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Preliminary Report

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Paired associative stimulation after spinal cord injury: who should undergo?

Abstract

Background: Paired associative stimulation (PAS) combines peripheral nerves stimulation (PNS) with transcranial magnetic stimulation (TMS) and it is believed to induce plastic changes in the human corticospinal tract after spinal cord injury (SCI). The aim of the present study was to investigate the advantages of PAS added to conventional rehabilitation protocol for patients with chronic SCI.

Methodology: The study was monocentric sham-controlled and involved 11 patients with lower paraparesis 3-12 months after the trauma. TMS was delivered over vertex using a round coil with 150% of resting threshold. ESPN of both n. peroneous and n. tibialis was performed with supramaximal intensity at fossa poplitea for 5 minutes for each nerve. The interval between TMS and PNS was individually defined (around 35ms). The intervention consisted 30 sessions of 1Hz PAS in total.

Results: After the intervention, the improvement of motor and sensory function (via ASIA impairment scale) was observed in both groups but the intergroup difference was insignificant (Mann–Whitney U test, p=0.0675). Spasticity (via modified Ashworth scale) was not changed significantly but 4 patients noticed more uncontrolled movements. Expectedly, patients with no peripheral M-response at the beginning do not demonstrated any improvements. The best functional outcome was found into patients with preserved MEP in the study group. Two patients with absent MEP at the beginning from the study group showed unstable MEP after a month.

Conclusion: PAS could be seen as an additional tool to facilitate the recovery after chronic SCI. Patients with preserved MEP may benefit more from this technique. On the other hand, the absence of M response could be considered as an exclusion criterion while the selection of individuals for PAS. The choice of stimulation protocols is still arguable that can lead to diverse and controversial results.

Volume 3 Issue 2 - 2018

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Received: April 10, 2018 | **Published:** April 24, 2018

Introduction

The estimated annual global incidence of spinal cord injury is 40 to 80 cases per million populations by the World Health Organization.[1] Up to 90% of these cases are due to traumatic causes. The severity of injury and its location on the spinal cord define recovery process and symptoms which may include partial or complete loss of sensory function or motor control of arms, legs and/or body. The functional impairment is assessed clinically using a range of scales as well as neurophysiological tools and measurements. The most used parameter is motor evoked potentials which is believe highly-correlated with limb motor score and functional outcome.[2] However, it is also assumed that even when clinically complete injury is observed and MEPs could not be recorded, there could be some preserved connections through the lesion but non-functional at the moment.[3] This is why techniques which could be able to enforce such kind of connections are widely studied last years.[4] As some animal research demonstrates, time dependent stimulation of neuros above and below the injury side may induce neuroplasticity and improve functional outcome.[5] A well-known method to stimulate lower motor neurons is peripheral nerve stimulation (PNS) which has been used mostly to prevent muscular and axonal atrophy in paretic limbs.[6–8] For upper neuros, it is transcranial magnetic stimulation (TMS) of the corresponding motor cortex.[9] Applied together, PNS and TMS are called paired associative stimulation (PAS) and are believed to strengthen excitatory synapses and inducing neural plasticity.[10] Depending on intervals between these two stimuli, PAS may induce long term inhibition or potentiation (LTP) underlaying neuro plasticity that correlates with an increase in muscle voluntary force.[11] Previous research suggested that spike timing-dependent plasticity of residual corticospinal-motoneuronal synapses after SCI could be a promising therapeutic target.[12] The aim of the present preliminary study was to investigate the advantages of PAS added to conventional rehabilitation protocol in chronic SCI.

Methods

These studies were approved by the Ethical Committee of Pirogov Center. All methods conformed to the Declaration of Helsinki and all participants provided written informed consent. Patients were screened for contraindications to TMS (i.e., the presence of metal implants, cardiac pacemakers, unexplained headaches, or history of seizures). Before the intervention, each patient underwent electroencephalography to exclude any abnormal brain activity. Eleven patients with lower paraplegia due to chronic spinal cord injury (≥3 months) were recruited for this study (Table 1). All lesions were the result of different kinds of trauma (motor vehicle accidents, sports injuries, industrial accidents) in the lower vertebrae of the thoracic spine or in the upper vertebrae of the lumbar spine. It was considered acceptable for this proof of principle study to recruit a heterogeneous group of patients that varied in the extent of motor and sensory loss, lesion location and time since SCI. The main goal was to detect any effects of PAS of the motor cortex on motor excitability

and functional recovery in order to determine general tendencies for further research. The study group comprised of three women and six men (mean age 25.4±6.5, range 18-42). The PAS was allied over the motor cortex corresponding to AH on both sides twice per day for 15 continuous days. The robot-assisted gait training (Lokomat, Hocoma AG, Volketwill, Switzerland) was used between PAS sessions. Additionally, each patient received individual conventional rehabilitation. Seven patients had undergone peripheral nerve stimulation of lower extremities 1-3 months prior to the study whereas TMS had not been applied to anyone. Pharmacological treatment involved mostly anticonvulsants and skeletal muscles relaxants. Additionally, three patients were prescribed with antidepressants due to previously diagnosed depression.

Table 1 The summary information about the patients

Patient	Gender	Age	Neuro-logical level	AIS	Time since injury (months)	Height (cm)	Conventional rehabilitation (times per day)	Prescribed medications
1	M	18	Th12	B	6	172	Kinesiotherapy (30'*14) Robotic walking (30'*14)	Pregabalin 150mg*3 Amitriptyline 25mg*3
2	M	32	Th8	B	9	169	Kinesiotherapy (30'*14) Robotic walking (30'*14)	Baclofen 10mg*3 Gabapentin 300mg*3
3	M	24	Th11	C	13	180	Kinesiotherapy (30'*14) Robotic walking (20'*10)	
4	F	20	Th7	C	18	174	Kinesiotherapy (30'*14) Robotic walking (30'*14)	Carbamazepine 200mg*3 Mianserin 30mg
5	M	20	L1	C	16	189	Kinesiotherapy (30'*14) Robotic walking (30'*14)	
6	F	33	Th11	C	22	162	Kinesiotherapy (30'*14) Robotic walking (30'*14)	
7	F	42	L1	D	21	158	Kinesiotherapy (30'*14) Robotic walking (20'*14)	Fluoxetine 40mg Clonazepam 1mg
8	M	35	Th6	B	13	178	Kinesiotherapy (1h*7) Robotic walking (30'*14)	
9	M	30	Th12	C	7	182	Kinesiotherapy (30'*14) Robotic walking (20'*14)	Baclofen 25mg*3
10	M	19	Th10	B	26	178	Kinesiotherapy (1h*7) Robotic walking (20'*12)	Pregabalin 75mg*2
11	M	28	Th12	C	14	176	Kinesiotherapy (1h*7) Robotic walking (30'*14)	

The equipment for PAS combined a Skybox (EMG, NCS and EP Systems) and Neuro MS/D magnetic stimulator (Neurosoft Ltd., Ivanovo, Russia). Magnetic stimuli were delivered over the lower limb motor cortex at 1Hz. A linen cap was tied tightly on the subject's head and taped to the skin of the forehead. The vertex (taken as the intersection of the inter-aural and nasion–inion lines) was marked on the cap. A round coil was placed onto the cap on the mid-sagittal plane (approximately 2cm posterior to the vertex). Slight adjustments to the coil position were made until MEPs of at least 1.0 mV were elicited from AH with minimal TMS intensity. The position of the coil was checked frequently during the intervention, and no changes were detected.

Peripheral electrical stimulation of both n. peroneous and n. tibialis was delivered onto fossa poplitea for 5 minutes for each nerve with supramaximal intensity, which was defined as minimum current level where the amplitude of motor responses did not increase anymore.

The exact spots of stimulation were determined using motor responses from corresponding muscles (AH and EDB). EMG recordings were performed using surface EMG electrodes (NeuroSoft, Russia) placed over the muscle belly of both AH and EDB. The reference electrode was placed over the external malleolus. EMG and stimulator trigger pulse data were recorded using Neuro-MVP 8 software (Neurosoft, Russia).

Across subjects, PNS stimulation intensity varied from 35 to 52 mA, using a 0.2 ms stimulus pulse width. TMS resting motor threshold (RMT) was determined using the right m. abductor pollicis brevis (APB). MT was the stimulator intensity that resulted in 5 of 10 MEP responses with amplitudes of~1.0 mV clearly distinguishable from background EMG [55±9.4% maximum stimulator output (MSO)]. The TMS intensity corresponding to 150% APB resting threshold was used for PAS in paretic legs. The inter-stimulus intervals (ISI) were individualized for each subject based on their estimated MEP latency. To achieve PAS induced facilitation of the motor system, the ISI was set so that the TMS was delivered at an ISI that was 8ms longer than the estimated MEP latency (35.2±2.2ms). Two hundred and forty stimulus pairs at a frequency of 1 Hz were delivered in a 4 min period for each nerve while the subject was laying. Subjects were asked to concentrate on foot movements.

The evaluation of motor and sensory scores for ASIA was performed independently by two experienced physiotherapists. The same physiotherapists estimated spasticity of the tested muscles using the modified Ashworth Scale (mAS). Neuophysiological evaluation was performed by an unblind specialist at the beginning, at the end and a month after the intervention. Neuophysiological evaluation was performed by an unblind specialist. MEPs were classified as normal, absent or delayed by the latency, which was calculated at the moment of a deflection of the response curve. A positive response was defined as the presence of a signal with more than 100mV. Responses with latency longer than 50ms were defined as 'delayed'. The MEP of the 'absent' group did not show positive response from 100% stimulation, with stimuli delivered at least three times to confirm no response. Nerve conduction study from AH and EDB was used to determine the maximal motor response (M-max) and a subsequent F-wave.

Data are presented as mean – standard error. Statistical significance was assessed by Wilcoxon signed rank tests with TIBCO Software Inc.

Results

Motor and sensory scores were assessed via the standard scale of American Spinal Injury Association Impairment Scale (AIS) at the Th5-S5 levels at the beginning of the study and the end. A moderate improvement was observed at motor (from 15.9±6.2 to 20.5±7.2, p=0.021). The intervention had no significant effect on sensory scores (from 69.8±10.5 to 72.8±9.3, p=0.064). Spasticity was not changed significantly but some patients noticed an increase in muscle tone but no neuropathic pain was reported. There were no effects on autonomic functions. The following adverse effects appeared: mild headache and pain at the place of stimulation in three patients and more uncontrolled movements in five patients. However, all these patients decided to continue the intervention.

The minimum and maximum F latencies (Fmin, F max), F amplitudes, and F persistence (pulses that generated F-responses, % of total amount) were analyzed from AH and EDB of every patient before and after the intervention. PAS did not affect these parameters significantly. The average change of personal and tibial nerve measurements by the intervention was F min 0.16±0.72 msec, p=0.72, F max 0.46±0.34msec, p=0.63, F amplitudes 0.12±0.2mV, p=0.47, F persistence 1–4%, p=0.38. At the beginning, 4 patients had no M-responses, 3 had normal M-responses and 4 had M-responses with low amplitude. Patients with no M-response at the beginning did not demonstrate any improvements. The M-response amplitude among other patients increased but not enough to reach statistical significance (Table 2).

Table 2 The summary of taken measurements before and after the intervention

	1st day	14th day	p-value
N. peroneus profundus			
Latency (ms)	4.03±0.98	3.97±0.73	0.562
Amplitude (mV)	3.51±1.72	4.92±1.94	0.073
Conduction velocity (m/s)	48.87±7.28	47.40±5.08	0.256
N. tibialis			
Latency (ms)	3.48±1.51	3.66±1.34	0.547
Amplitude (mV)	8.92±4.02	10.61±5.12	0.153
Conduction velocity (m/s)	51.07±6.78	50.40±8.08	0.556
Clinical outcomes			
Motor ASIA	15.9±6.2	20.5±7.2	0.021
Sensory ASIA	69.8±10.5	72.8±9.3	0.064
mAS	2.2±1.2	2.8±1.5	0.102
Absent MEP	4	2	
Delayed MEP	7	9	

Conclusion

The present study demonstrated possible benefits of PAS added to conventional rehabilitation and determined some directions for further investigations. Firstly, the presence of MEPs indicates better outcome while MEPs can appear during the treatment if it was not evoked at the beginning. Secondly, patients with progressive peripheral damage with absent M-response due to denervation or muscle atrophy probably would not benefit from PAS. The choice of stimulation protocols is still arguable that can lead to diverse and controversial results. A challenging issue is to define ISIs especially if MEPs are delayed or absent and require more standardization.

Acknowledgements

None.

Conflict of interest

Authors declare that there are no conflicts of interest.

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Citation: Novak EV, Daminov VD. Paired associative stimulation after spinal cord injury: who should undergo?. *Int Phys Med Rehab J.* 2018;3(2):170–173. DOI: 10.15406/ipmrj.2018.03.00097

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Citation: Novak EV, Daminov VD. Paired associative stimulation after spinal cord injury: who should undergo?. *Int Phys Med Rehab J.* 2018;3(2):170–173. DOI: 10.15406/ipmrj.2018.03.00097