Restoration of arm and hand functions via noninvasive cervical cord neuromodulation after traumatic brain injury: a case study

Abstract

Background: Traumatic brain injury (TBI) survivors often suffer permanent sensorimotor deficits resulting paralysis. Neuromodulation via transcutaneous electrical stimulation (tES) has recently shown significant improvements of upper-limb functions in quadriplegic patients with cervical cord injury. However, the effects of tES on treating TBI quadriplegics with similar upper-limb deficits are still unknown.

Objectives: To investigate the effects of cervical tES on upper-limb functional rehabilitation in a chronic TBI patient, and to identify the optimum stimulation parameters of tES.

Methods: The patient was provided with two-phase intervention: 1) voluntary physical training (vPT) and 2) tES along with vPT (tES+vPT). Biphasic tES were delivered at C4 and C6 cervical cords. Clinical assessments including Modified Ashworth Scale (MAS), Fugl-Meyer Assessment for Upper Extremity (FMA-UE) and Action Research Arm Test (ARAT) were conducted before and after each training phase, and also evaluated 1-month follow-up after the last intervention.

Results: Our results indicate that vPT alone only contributed to a release of muscle spasticity of the patient's both arms; while tES+vPT further released the spasticity of his left arm, and improved voluntary motor function on both arms with increased FMA-UE (>35% on both arms) and ARAT (>40% on the right and >25% on the left

arm) scores. The grip force also increased after the tES+vPT treatment. We found that 1 ms biphasic tES at 30 Hz produced optimum motor outputs.

Conclusion: The study demonstrates for the first time the potential benefits of cervical tES on improving upper limb motor functions in a patient with chronic TBI.

Keywords: traumatic brain injury, bilateral paralysis, transcutaneous electrical stimulation, neuromodulation, motor restoration.

1. Introduction

Traumatic brain injury (TBI) is one of the leading causes of disability with increasing incidence and prevalence being recorded worldwide [1 2]. More than 30% of patients after TBI have been found to suffer abnormal upper limb kinematics, such as delayed movement latency, ataxia, and muscle spasticity [3]. Longitudinal studies have reported that TBI survivors commonly suffer residual long-term motor impairments, which results in socioeconomic burdens and reduces an individual's quality of life [4 5]. Multiple therapeutic modalities for reversing post-TBI motor disabilities have been trialed, including occupational and physical rehabilitation. The benefits of these treatments, however, are found to be concentrated within the first six months of injury [6] and reach a plateau around one year after [7]. To achieve long-term therapeutic effects, therefore, there is a critical need for more effective treatment.

Recent developments of neuromodulation therapies for the nervous system to promote functional recovery in patients with chronic motor disorders have shown significant promise [8 9]. The burgeoning interest for which mainly relates to the

development of electric neuromodulation strategies, including invasive stimulation directly to the central nervous system – such as deep brain stimulation (DBS) via subdural electrodes on the cortical surface [10 11] and spinal cord stimulation (SCS) via epidural electrodes at cervical levels [12 13]. Although many studies have shown that direct neurostimulation can strengthen synaptic connections and facilitate the morphological changes in a neuronal reorganization that lead to functional improvements [14-16], the economic cost of this approach in clinical practice is high and the invasive nature potentially raises infection risks and rejection reactions [17 18]. In contrast, noninvasive stimulation therapies are less expensive, easier to administer and have a lower risk of side effects. However, the problem remains that many TBI survivors have undergone craniotomy, craniectomy, or other neurosurgical treatments, and skull defects or skull plates are commonly seen in this patient population [8]. Thus, the exact shape of the induced current by transcranial magnetic stimulation (TMS) can be complicated by variations in intracranial anatomy [19 20]. Plates or defects can also alter the direction of the current flow in transcranial direct-current stimulation (tDCS) [21 22]. Therefore, current clinical practice favors a non-invasive stimulation technique that can remain largely unaffected by anatomical changes in the brain.

Spinal cord neuromodulation via transcutaneous electrical stimulation (tES) is a noninvasive treatment that utilizes a unique waveform of electric current to reach the spinal networks from the skin surface [23]. Recent studies have shown significant sensorimotor improvements in quadriplegic patients with cervical spinal cord injury

(SCI). For example, Gad *et al.* reported the long sustainability of handgrip force motor improvement after transcutaneous stimulation [24] and related studies demonstrate that cervical stimulation can facilitate neuroplasticity that results in long-lasting motor control improvement [25]. Early spinal cord stimulation (SCS) studies raised a therapeutic direction in terms of producing electric stimuli from the cervical dorsal column to apply selective electrical stimulation to the brain [13 26]. Most SCS studies were aimed at giving systematic sensory inputs [12 27 28], with others utilizing cervical epidural stimulation to raise passive contractions at neck and shoulder muscles and reporting positive effects in improving upper motor function and reducing muscle spasticity [13 29]. However, the effects of tES on treating post-TBI quadriplegia patients with similar upper limb deficits of cervical SCI are still unknown. Consequently, the present study has been designed to test the effects of non-invasive cervical tES, along with repeated physical training on improving upper limb functions in a chronic TBI patient.

2. Methods

2.1 Clinical Characteristic of the Subject

A 41-year-old male who experienced head trauma from a fall accident six years ago participated in the study. He quickly received emergency treatment after the accident and did not demonstrate any serious disturbance of consciousness or language impairment in the first month after the injury's acute phase. After the acute recovery, he continued to receive physical exercise three times a week on the upper extremities.

The screening test prior to the study demonstrated that the patient was able to sit independently with mild impairment on trunk control. He could also conduct weak voluntary contraction during the motions of elbow, wrist and finger joints in both arms, while more severe motor deficits existed on the right side. Furthermore, the patient showed increased muscle tone at finger, wrist and elbow joints in both upper limbs. The patient's right shoulder had a more severe contracture with passive range of motion (ROM) limited in 0–35º in anterior flexion and 0–20º in abduction direction, compared to the left shoulder joint with passive ROM in 0–70º in anterior flexion and 0–55º in abduction direction. The screening assessments illustrated that the patient had moderate upper limb motor dysfunction despite having received stand-of-care rehabilitation and additional long-term physical training.

2.2 Procedures

This study is registered with ClinicalTrials.gov, number NCT04183998. The patient was informed of the purpose and content of this study, then signed informed consent for a treatment protocol and physiological monitoring approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University. A detailed timeline of the study is illustrated in **Figure 1**.

Baseline data consisted of clinical assessments that included Fugl-Meyer Assessment for Upper Extremity (FMA-UE) [30], Action Research Arm Test (ARAT) [31], Modified Ashworth Scale (MAS) [32], manual muscle testing (MMT) [33] and hand grip force to evaluate the patient's upper limb motor functionality. The subscales

of FMA-UE, i.e. FMA shoulder/elbow (FMA-SE) and FMA wrist/hand (FMA-WH) were also recorded independently to reflect the motor function of different upper limb segments. In order to ensure the stability of the patient's state, these pre-training assessments were conducted three times prior to beginning the study. A Functional Independence Measurement (FIM) [34] questionnaire was also used to address the patient's ability to perform daily living activities.

During the 1-week baseline evaluation, we tested the effects of cervical tES to assist the patient's motor performance via a series of sponge grasping-releasing tests in both horizontal and vertical directions (**Table 1**). In the horizontal task, the patient was instructed to grasp a sponge (thickness 5 cm, weight 30 g) placed on one side of a table, to transport the sponge 50 cm horizontally then release it, after 10-s rest, reversing the process and putting the sponge back on the initial point. In the vertical task, he was instructed to grasp the sponge on the midline of the lower layer of a shelf, lift it through a vertical distance of 17 cm, place it on the midline of the upper layer of the shelf, then reverse the process till back to the initial status. Two 2.5 cm self-adhesive round electrodes (Axelgaard Manufacturing Co., Ltd., USA) were attached to the skin at the midline of a C3-4 and C6-7 spinous process to serve as cathodes, and two 5×10 cm self-adhesive rectangular electrodes (Guangzhou Jetta Electronic Medical Device Manufacturing Co. Ltd., China) were placed symmetrically over both side acromions to serve as anodes. Previous studies with the same setup showed effective upper-limb motor improvements in quadriplegic SCI patients [23-25 35]. We tested different stimulation schemes with varied pulse and

frequencies, as shown in **Table 2**, with a Visual Analogue Scale (VAS) [36] used to identify the patient's pain level during stimulation. The degree of completion for each task and elapsed time served as the criteria to decide the optimal output.

After the sponge grasping-releasing motion tests with different tES parameters, the stimulator was set to biphasic, rectangular, 1 ms single pulses at a frequency of 30 Hz for therapeutic stimulation. Electromyography (EMG) electrodes (YD30-6, YanchengTianrun Medical Instrument Factory, China) were placed on the muscle belly of the four muscles: extensor digitorum (ED), flexor digitorum (FD), triceps brachii (TRI), and biceps brachii (BIC), in both arms. The EMG signals were amplified (×1000), filtered (10 to 500 Hz band-pass and 50 Hz notch) and digitized (1 kHz) by a wireless EMG acquisition system (BTS TeleEMG, BTS Engineering, Italy).

Subsequently, the patient was provided with a two-phase interventional training program: Phase I – conventional voluntary physical training (vPT) targeting both upper limbs for the first five sessions; Phase II – concurrent tES and vPT intervention (tES+vPT) for the next five sessions (**Figure 1**). The vPT included standard stretching, active-assistive range of motion exercises, and intensive gross and fine motor skill training, which resembled most of the daily upper-limb motor tasks. The total dosage of vPT in Phase I was 15 hours over two intervention weeks, approximately 3 hours/session and equally divided for two arms. During Phase II, vPT was the same as in Phase I and noninvasive tES was given after 2-hour vPT, applied synchronously with voluntary and intensive gross and fine motor-skill training, for approximately 60 minutes/session over two intervention weeks. During the tES-assisted training, the

patient was always aware of the presence of the optimal scheme stimulation, which they described as a tingling sensation localized to the neck and acromion. These sensations never reached a level of any discomfort and, at the same time, the stimulation intensity did not induce any visible muscle contraction throughout the training. The total training time for both interventions was 3 hours. The patient was allowed to have a 5-min rest between each two consecutive 30-min training sessions in order to avoid fatigue. Blood pressure was measured and recorded during rest time in all training sessions, while MMT and grip forces were evaluated at the beginning of each training session to track the variation pattern in muscle strength. The MMT score demonstrated in this study comprised of six muscles tested bilaterally (finger abductors, wrist extensor, wrist flexor, TRI, BIC, deltoid) similar to the previous study [25]. There was a progress assessment right after Phase I and a post-training assessment right after Phase II involving FMA-UE and its subscales, ARAT, and MAS measurements. Furthermore, a follow-up measurement involving all clinical assessments was conducted one month after the last Phase II training session.

2.3 Data analysis

The EMG data was processed using MATLAB (Matworks Inc., Natick, MA, USA) and first filtered with a 10–200 Hz 4th order Butterworth bandpass filter. The root-mean-square envelopes were then calculated with a sliding window of 100 ms. Then the average rectified value was calculated from the envelope using the formula:

$$\overline{EMG} = \frac{1}{T}\sum_{t=0}^{T} EMG(t) \times \Delta t, \text{ [37]}$$

where EMG(t) is the time-varying EMG signal envelope of the muscle during the sponge grasping-releasing motion task, Δt is the sampling time, and T is the signal length.

3. Results

At the beginning of the study, the patient had moderate trunk control (Trunk Impairment Scale score [38] was 6/7 in the static sitting balance item and 7/10 in the dynamic sitting balance item). The grip forces of the patient's left and right hands were 2.5 kg and 1.8 kg, respectively. The patient completed both horizontal and vertical tasks independently with his left arm but needed left-hand support holding the right wrist when conducting the task with the right arm. Baseline clinical scores suggest moderate motor deficits with significantly high muscle tone at the entire upper limbs as chronic TBI sequela.

Among all the tested stimulation configurations in the sponge grasping-releasing test, we found that 1 ms tES at 30 Hz with 25 mA stimulation intensity could help the patient achieve the maximal degree of completion with the least time to finish the task – 100% motion completion in 29s with tES for left arm (baseline without stimulation: 100% completion in 50s) and 80% completion in 58s with tES for right arm (baseline without stimulation: 80% completion in 78s without stimulation), without discomfort (pain level <3 by VAS) according to the patient's self-report (**Table 2**).

After completing Phase I of the study, we found that vPT did not significantly improve the patient's upper limb motor function, as reflected by a minor FMA-UE

score increase (39/66 to 41/66 on the left and 22/66 to 23/66 on the right) (**Figure 2**). Concurrent cervical tES+vPT improved the patient's voluntary motor function with the total FMA-UE increasing to 52/66 on the left arm and 35/66 on the right. In the left arm, the increment of FMA scores mainly occurred in the shoulder-elbow segments (>40% in FMA-SE, and >25% in FMA-WH), while in the right arm the increase was observed as comparable to both shoulder-elbow and wrist-hand segments (>58% in FMA-SE, and >60% in FMA-WH). The improvement lasted even after one month of therapy, as shown by follow-up FMA-UE scores of 50/66 on the left arm and 30/66 on the right.

Similar to the FMA-UE score, we found little or no increase in ARAT scores (29/57 to 31/57 on the left and 14/57 to 14/57 on the right) after Phase I with only vPT (**Figure 3**). While motor functional improvement following tES+vPT (Phase II) was observed in the ARAT scores reflecting hand functions with grasping, gripping, pinching and gross movement, which increased to 37/57 on the left and 19/57 on the right. The improvement with a 27.5% increment on the left was mainly due to the reduction of time cost to complete gripping and pinching motions whereas, in contrast, the 40% increment of scores on the right was attributed to the improvement in gross movement degree of completion. The ARAT scores, however, decreased in the one-month follow-up, manifesting with slower and clumsy movements (33/57 on the left and 15/57 on the right).

After Phase I with vPT alone, the patient showed a release of muscle spasticity in both arms, as illustrated by the MAS scores, while the release was further promoted

after tES+vPT training (**Figure 4**). The scores decreased in mid-term assessment right after Phase I (left finger: 3 to 2 grade; left elbow: 2 to 1 grade; right finger and wrist: 2 to 1 grade; and right elbow: 2 to 1+ grade). Furthermore, following the tES+vPT treatment in Phase II, MAS scores further decreased in the patient's left arm (left finger: 2 to 1 grade; and left wrist: 2 to 1+ grade). The one-month follow-up results showed durable improvement with the same MAS scores in the left arm and slightly increased MAS scores in the right (right finger and wrist: 1 to 1+ grade).

On the left side, muscle strength and muscle tone were initially higher when compared to the right side, as illustrated by MMT (**Figure 5a**) and MAS (**Figure 5b**) scores, according to the baseline. Composite MMT from 6 muscles increased from 20/30 to 22/30 points on the left side and from 8/30 to 9/30 points on the right over the 5 sessions of vPT and further promoted by 4 points (26/30) on the left and 2 points (11/30) on the right following tES+vPT treatment. The grip forces only increased during Phase II and stabilized at 5.3 kg (112% increment) on the left hand and 3.2 kg (78% increment) on the right. The improvement of muscle strength could be maintained even after one month of vPT+tES treatment. Additionally, as the patient self-reported smoother and more voluntary upper limb movements during self-feeding at home, by the end of the study, the FIM score had increased by 1 point (**Table 3**).

The EMG average rectified value of the sponge grasping-releasing task in the four upper limb muscles, i.e. TRI, BIC, FD, and ED, were shown in **Figure 6**. Before training, the EMG value dropped in all muscles when cervical stimulation was applied, except in the left biceps. Then, after training, the EMG value further decreased in all

muscles, with a decrease in value meaning that less effort was required to complete the same task.

No adverse effects were observed throughout the study. Resting-to-training blood pressures were found from 66/101 to 80/120 (diastolic/systolic pressure) and heart rate ranged between 66–78 beats/min during the training. No hyperemia or other skin reaction was observed surrounding the stimulation sites. The patient described good tolerability with respect to the stimulations.

4. Discussion

In the current study, we present a patient with chronic TBI quadriplegic showing motor improvements for the first time following cervical tES treatment. Almost all motor functions of the hands and arms, including muscle strength, grip force, and pace of pretension, were immediately facilitated with several stimulation schemes, while the optimal scheme in biphasic rectangular stimulation waveform at 1 ms pulses, 30 Hz frequencies filled with a carrier frequency of ~10 kHz could elicit the patient's best performance when conducting the sponge grasping-releasing tests (see **Table 2**). The waveform setting was similar to that adopted in cervical SCI rehabilitation for upper limb motor restoration [25]. This raises the possibility that tES could lead to a temporal change in neural circuits to strengthen the corticospinal connection to the descending neurons [39 40]. As demonstrated in the sponge grasping-releasing test with the stimulation, the patient presented less time cost but the same degree of completion for the motion tasks, giving prominence to the right arm especially.

Similar findings were also observed in the previous SCS studies [13 41]. This suggests that the temporal/immediate effect of tES could be more likely to modulate cervical spinal networks and promote the transmission of neural signals rather than to restore the disabled cortical functions.

Through the two-phased training sessions, we compared the effects of vPT alone, and vPT with tES. The outcomes of the two approaches illustrated that vPT alone can release the chronic sequel hypertonia of TBI, while vPT with tES could further carry out sustained effects in upper-limb motor improvements, e.g. dexterity, which could be maintained for one month without the stimulation. The result indicated that tES possibly elevated the excitability of cortical neural networks; for instance, a cerebellar hemisphere for muscle tone management [42 43], and precentral gyrus for volitional motion control [44]. A recent electrophysiological study [45] reported that tES could activate primary afferent fibers within multiple posterior roots. Previous SCS studies also indicated that stimulation to the spinal cord could be delivered via the ascending pathway to the sensorimotor cortex in treatment for patients with TBI in a persistent vegetative state [28 29]. The sustained improvements of hand and arm functions appearing in this study could be explained as the gradual neuroplastic change followed by the constant ascending input to the cortex during the period of study. Another possibility is that the stimulation to the skin could increase afferent fiber activities and directly increase motor neuron excitability, as reported in an early animal study [46]. Nevertheless, the motor improvement following tES appeared immediately, especially for the motor independence of each upper limb joint (see

Figure 2) and sustained for at least one month. The study also illustrated two major effects of cervical tES: the release of abnormally increased muscle tone (see **Figure 4**) and the reduction of excessive muscle activities (see **Figure 6**). Furthermore, the intensity of tES adopted in this study did not induce any muscle contraction during the training, despite early SCS studies recommending stimulation with robust muscle contraction for muscle strengthening in TBI rehabilitation. This indicates that motor improvement is acquired following the recovery of neuron networks and that powerful stimulus is not strictly required for TBI treatment.

This study's findings offer an extension to the work of other groups who have studied the upper-limb training effect of cervical tES in patients with chronic TBI quadriplegia. In the present study, the patient with TBI demonstrated similar quadriplegia to patients with cervical SCI. Moreover, his upper limb motor improvement following concurrent tES+vPT intervention was also similar to the training outcomes in cervical SCI patients. We suggest that tES should be effective for upper-limb motor recovery in the treatment of upper motor neuron injury symptoms. Furthermore, the clinical results demonstrate different recovery patterns in the left and right arms of the patient. This is reasonable because of the distinct severity of motor deficits at the two sides, which means that one tES waveform illustrates two treatment directions for the different degrees of paralysis: 1) reconstruction for lost function, e.g. restoration of right-hand gross movements during ARAT, though the effect substantially degraded in one month without the stimulation, and; 2) enhancement for residual function, e.g. acceleration of left-hand grasping

speed during ARAT, and the effect was durable in this study even without the stimulation. However, this phenomenon's mechanism is still unknown and precisely how tES activates the cortical neural network has not been verified. We suggest future clinical studies on a larger sample of patients after TBI in attempts for sensorimotor recovery with this novel treatment.

5. Conclusions

The findings recorded here show the positive effects of non-invasive cervical stimulation, tES combined with vPT, and vPT in upper-limb motor rehabilitation. The immediate effects of the combinational treatment were found to be enhanced dexterity and increased muscle force, while long-term effects were the release of hypertonia and the facilitation of the patient's volitional motion coordination. This study demonstrates for the first time the therapeutic potential of non-invasive spinal cord electrical stimulation for a combination of volitional physical activities in respect of chronic TBI patients. More investigations with more patients are needed to find the different effects of a variety of tES stimulation schemes.

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Table 1. Primary measure of degree of motion completion:

Degree of Motion Completion			
Horizontal Task		Vertical Task	
Motion Independence	10%	Motion Independence	10%
Reach for Sponge	5%	Reach for Sponge	5%
Grasp the Sponge		Grasp the Sponge	
Hand Open	5%	Hand Open	5%
Hand Close	5%	Hand Close	5%
Lift Up>5cm	5%		
Lateral Motion Length		Vertical Motion Status	
5cm	5%	Lift Up>5cm	5%
25cm	5%	Lift to Upper Layer	5%
50cm	5%		
Motion Reverse	5%	Motion Reverse	5%
Arm Withdraw	5%	Arm Withdraw	5%
Total Percentage	55%		45%

N.B. The 80% degree of completion of patient's right arm was mainly due to the deduction of motion independence during both horizontal and vertical tasks.

476 **Table 2.** Stimulation schemes in the sponge grasping-releasing test:

Horizontal + Vertical Tasks					
Biphasic Rectangular	**Left Arm**		**Right Arm**		**VAS-Pain**
Waveform Schemes	Completion	Time	Completion	Time	**Level**
Without Stimulation (Baseline)	100%	50.47s	80%	78.51s	0
0.5ms 20Hz	80%	55.12s	70%	82.13s	2.5
0.5ms 25Hz	100%	50.65s	80%	79.45s	3
0.5ms 28Hz	100%	48.25s	80%	68.51s	3-4
0.5ms 30Hz	100%	48.81s	80%	72.33s	4
1ms 20Hz	100%	28.13s	80%	63.82s	2-3
1ms 25Hz	100%	27.51s	80%	60.15s	2-3
1ms 28Hz	100%	26.30s	80%	59.08s	3
1ms 30Hz	100%	25.66s	80%	57.89s	3
1ms 32Hz	100%	30.45s	80%	58.56	4

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Table 3. Demonstration of Functional Independence Measurement (FIM) scores of the TBI patient:

Functional Independence Measurement			
	Pre	Post	Follow-up
Self-Case (42)	12	13	13
Sphincter Control (14)	4	4	4
Transfer (21)	6	6	6
Locomotion (14)	6	6	6
Communication (14)	14	14	14
Social Cognition (21)	21	21	21
Total Score (126)	63	64	64

Figure Legends

Figure 1. Detailed timeline of the study. Patient was recruited and tested for his suitability for the study. After baseline motor assessment and stimulation scheme test the patient went through two phases of treatment, each phase containing 5 training sessions: *Phase I* with only voluntary physical training (vPT), and *Phase II* with vPT combined with transcutaneous electrical stimulation (tES). Motor assessments were conducted again after 1 month secession of the treatment (follow-up).

Figure 2. Fugl-Meyer Assessment for upper extremity (FMA-UE) score of left and right arms during baseline assessment, with voluntary physical training (vPT), with transcutaneous electrical stimulation combined with voluntary physical training (tES+vPT), and at 1 month follow-up after the training programme. **SE:** shoulder-elbow; **WH:** wrist-hand.

Figure 3. Action Research Arm Test (ARAT) score of left and right arms during baseline assessment, with voluntary physical training (vPT), with transcutaneous electrical stimulation combined with voluntary physical training (tES+vPT), and at 1 month follow-up after training programme.

Figure 4. Modified Ashworth Scale (MAS) score of finger, wrist and elbow joints in left and right arms during pre-training assessment, with voluntary physical training (vPT), with transcutaneous electrical stimulation combined with voluntary physical training (tES+vPT), and at 1 month follow-up after training programme. Note that the score for right fingers overlapped that of the right wrist.

Figure 5. a) Manual Muscle Testing MMT and b) grip force of left and right hands during baseline assessment, at each session of voluntary physical training (vPT), at each session of transcutaneous electrical stimulation combined with voluntary physical training (tES+vPT), and at 1 month follow-up after training programme.

Figure 6. Average rectified EMG value of triceps (TRI), biceps (BIC), extensor digitorum (ED) and flexor digitorum (FD) in left and right arms during baseline, pre-training and post-training sponge grasping-releasing task. The baseline recording was conducted without transcutaneous spinal cord stimulation, while the pre- and post- training tasks were conducted with stimulation.