He was also able to dress by himself. At one-month follow-up, he was able to walk up and down stairs using a tripod cane. Details of the outcomes measures are presented in Table 3.

6. Discussion

The purpose of this case report was to investigate the effects of a four week intervention combining FES with stationary cycling and STS training on balance performance and mobility in a patient with a severe TBI. The results revealed improvements in active ankle dorsiflexion and muscle strength (reducing foot drop), walking speed, and balance. There is conflicting evidence in the literature concerning the effects of lower limb FES on postural control and mobility. Lo et al. reported that cycling combined with FES decreased spasticity and improved postural control

Table 3
Outcome measures.

	MMT	PROM	AROM	WS10MD	TUG	Brief-BESTest
Baseline	3+	10	4	0.84	46	7
Post-test (session 6)	5	12	9	0.92	40	9
Completion (session 12)	5	12	12	1.07	28	9

MMT = manual muscle test; PROM = passive range of motion; AROM = active range of motion; WS10 M = walk speed over 10 m distance; TUG = timed up and go test; Brief-BESTest = brief-balance evaluation system test.

in individuals with stroke [11]. However, de Sousa et al. showed that FES with cycling did not improve mobility and muscle strength in individuals with stroke [17]. To the authors' knowledge, this is the first time that STS has been used to improve strength and coordination between the trunk and lower limbs for the maintenance of center-of-mass stability [18]. STS competence has been shown to have a strong correlation with balance ability [19] and mobility in individuals with stroke [20]. Low-frequency and high-pulse amplitude electrical stimulation was previously used to increase contraction time and motor unit activation and to stimulate fatigue-resistance muscle fibers selectively [21,22]. It is possible that the simultaneous application of FES (involuntary strength training) combined with demanding exercise tasks (voluntary strength training) can improve the mechanical output of muscles. Also, the nociceptive cutaneous stimulation and sensory input produced by FES on one side and activation of the synergistic muscle pattern produced during stationary cycling and STS could modulate neural drive and central adaptation [23]. Therefore, the cumulative effects of FES combined with demanding volitional activity has the potential to improve muscle performance, walking ability, and balance control in this case.

7. Conclusion

This case study demonstrated that four weeks of FES combined with stationary cycling and STS has the potential to improve muscle strength and ROM, walking velocity, and balance performance in a patient with a severe TBI. Future studies with a large sample size and control group are recommended to gain a greater understanding of the effects of FES combined with tasks such as stationary cycling and STS.

Ethical approval

The ethical committee approval was not needed as this is a case report type article. However, the written informed consent was obtained from the patient to publish the clinical data.

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This study is not funded.

Author contribution

ME: Study concept, design, data collection, writing the manuscript draft. NNA: Study concept, design, data validation, revising the manuscript, supervision. SH: Data validation, revising the manuscript. AS: Study concept, design, data collection, revising the manuscript. SAA: Data collection. All authors read and approved the final manuscript for submission.

Declaration of competing interest

The authors report no conflict of interest.

Registration of research studies

Not applicable.

Guarantor

Masoome Ebrahimzadeh.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interests with respect to the research, authorship, and/or publication of this article.

Patient's consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Research registration

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.103122.

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Neuromuscular electrical stimulation for the head-injured patient

Baker, Lucinda L. et al. (1983)
Physical Therapy & Rehabilitation Journal, 63(12): p1967-p1974.
DOI: 10.1093/ptj.63.12.1967

SUMMARY

Recent research has shown that electrical stimulation is effective in treatment programs designed to maintain or gain range of motion, to facilitate voluntary motor control, and to strengthen muscles weakened by disuse. All of these treatment goals are relevant to the head-injured patient who frequently demonstrates profound disuse atrophy, joint contractures with excessive muscle tone, and decreased voluntary motor capabilities. As the cognitive status of the head-injured patient improves, electrical stimulation can be incorporated into traditional treatment programs to enhance their effectiveness. This article discusses using neuromuscular electrical stimulation with programs aimed at managing contractures, reducing spasticity, and facilitating voluntary motion. The limitations of electrical stimulation in the head-injured patient population are addressed.

https://academic.oup.com/ptj/article-abstract/63/12/1967/2727544?redirectedFrom=fulltext&login=false

Use of electrical stimulation in brain injured patients: a case report

Oostra, K. et al. (2009)
Brain Injury, 11(10): p761-p764.
DOI: 10.1080/026990597123133

SUMMARY

After failure of other therapeutic measures, electrical stimulation was applied to promote gait rehabilitation in a patient with severe brain injury and complete left hemiplegia. The favourable results reported in the literature were confirmed. Despite the long interval between injury and institution of electrical stimulation, independent ambulation was quickly restored.

https://www.tandfonline.com/doi/abs/10.1080/026990597123133?journalCode=ibij20

Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters

Chipchase, Lucy S. et al. (2010)
Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 122(3): p456-p463.
DOI: 10.1016/j.clinph.2010.07.025

SUMMARY

Peripheral electrical stimulation (ES) is commonly used as an intervention to facilitate movement and relieve pain in a variety of conditions. It is widely accepted that ES induces rapid plastic change in the motor cortex. This leads to the exciting possibility that ES could be used to drive cortical plasticity in movement disorders, such as stroke, and conditions where pain affects motor control. This paper aimed to critically review the literature to determine which parameters induced cortical plasticity in healthy individuals using ES. A literature search located papers that assessed plasticity in the primary motor cortex of adult humans. Studies that evaluated plasticity using change in the amplitude of potentials evoked by transcranial magnetic stimulation of the motor cortex were included. Details from each study including sample size, ES parameters and reported findings were extracted and compared. Where data were available, Cohen's standardised mean differences (SMD) were calculated. Nineteen studies were located. Of the parameters evaluated, variation of the intensity of peripheral ES appeared to have the most consistent effect on modulation of excitability of corticomotor pathway to stimulated muscles. There was a trend for stimulation above motor threshold to increase excitability (SMD 0.79 mV, CI -0.10 to 1.64). Stimulation below motor threshold, but sufficient to induce sensory perception, produced conflicting results. Further studies with consistent methodology and larger subject numbers are needed before definitive conclusions can be drawn. There also appeared to be a time effect. That is, longer periods of ES induced more sustained changes in cortical excitability. There is insufficient evidence to determine the effect of other stimulation parameters such as frequency and waveform. Further research is needed to confirm whether modulation of these parameters affects plastic change.