

Repetitive Transcranial Magnetic Stimulation and Stroke Rehabilitation

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Running title

rTMS in stroke patients

Keywords

Stroke - repetitive Transcranial Magnetic Stimulation - finger dexterity - Occupational therapy - Serum - Tryptophan - L-kynurenine - Kynurenic acid - Anthranilic acid

Neurorehabilitation involves a wide spectrum of different approaches of treatment modalities and is a notable period for patient after stabilization of patient's neurologic injury. In 1985 Barker and co-authors introduced transcranial magnetic stimulation (TMS) as a noninvasive and safe brain stimulation technique [1]. TMS can be delivered via single-pulse, double-pulse, paired-pulse and low or high frequency repetitive pulses (rTMS) [2-8]. Depending on stimulation parameters i.e. frequency, rate, and duration, application of repetitive stimuli to cortical regions can enhance or decrease the excitability of the affected brain structures [2-4]. In the last years the development of stimulators significantly progressed, specially discharging at high frequencies up to 100 Hz and the application of TMS expanded into the areas of behavioral and cognitive functions assessment, as well [9-10].

rTMS is the method currently used as a treatment modality for stroke patients with spastic movement disorders mainly due to its ability to modulate the excitability in the motor cortex over longer time periods (compared to other types of TMS) [11-17].

For evaluation of the clinical outcome, the patients' abilities are evaluated before and after rTMS therapy by the National Institute of Health Stroke Scale (NIHSS) and Barthel – Index [18]. Moreover spasticity is evaluated by modified Ashworth Scale before and after rTMS application [19].

In good correlation with previously published investigations [13-16] also our study revealed the improvement of motor ability in stroke patients after rTMS [12, 20]. Furthermore, augmentation of motor performance and a moderate reduction of spasticity could be seen and this is in line with previously published observations [11]. Interestingly, we observed that the effect of rTMS had a significant impact on the output of occupational therapy if these trials were performed immediately after rTMS. An increase of finger dexterity and amelioration of Barthel Index was found [21]. Importantly, in patients with high nursing needs, less service was required if the occupational therapy was performed right way after rTMS [21]. These are observations particularly for optimizing the therapy management.

In our study, among 45 stroke patients recruited for rTMS, 34 patients (76 %) finished the rTMS stimulation program and these patients experienced positive effects.

In 9 patients the therapy with rTMS was interrupted because of enhanced activities of generalized sharp waves observed by EEG and these patients were no further applied to rTMS and were excluded from this study according to the investigation protocol and two patients due to a high number of other therapies wished to be excluded from this study [20]. Investigation of NIHSS and Barthel-Index revealed significant improvement in patients' abilities after rTMS applications [20]. NIHSS before rTMS was 4.18 ± 0.39 and after 10th rTMS application was 2.97 ± 0.38 and Barthel-Index before rTMS was 58.48 ± 4.85 and after 10th rTMS was 74.38 ± 3.9 [20]. Tonus evaluation following modified Ashworth Scale revealed a reduction of spasticity after rTMS, however the effect was not statistically significant. Ashworth Scale before rTMS was 1.6 ± 0.2 and after rTMS was 1.4 ± 0.2 . More data would be necessary to confirm these positive therapeutic effects of rTMS by stroke patients.

In stroke patients the occurrence of memory and cognition impairment as well as of the development of post-stroke depression is well known. Strafella and co-workers, 2001 showed significant effect of rTMS of the human prefrontal cortex on release of endogenous dopamine in caudate nucleus and they suggested therapeutic use of rTMS in neurological and psychiatric disorders [22].

Data from our research [20, 25] and from other institutions [23, 24] showed that L-tryptophan metabolism along the kynurenine pathway is significantly enhanced in the serum of stroke patients. This investigation gained particular importance since some metabolites of this pathway exert neuro-modulatory activities for example kynurenic acid which is known as an antagonist of ionotropic glutamate NMDA receptors and of nicotinic cholinergic subtype $\alpha 7$ receptors [26, 27] and its involvement in neurological and neuropsychiatric diseases has been suggested.

In our previous study we demonstrated for the first time that rTMS affects L-tryptophan metabolism along kynurenine pathway in the serum of stroke patients significantly [20]. Notably, the value of L-kynurenine/L-tryptophan ratio is increased after rTMS indicating the ability of rTMS to influence the degradation of L-tryptophan in the serum. Furthermore, the anthranilic acid/kynurenic acid ratio values were significantly increased after rTMS and this effect might indicate its neuromodulatory ability.

There are studies demonstrating changes of plasma levels of a variety of hormones including cortisol, prolactin and thyroid stimulating hormone after rTMS [28, 29].

Revealed data are inconclusive, and it is reasonable that the disperse results are due to different age and sex distributions. Our study revealed differences in effect of rTMS on prolactin with respect to the age and sexin stroke patients [20]. Interestingly, we demonstrated that only in female stroke patient with an age from 52-70 years the prolactin levels were significantly lowered after rTMS. It is likely that rTMS indirectly blocks the secretion of prolactin, due to release of dopamine [22].

In summary Improvement of daily activities of living and of motor performance in stroke patients was revealed after rTMS. Notably, a significant amelioration of finger dexterity and increase of Barthel Index values could be achieved when occupational therapy immediately followed rTMS treatment; therefore it is obvious that management of the rehabilitation process is particularly important.

Furthermore, evaluation of therapies together with neurochemical investigation of human material is decisive for improvement of therapeutic strategies.

Conflict of interest

The authors declare no conflict of interest.

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