Case report

Usefulness of robotic gait training plus neuromodulation in chronic spinal cord injury: a case report

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Context: Spinal cord injury (SCI) affects more than 2.5 million people worldwide, often leading to severe disability. Thus, a proper management of individuals with SCI is required either in the acute or in the post-acute rehabilitative phase.

Findings: A 31-year-old man, affected by chronic SCI, underwent two different intensive rehabilitation treatments, including either LokomatPro or a paired LokomatPro-rTMS training. We evaluated the clinical, kinetic, and electrophysiological parameters before and after each training session. In particular, the intensive robotic training was articulated in a total of 40 one-hour training sessions (i.e. 5 times a week for 8 weeks), whereas the rTMS sessions were delivered 3 days per week for 3 consecutive weeks, just before the LokomatPro session. Only at the end of the experimental treatment, we observed an important improvement in nearly all parameters we investigated.

Clinical relevance: The combined LokomatPro-rTMS rehabilitation may be a valuable approach in improving the motor function in patients affected by SCI, even in the chronic phase.

Keywords: LokomatPro, Repetitive transcranial magnetic stimulation, Robot-assisted gait therapy, Spinal cord injury, Spinal plasticity

Introduction

Spinal cord injury (SCI) consists in temporary or permanently loss of motor, sensory, or autonomic functions after either traumatic or non-traumatic spinal cord damage. SCI prevalence has been reported to be very different in many countries, with a worldwide prevalence of around 2.5 million people. The localization and the type of damage of the spinal cord and its roots determine the different clinical pictures (ranging from various levels of incomplete forms up to a complete SCI), and the functional and rehabilitation outcomes.¹ Indeed, SCI requires an intensive rehabilitative approach in nearly all cases, since SCI frequently results in severe functional impairment, even when an adequate acute treatment has been performed.² To this end, growing evidence is demonstrating the effectiveness of the robot-assisted gait therapy (RAGT) in improving the SCI rehabilitative functional outcomes.³ RAGT automates locomotion therapy on a treadmill with or without a body weight support system (BWSS),

potentially improves the traditional therapeutic interventions, and allows walking similar to the over-ground gait with adequate proprioceptive and sensory feedback. On the other hand, growing evidence is showing that neuromodulation can reduce the motor impairment and promote spinal fiber functional restoration.⁴ In particular, repetitive transcranial magnetic stimulation (rTMS) approaches have been implemented with promising results either in human or experimental models.⁵ Herein, we describe the application of a combined neurorobotic-non-invasive neuromodulation rehabilitative protocol in a case of post-traumatic incomplete SCI in the chronic phase.

Case description

An otherwise healthy 31-year-old man, affected for around 20 months by incomplete post-traumatic SCI following a motorbike accident, came to our observation for an intensive neurorehabilitation treatment. The neurological examination showed a moderate to severe paraparesis, hypoesthesia below the umbilicus, urge incontinence, and erectile dysfunction (American Spinal Injury Association Impairment Scale -ASIA: C;

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Lower Extremity Motor Score -LEMS: 3). A spinal cord MRI-scan showed a T2-hyperintense lesion at T10. The lower-limb somatosensory evoked potentials showed a P40 latency of 46 (right) and 45 ms (left) (N22 of 21.4 and 21.5 ms, respectively) and bilateral amplitude of $\sim 4 \mu\text{V}$, whereas the motor central conduction time (CCT) was bilaterally ~ 37 ms.

The patient performed a neurorobotic treatment by means of the Lokomat device (Hocoma; Volketswil, Switzerland). Lokomat is a robotic device, consisting of powered gait orthoses with integrated computer controlled linear actuators at each hip and knee joint, a BWSS, and a treadmill.⁶ In our protocol, we used a Lokomat with an Augmented Performance Feedback (APF) (i.e. the LokomatPro) that provides motivating, challenging and instructive functional feedback in virtual environments. As virtual reality enhances the patient's active participation during the robot-assisted training, the APF encourages and helps improving the patient's compliance. The patient performed a 40-minute session per day, between 9 A.M. and 12 P.M., from Monday to Friday, for 8 consecutive weeks, for a total of 40 sessions. The amount of BWS was initially set at 70% of the patient's weight, then decreased according to the patient's load tolerance ($61 \pm 6\%$), and the gait speed was adjusted in order to make the exercise comfortable for the patient (1.5 ± 0.3 Km/h). The entire session was supervised by a Lokomat-trained physiotherapist.

We measured some clinical (AIS, LEMS), kinetic (hip and knee flexion/extension force and stiffness, LokomatPro guidance force), and electrophysiological parameters (resting motor threshold (RMT) and motor evoked potential (MEP) peak-to-peak amplitude from right tibialis anterior, CCT, and motor unit estimation number (MUNE) from right vastus lateralis) before (baseline1) and after the treatment (post-LokomatPro). MUNE provides a numeric estimation of the number of axons innervating a muscle or a group of muscles, thus approximately quantifying the motoneurons' degeneration after SCI,⁷ and it is calculated as the ratio of the maximal compound muscle action potential divided by the average of surface motor unit potentials. Indeed, this estimation index is a marker of different phenomena of neuronal plasticity, reversible trans-synaptic degeneration, and local functional depression within spinal motor units.⁷ We evaluated the significance of each parameter modification through the reliable change index (RCI). This hails from the difference between participant's pre-test and post-test scores, divided by the standard error of the difference. If the RCI is 1.96 or more,

the difference is statistically significant (since 1.96 equates to the 95% confidence interval). In other words, the difference between two scores has to be at least 1.96 times the standard error of the difference to be significant.

After the first neuro-robotic session, the patient showed a very mild improvement concerning kinetic parameters (reduction of hip and knee stiffness), and non-significant clinical and electrophysiological changes (Table 1). The patient did not report any side-effect either during or following the entire Lokomat treatment.

Such aforementioned after-effects disappeared after one month of rest, when the patient came back to our observation (baseline2) (Table 1). Thus, we implemented a second LokomatPro session paired to an rTMS paradigm (experimental procedure), in an attempt to ameliorate patient's outcomes. The LokomatPro session was performed analogously to the first one (i.e. 40-minute session/day, 5 times a week for 8 consecutive weeks) with the same robotic device and parameters at the beginning of the experimental procedure. rTMS sessions were applied in the morning (between 9 A.M. and 12 P.M., just before starting the neuro-robotic training), 3 times per week (Monday, Wednesday, and Friday) for the first 3 weeks of treatment (for a total of 9 rTMS sessions). Then, the patients continued the daily LokomatPro sessions without rTMS for the remaining 5 weeks.

rTMS was delivered by a Magstim Super-Rapid2 stimulator (Magstim Company, Whitland, UK) equipped with a double-cone coil (each wing measuring 110 mm in diameter) that was perpendicularly held over the vertex, in order to trigger both leg primary motor areas. The stimulation site was identified according to a recently performed brain MRI scan and the RMT from right tibialis anterior muscle. RMT was defined as the intensity that evoked a MEP amplitude of $50 \mu\text{V}$ in 5-out-of-10 consecutive stimulations.⁸ Hence, we measured the MEP amplitude. All the rTMS sessions were conducted with the patient lying supine. We applied 60 bursts of 20 pulses at 10 Hz with inter-train intervals of 10", for a total of 1200 pulses, nearly Cz. The intensity of stimulation was set as 90% of the RMT. The patient did not report any side-effect either during or following the stimulation sessions.

We observed an amelioration of ASIA (i.e. from class C to D) and LEMS (from 3 to 9) scores, and a statistically significant reduction of hip and knee stiffness, device guidance force, BWS (from $61 \pm 6\%$ to $57 \pm 3\%$), and an increase of hip flexion-extension force, MEP amplitude, MUNE, and speed (from $1.5 \pm$

Table 1 Resumes the parameters studied at baseline (baseline1), and after the Lokomat training alone (Post-LokomatPro), one month of rest (baseline2), and the experimental procedure (Post-rTMS-LokomatPro). The significance of each parameter variation is indicated by the superscript RCI value (when >1.96).

Parameters	Baseline1		Post-LokomatPro	Baseline2	Post-rTMS-LokomatPro
			40 daily sessions 5 times per week 8 weeks		40 daily sessions 5 times a week 8 weeks rTMS during the first 3 weeks at alternating days
Clinical	C		C	C	D
AIS					
LEMS	1,1,1,0,0		2,2,1,0,0	1,1,1,0,0	3,3,3,0,0
Electrophysiological					
RMT(%)	65		64	65	64
% unconditioned MEP	100		108	102	140 ^{2.7}
CCT (ms)	30		30	30	29
MUNE	36		40	35	52 ^{2.3}
Kinetic					
Stiffness (N•m/degree)	Hf	0.42	0.37	0.43	0.29 ^{4.5}
	He	0.46	0.37 ^{3.2}	0.45	0.36 ^{3.2}
	Kf	0.19	0.15 ^{2.3}	0.19	0.12 ^{2.8}
	Ke	0.23	0.19 ^{2.3}	0.23	0.11 ^{3.1}
Force (N•m)	Hf	13	25	14	35 ^{3.1}
	He	0	0.3	0.1	1.5 ^{2.8}
	Kf	0	2	0.1	4.5
	Ke	0.4	0.8	0.5	1.5
DGF (%)	100		85	96	60 ²

AIS: American Spinal Injury Association Impairment Scale; LEMS: Lower Extremity Motor Score (the scores refer to hip flexors, knee extensors, ankle dorsiflexors, long toe extensors, and ankle plantar flexors, respectively); RMT: resting motor threshold; MEP: motor evoked potential; CCT: motor central conduction time; MUNE: motor unit estimation number; Hf, He: hip flexion-extension; Kf, Ke: knee flexion-extension; DGF: device guidance force; N•m: Newton x meter.

0.3Km/h to 1.7 ± 0.2 Km/h) after the combined treatment (Table 1), whereas only a mild reduction of hip and knee stiffness (Table 1) was noted after the first neuro-robotic treatment.

In addition, an improvement of erectile function was also noted only after rTMS application (International Index of Erectile Function-IIIEF from 6 to 16).

Discussion

The importance of an intensive and early RAGT during the acute/sub-acute phases of SCI in improving the lower limb performances is well-known. Indeed, RAGT may contribute to restore the central motor command (by shaping the cortical control of spinal interneuron circuits generating patterned motor activity, enhancing the residual cortico-spinal tract functions, and modifying spinal reflex function), strengthen bone structure, preserve joint range of movements, and preventing muscle atrophy.⁹ Instead, RAGT usefulness in chronic SCI is still debated.^{10,11} Notably, the Lokomat-Pro training alone did not significantly improve the clinical, kinetic, and electrophysiological outcomes in our patient.

Since there are no standardized robotic neuro-rehabilitative protocols, to date, the poor LokomatPro after-effects could depend on some methodological issues,

including the sessions' number, training total duration, and conventional physiotherapy combination. Indeed, in our case, such mild after-effects disappeared after one month of rest.

Instead, the combination of rTMS with LokomatPro training induced a significant improvement in nearly all clinical scale scores, MEP amplitude, MUNE, and the other kinetic parameters.

Notably, although the rTMS-LokomatPro beneficial effects could be simply related to the prolongation of the robotic rehabilitation protocols (i.e. LokomatPro alone followed by rTMS-LokomatPro), we believe that patient improvement was related to such combined approach. In fact, the rTMS-LokomatPro after-effects were significantly greater than those expected by the summation of the two Lokomat sessions, also taking into account that the mild improvement observed after the standard Lokomat treatment disappeared before the beginning of the experimental protocol.

Whereas the usefulness and feasibility of non-invasive neuromodulation paradigms regarding sensory and motor function impairment, spasticity, and neuropathic pain are known, the underlying neurophysiologic mechanism are still partially unclear.¹² Key elements may include cell death limitation (owing to anti-excitotoxic and anti-apoptotic phenomena), cell regeneration

(sprouting of new axons, guidance of axon to proper targets), cell replacement (e.g. stem cell induction), remyelination (oligodendrocyte function), and spinal plasticity modulation (reduced inhibition).¹³

We may hypothesize that our rTMS paradigm could have strengthened the RAGT's effects thanks to either direct cortico-spinal or trans-synaptic spinal effects.¹⁴ Indeed, it has been shown that rTMS could decrease intracortical inhibition phenomena and shape I-waves, allowing the recruitment of the spared corticospinal tract fibers, and thus improving the motor functions.¹² Notably, the rTMS-induced functional recovery seems to not depend on spinal conductivity improvement, as evoked potentials latencies did not vary. Hence, it is possible to hypothesize that the rTMS could have induced compensatory plasticity mechanisms and recruited stunned or dysfunctional spinal motor-neurons (or inter-neurons, possibly including the Onuf centre neurons, which are responsible for the erectile function), as suggested by the significant MUNE increase.¹⁵

Moreover, the rTMS-LokomatPro protocol significantly reduced the patient's lower limb stiffness, which notoriously influences motor function recovery. To this end, it has been shown that high frequency rTMS over M1 can reduce H-reflex size in both healthy individuals and several neurological diseases.¹⁴ The increase of M1 excitability and the reduction of descending corticospinal inhibitory influences on spinal cord may modulate segmental spinal excitability.¹⁶

The main limiting factor in our case-report is that we did not apply a sham rTMS session. Nonetheless, growing evidence in literature supports the absence of a placebo effect of rTMS.¹⁴ Thus, our rTMS-LokomatPro after-effects could be reliably due to the neuromodulation properties of the rTMS procedure we applied.

Conclusions

In conclusion, taking into account the common case-study limitation factors (such as inter-related issues of methodological rigor, researcher subjectivity, and external validity), we may argue that the combined TMS-neurorobotic approach could be beneficial in improving motor function recovery in patients with chronic incomplete SCI, without any significant side effect of both Lokomat training and rTMS. Nevertheless, more investigations are needed to further assess functional benefits of different protocols and applications, as well as the effect of alternative cortical sites of stimulation on neuroplasticity.

Disclaimer statements

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Conflict of interest None.

Ethics approval None.

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