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Neuromodulatory approach in paroxysmal neurological disorders

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Abstract

Background: Nowadays, neuro-modulation offers different devices and techniques in the treatment of neurological patients suffering from paroxysmal disorders, such as epilepsy and migraine. Among non-pharmacologic therapies, rTMS shows good results.
Material and methods: A longitudinal, double-blinded, rTMS-intervention study was conducted on 42 subjects with episodic migraine (with and without aura, 2-14 attacks per month). After a baseline follow-up for 1 month, subjects had 6 sessions of rTMS during 2 weeks and received multifocal rTMS or sham stimulation, with further 3-month assessment via questionnaires on headache frequency .
Results: After stimulation, the real rTMS group showed a reduction in the number of attacks – 7.5 ± 3.7 at baseline to 3.8 ± 2.7 attacks at 3 months' period ($p<0.05$) with an effect lasting at least three months. The number of attacks was also reduced in the placebo group (7.3 ± 3.6 to 4.4 ± 2.9) ($p>0.05$). There was a significant reduction in the intensity of attacks over 4-week therapy in the treatment group (6.7 ± 1.5 at baseline; 5.3 ± 2.5 at 4 weeks ($p<0.05$). The conducted questionnaires revealed a positive impact on quality of life and functional outcomes. There were no serious adverse events reported.
Conclusions: Our study showed evidence that the experimental rTMS protocol significantly reduced the frequency and intensity of migraine attacks compared to placebo treatment with no serious adverse events.
Key words: transcranial magnetic stimulation, multifocal, migraine.

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Introduction

Nowadays, neuromodulation offers different devices and techniques in the treatment of neurological patients suffering from paroxysmal disorders, such as epilepsy and migraine. rTMS has shown good results among other non-pharmacologic therapies. Transcranial magnetic stimulation (TMS) was introduced for the first time in 1985, as a method of noninvasive stimulation of the human cortex [1, 2], offering the possibility of studying the connection between the anatomical and functional elements of the human cortex [3]. Currently, rTMS is considered a useful tool in the management and treatment of several disorders originating in the cerebral cortex [4]. The small intensity currents induced by the magnetic field have an impact on various mechanisms at cellular level being able to change the expression of neurotransmitters, thus resulting in modulation of pathophysiological pathway of migraine.

The primary mechanisms causing migraine attacks still remain largely unrecognized due to the complex and dynamic organization of processes in the brain neuronal networks. Cortical excitability has been suggested to be dysfunctional in patients with migraine [5]. The ability to modulate cortical activity and induce persistent, plastic effects renders repetitive transcranial magnetic stimulation (rTMS) as a potential therapeutic approach.

Several studies demonstrate that TMS can reduce the frequency and severity of migraine attacks [6, 7]. Possible mechanisms involve induction effects on blood-flow, peripheral nerve sensing, cortical excitability and the release of cytokines or inflammatory neuropeptides [8-10].

The purpose of our study was to evaluate the efficacy and tolerability of multifocal rTMS for migraine prevention. The study hypothesis states that multifocal rTMS reduces the frequency and intensity of migraine attacks in comparison to a baseline period, and that this effect exceeds a possible placebo effect. Furthermore, it hypothesized that this stimulation protocol can induce improvements in quality of life scores: Headache impact test 6 (HIT-6), Migraine disability index score (MDIS), and Headache disability index (HDI).

Material and methods

A longitudinal, double-blinded, rTMS-intervention study was conducted on subjects with episodic migraine (both with and without aura, 2-14 attacks per month). The research project was approved by the Research Ethics Committee of Nicolae Testemitanu State University of Medicine and Pharmacy (No 90 of June 19, 2018). After a 4-week baseline period, the subjects underwent 6 intervention sessions within 2 weeks to receive either multifocal experimental rTMS or a placebo-treatment (randomized trial

was performed by a researcher blinded to every aspect of the study except randomization codes). The blinding of subjects was performed by means of a specific round biconcave active/placebo coil, which depending on the randomization code could act as an active coil (applying the experimental protocol) or sham (that was vibrating and making sounds imitating the real rTMS stimulation). A total number of forty-two subjects were eligible to participate in the study. The overall group baseline description is presented in table 1 and age-related group distribution in figure 1.

The test findings were evaluated via the IBM SPSS Statistics v. 23, Microsoft Office Excel program; the Student-test was applied to process the statistical mean values, repeated measures ANOVAs were performed separately for both groups. To determine the statistical significance, the P value should have been less than 0.05 [11].

Table 1

Group baseline characteristics

Variables	Total (n=42)	Real (n=22)	Sham (n=20)
Female, n (%)		19 (86.3%)	20 (100%)
Age in years (M ± SD)		38.4 ± 10.2	41 ± 12.6
Range		20 – 58	22 - 62
Headache frequency per month (M ± SD)		7.5 ± 3.7	7.3 ± 3.6
Range		2 – 14	3 – 14
Pain intensity (M ± SD)		6.7 ± 1.5	6.2 ± 1.2
*HIT-6 (M ± SD)		63.4 ± 6.3	64.2 ± 4.4
• HDI (M ± SD)		64.2 ± 17.4	55.4 ± 22
†MIDAS (M ± SD)		36.5 ± 22.9	35.9 ± 23.9

* – Headache Impact Test, • – Headache Disability Index, † – Migraine Disability Assessment Score.

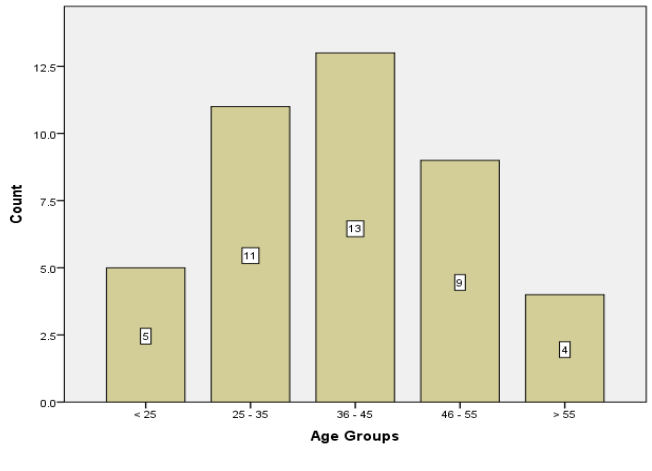

Fig. 1. Age group distribution. Subjects aged 36-45 years old were registered as the dominant age group, data similar to those presented in other studies

Study design

After signing the informed consent, subjects were asked to fill out a headache diary for 4 weeks and complete the HDI, HIT-6, and MDIS questionnaire prior to the first stimulation session. Frequency and severity of migraine attacks assessed within the 8 weeks, following the intervention serve as primary outcome variables. Quality of life questionnaires were conducted on follow-up dates (fig. 2).

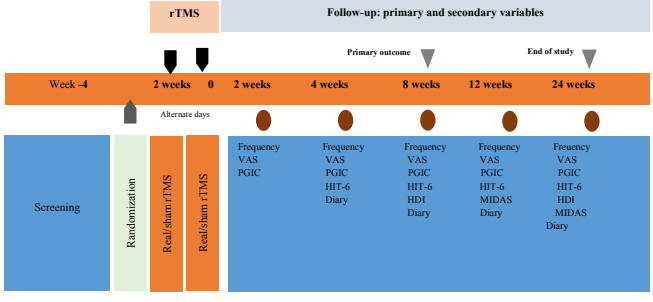

Fig. 2. Study design

Stimulation protocol

The stimulation protocol consisted of 2 steps, a swipe-stimulation and a spot burst stimulation. High frequency rTMS comprised 140 pulses/train in trains at 60% of motor threshold, followed by 5 pulses/train in trains at 85% of motor threshold, applied over cortex within a predefined multifocal delivery scheme consisting of 11 points marked on individual caps according to the 10-20 EEG system during the first session (fig. 3).

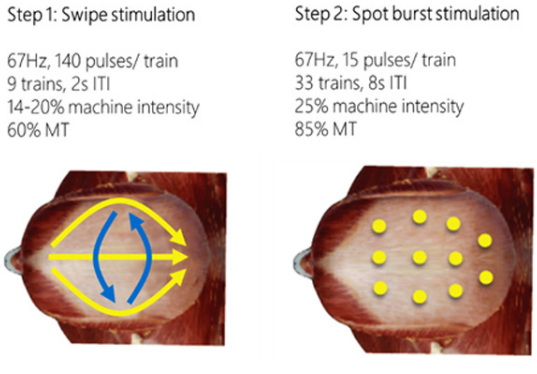

Fig. 3. Graphic representation of the experimental stimulation protocol (Neurophysiology Laboratory, Department of Neurology, Emergency Medicine Institute)

Safety

Stimulation procedures had been performed respecting the IFCN committee safety protocols and recommendations [12].

Results

42 eligible subjects were included in the data analysis. After stimulation, the real rTMS group showed a reduction in the number of attacks – 7.5 ± 3.7 at baseline to 3.8 ± 2.7 attacks at 3 months' period ($p<0.05$). The effect lasted at least three months.

The number of attacks was also reduced in the placebo group (7.3 ± 3.6 to 4.4 ± 2.9) ($p>0.05$). There was a significant reduction in the intensity of attacks at 4 weeks after the treatment in the treatment group (6.7 ± 1.5 at baseline; 5.3 ± 2.5 at 4 weeks ($p<0.05$). The primary outcome results are presented in fig. 5. The assessment of secondary outcomes

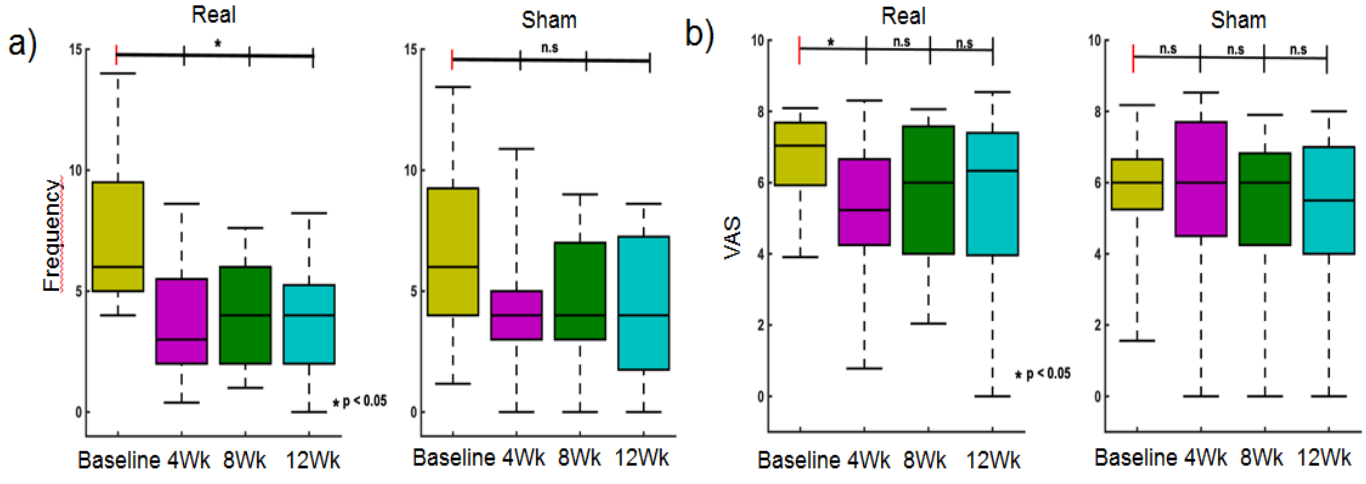

Fig. 4. Primary outcomes. Mean changes in headache frequency (a) and intensity (b) at baseline and follow-up. The frequency of migraine attacks was significantly reduced in the treatment group for 3-month following stimulation. The severity of the attacks was markedly reduced over 4 weeks after stimulation (p<0.05) in the treatment group, whereas the sham group showed a slight reduction

in real rTMS group had shown an overall reduction in all variables: HIT-6 scores – 63.4 ± 6.3 at baseline to 54.1 ± 8.3 at 12 weeks, compared to sham group – 64.2 ± 4.4 at baseline to 56.7 ± 8.9 at 12 weeks follow-up; HDI real rTMS 64.2 ± 17.4 at baseline to 48.5 ± 24.5 at 8 weeks vs 55.4 ± 22.1 at baseline to 40.7 ± 24.1 at 8 weeks; the same effect was observed in MIDAS scores – real rTMS group 36.5 ± 22.9 at baseline to 20.9 ± 23.2 at 12 weeks vs 35.9 ± 25.9 at baseline to 19.4 ± 19.2 at 12 weeks in sham rTMS group. The conducted questionnaires revealed a positive impact on quality of life and functional outcome in both groups, more prominent in the real rTMS group but with no statistical inter-group difference (p>0.05). There were no serious adverse events reported.

Discussion

This present study hypothesized that the observed positive effect in the reduction of headache frequency and intensity of the real (experimental) rTMS protocol compared to placebo could be explained by the changes in the cortical excitability and function obtained by direct cortical magnetic stimulation [8] as well as by the modulatory effect on peripheral nerve sensing activity (ophthalmic branch of the trigeminal nerve and greater occipital nerve (C2)) [9]. The changes in the assessment questionnaires of quality of life (HIT-6, HDI, MIDAS) could be partially explained by the improvement in primary outcomes (headache frequency and intensity) [13] as well as by the modulation of cortical areas engaged in mood and affective behavior [14-17]. One of the limitations of the study is the relatively small number of analyzed subjects, as well as the fact that assessment by such scales as HIT-6, HDI and MIDAS, though a standard in migraine research, carries a subjective recall bias in both groups [18]. In addition, based on the novelty of the rTMS as a treatment option, another possible bias could be considered high subject treatment expectations [19]. Further research is needed in order to confirm the experimental rTMS protocol usefulness and non-inferiority to already existing therapeutic TMS protocols [20].

Conclusions

Our study showed compelling evidence that the experimental rTMS paradigm reduces the number and severity of migraine attacks compared to placebo treatment. Multifocal rTMS should be considered a novel and effective prevention treatment approach for paroxysmal disorders, such as episodic migraine in adults. An important fact is that the experimental protocol was well tolerated and showed no serious adverse events.

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Authors' contribution
PL carried out the study, elaborated the manuscript. SG was the principal investigator and supervised with due diligence the course of the study. Both authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
The research protocol No 90 (of June 19, 2018) was approved by the Research Ethic Board of *Nicolae Testemitanu* State University of Medicine and Pharmacy.

Conflict of Interests
The authors have no conflict of interests to declare.