

A title of the paper

Theta Burst Stimulation in the Treatment of Chronic Orofacial Pain: A Randomized Controlled Trial

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Short title

TBS in the treatment of orofacial pain

Summary

Theta burst stimulation (TBS) is a modified form of high-frequency repetitive transcranial magnetic stimulation (rTMS) with promising effect in chronic pain. The aim of our double-blind, sham-controlled, parallel-group, randomized study was to assess an efficacy of intermittent TBS (iTBS) in the treatment of patients with chronic orofacial pain.

Nineteen patients (twelve females) with chronic orofacial pain were prospectively included and randomly assigned to single session of an active (iTBS) or sham (intermediate TBS; imTBS) stimulation delivered to the primary motor cortex (M1) contralateral to painful side. The primary outcome was pain relief assessed using a visual analogue scale (VAS) after stimulation and at the end of two-week follow up. The secondary outcomes were changes in the quantitative sensory testing (QST). QST set the threshold for thermal and tactile (touch) sensation in the affected facial area.

Intermittent TBS, compared with the sham, showed significant improvement in VAS after stimulation, but not at the end of two-week follow-up. Regarding the secondary outcomes (QST), we failed to find any significant difference between iTBS and sham.

Our findings demonstrate that iTBS of M1 transiently provides transient and modest subjective pain relief in chronic orofacial pain.

Key words

Repetitive transcranial magnetic stimulation (rTMS)

Theta burst stimulation (TBS)

Pain

Analgesic effect

Introduction

Recent studies have demonstrated that the application of the rTMS targeted on the M1 motor cortex is effective in the treatment of pain. A group of European experts have accepted with level A (definite efficacy) an analgesic effect of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain (Lefaucheur et al. 2014). In addition, the effectiveness of rTMS seems to increase with higher stimulation frequency (Leung et al., 2009; Torta et al. 2013). Studies using imaging techniques have shown that rTMS affects not only the electrochemical processes in the brain, but also reorganizes the structure of the cerebral cortex and other brain areas involved in the development of chronic pain (Hirayama et al. 2006).

Theta burst stimulation (TBS) is a modified form of high-frequency repetitive transcranial magnetic stimulation. TBS can in the human motor cortex produce a long-term potentiation / depression (LTP / LTD) – like effect on cortical synapses by using “bursts” of 3-5 pulses at 50 Hz, repeated five times per second / once per 200 milliseconds) (Huang et al., 2004, 2005, 2011). TBS produces a controllable, consistent, long-lasting, and powerful effect on motor cortex physiology and behavior after an application period of only 20-190 s (Huang et al., 2004, 2011). In the case of TBS, the direction of the after effects depends on whether the bursts are delivered continuously (continuous cTBS, producing LTD - like effects) or intermittently (intermittent iTBS producing LTP - like effects). When the length of the train of bursts and the pause between the trains are longer than those of iTBS and the train is shorter than that of cTBS there may be no significant after effect – intermediate TBS (imTBS) (Huang et al., 2005; 2009). Enhanced analgesic effect of TBS used as a priming of 'conventional' 10 Hz rTMS compared to 10 Hz rTMS without priming delivered to M1 has been reported in recent study (Lefaucheur 2012).

Prevalence of orofacial pain varies greatly according to various sources and studies and it affects 10-50% of the adult population (Johannes et al, 2010). The most common cause of orofacial pain is the pain with dental origin following dental treatment or surgery. It is important to perform precise intraoral and X-ray examination and test the thermal sensation (heat and cold). Pain, especially in the acute stage, is radiating from the upper jaw to temporal area or into the ear (sometimes simultaneously) and via the lower jaw to the neck. For these types of pain a prevention and early dental examination are important. Chronic pain emerged after dental treatment or dental surgery is often very intractable. Recent studies (Rokyta and Fricova, 2014; Fricova et al., 2013) suggest as possible mechanism of atypical odontalgia pathophysiology the involvement of the peripheral and central nervous system. Inflammatory changes are likely to start the peripheral and central sensitization but mostly they remain undetected for a long period of time. The treatment of orofacial pain starts with pharmacotherapy. For the pharmaco-resistant pain is necessary to use the special electric and magnetic stimulation. If compared the side effects the pharmacotherapy and neuromodulatory methods, the second ones have a minimum of side effects (Nizard et al., 2012).

The aims of our prospective, double-blind, placebo-controlled, randomized, parallel-group study was 1/ to prove an efficacy of intermittent iTBS in the treatment of patients with chronic orofacial pain and 2/ to compare the treatment efficacy of iTBS to imTBS protocol (sham / placebo stimulation). TBS was applied over the contralateral motor cortex on the somatotopic sites corresponding to the location of pain. With regard to previous studies, we hypothesized significant decrease of values in visual analogue scale (VAS, subjective scale of pain intensity) and quantitative sensory testing (QST, objective assessment instruments). After the imTBS treatment we hypothesized no significant changes of VAS and QST.

Methods

Participants

In our study we prospectively included subjects with chronic orofacial pain who met the following inclusion criteria: (a) orofacial pain syndrome in duration at least 6 months, intractable pharmacotherapy resistant pain (defined as the persistence of pain despite at least two attempts at pharmacological treatment in the past, both of sufficient dose and sufficient time), (b) stable analgesic medication for at least 1 month before the start of the study and throughout its course and during 2 weeks follow-up evaluation, (c) 18-65 years of age, (d) the absence of severe organic brain damage or other serious diseases, which could interfere with rTMS (epilepsy) and the absence of any metallic implants in the body (restrictions similar to those for an MRI).

The local Ethics Committee of the 3rd Faculty of Medicine reviewed and approved this study, and a written informed consent to participate in the research was obtained from all subjects. The study was carried out in accordance with the latest version of the Declaration of Helsinki. As part of the informed consent, patients were informed about the nature of the study, the clinical course, treatment effects, possible side effects and possible complications of treatment. Participation in the study was voluntary and without any financial reward.

Study design

This single-center study involved a two-arm double-blind, placebo-controlled, randomized single session trial with two-week follow up. Patients were randomly allocated according to permuted block design, in a 1:1 ratio (no stratification) to either active (A) or sham (S) TBS session. The patients and raters were blind to treatment. The only clinician administering rTMS was aware of the treatment group.

Measures

The participants were clinically evaluated three times during the study; first and second measures were performed before and after TBS application (within 60 minutes), third measure after two weeks follow-up. In all cases, the evaluator was blinded to the type of stimulation (active or sham). The initial examination included a detailed anamnesis to determine the type and nature of pain. For the measurement of rTMS effect both subjective and objective evaluations were used. Pain was assessed using a visual analogue scale (VAS, Khedr et al., 2005), subjective scale using a scale of 0 to 10 points (0 representing the absence of pain and 10 being maximum pain) and by quantitative sensory testing (QST), objective assessment instruments which set the threshold for thermal and tactile (touch) sensation in the affected facial area (Fricova et al., 2013). Thermal sensation was assessed using a specially modified device creating increasing irritation by a stream of warm air (the temperature of which ranged between 44°C and 55°C). Mechanical sensitivity, specifically, tactile threshold, was determined using von Frey hairs (Touch- test sensory evaluators, North Coast Medical). Additional measurements of influencing of depressive and anxious symptoms were assessed by the Beck Depression Inventory (BDI) and by the Beck Anxiety Inventory (BAI).

TMS methods

The motor threshold (MT) was assessed at the place of the left musculus pollicis abductor brevis (this area is standardly used for identification of MT and it is also more accurate than stimulating an orofacial area). MT of the left abductor pollicis brevis muscle was determined as the lowest strength of transcranial magnetic stimulation needed to elicit 5 or more electromyographic responses (EMG Neurosign 400) $\geq 50 \mu\text{V}$ within 10 trials.

The active stimulation protocol, intermittent theta burst stimulation (iTBS) included 3 pulses, frequency 50 Hz, 200 milliseconds repetition (3 pulses 5 times per second), duration of application 2 seconds, following intertrain interval of 8 s, in 20 series (in total 600 pulses / session). The place of TBS application was localized by functional localization (Klířová et al., 2006) using supra-threshold intensity under the control of the visual motor response at the place corresponding to the somatotopic localization of affected (contralateral) orofacial M1 area. Then, TBS was applied with the intensity of 90% of the MT.

The sham (inactive) stimulation protocol, intermediate theta burst stimulation (imTBS) included 5 seconds duration of 50 Hz (3 pulses 5 times per second), 75 pulses in 5 seconds, following intertrain interval 10 seconds (in total 600 pulses again) (figure 1). Intensity and site of application were same as in iTBS.

rTMS stimulation was applied using an air-cooled, 70-millimeter coil creating a magnetic field of 1-2 Tesla in a time interval of 100-200 ms using a Magstim Super Rapid stimulator (Magstim, Whitland, United Kingdom).

Statistical Analysis

Baseline demographic and clinical characteristics for both groups at baseline and between treatment groups were compared using the unpaired t-test or Mann-Whitney U test for continuous variables and the Fisher's exact test for categorical variables. The primary outcome was set as change in the visual analogue scale (VAS) after stimulation and at the end of two-week follow up, and the secondary outcomes as change in the quantitative sensory testing (QST). A general linear model for a parallel-group design with group as a between-subjects factor, and time (before, after and week 2) and side (affected, unaffected) as the within-subjects factors followed by Bonferroni post-hoc tests was used to compare the analgesic effect (VAS, QST) between active and sham TBS group and least square (LS) mean

differences were calculated. All repeated measures effects are reported with the original degrees of freedom and Greenhouse-Geisser corrected p-values. All statistical analyses were performed using the STATISTICA 9.0 (Statsoft Inc., Tulsa, OK) software; all tests were two-sided; and $p < 0.05$ was regarded as being statistically significant.

Results

Nineteen patients (12 females; age: 57.3 ± 13.4) were randomly assigned to single session with active (N=10) or sham (N=9) TBS.

The two randomized groups did not differ significantly in sex, age, or in baseline values of the scales VAS, BDI and BAI. Detailed demographic and clinical data of the study subjects are shown in table 1. All subjects underwent all measures. Overall, TBS was tolerated well with mild side effects primarily comprising mild and transient headache.

Comparing VAS scores changes, the general linear model revealed a group to time interaction ($F(2,34)=10.56$, $p < 0.001$). In post hoc analysis superiority of active TBS over sham was found after application ($p=0.02$; LS mean difference of 2.3; 95%CI 0.7 to 3.8) but not after two weeks ($p=0.47$) (figure 2). Detailed VAS scores are shown in table 2.

Regarding the objective measurements (QST), we failed to demonstrate significant group to side to time interaction in both the thermal ($F(2,34)=1.40$; $p=0.26$) and tactile ($F(2,34)=2.01$; $p=0.15$) thresholds. When only affected side was included in analyses, a group to time interaction showed a trend towards significance in case of tactile threshold ($F(2,34)=2.93$; $p=0.07$). Detailed QST scores are shown in table 2. The depressive and anxious symptoms (BDI and BAI) remained unchanged in both groups throughout the study.

Discussion

In our study, we proved an efficacy of intermittent iTBS in the treatment of patients with chronic orofacial pain and compared the treatment efficacy of iTBS (active stimulation) to imTBS protocol (sham / placebo stimulation). TBS was applied over the contralateral motor cortex on the somatotopic sites corresponding to the location of pain. The primary outcome was pain relief assessed using a visual analogue scale (VAS) after stimulation and at the end of two-week follow up. The secondary outcomes were changes in the quantitative sensory testing (QST). QST set the threshold for thermal and tactile (touch) sensation in the affected facial area.

Our results in subjective evaluation of pain confirm analgesic effect of iTBS not of imTBS. Comparing tactile and thermal perception change, we did not find statistically significant changes as well nevertheless the changes were near significant range. In iTBS active group, we detected a decrease of QST scores in affected facial area not in sham imTBS group. Our results partially confirm our expectations – after iTBS we hypothesized decrease in VAS and QST and after imTBS we hypothesized no significant changes.

Our results are in partial agreement with previous findings (Lefaucheur et al. 2014; Leung et al., 2009; Torta et al. 2013). A group of European experts (Lefaucheur et al., 2014) was commissioned to establish guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) from evidence published up until March 2014, regarding pain, movement disorders, stroke, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, consciousness disorders, tinnitus, depression, anxiety disorders, obsessive-compulsive disorder, schizophrenia, craving/addiction, and conversion. There is a sufficient body of evidence to accept with level A (definite efficacy) the analgesic effect of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain. In our study, the place of TBS application was localized by functional localization (Klířová et al., 2006) using supra-

threshold intensity under the control of the visual motor response at the place corresponding to the somatotopic localization of affected (contralateral) orofacial M1 area. The main question is whether this effect could be of interest in the therapeutic management of patients with neuropathic pain in daily clinical practice. TBS delivered as a continuous (cTBS) or intermittent (iTBS) train, the former protocol being “inhibitory” and the latter being “excitatory”, according to the changes produced in MEP size when cTBS/iTBS is applied to the M1 of healthy subjects (Huang et al., 2005). Several studies in clinical participants have shown the analgesic effect of HF rTMS of M1 contralateral to the pain side in neuropathic pain (Andre-Obadia et al., 2014; Lefacheur et al., 2011, Antal et Paulus, 2010).

In Transcranial Magnetic Stimulation (TMS), a brief (0.2 ms) and powerful (0.2-4.0 T) magnetic pulse is generated by the coil. The coil is excited by the pulsing electric current, that reaches its maximal intensity within 0.1-0.2 ms and then decreases to zero during next 0.5-1 ms. Rapid ramping of the magnetic flux leads to formation of an eddy currents in the conductive sections of the tissue. Eddy currents flow in closed loops in planes perpendicular to the magnetic field. Due to the principle of induction of the electric field in the tissue, the stimulating magnetic field can be effectively applied only within pulses. The pulse ramp rate and the peak intensity are the main parameters affecting the unit dose of the stimulation. Stimulation using rhythmic trains of magnetic pulses with repetition rate up to 100 Hz is referred as a repetitive TMS (rTMS). Different repetition rates have distinct effects on brain activity. TMS, in which single pulses are used instead of trains of pulses, is sometimes referred to as a single-pulse TMS. Single-pulse TMS has been developed as a diagnostic method for evaluation of cortico-spinal pathway. During stimulation of the motor cortex with single magnetic pulses of sufficient intensity an acute depolarisation of whole population of neurons occurs. It is followed by excitation of neuronal pathways from brain through the spinal cord to the muscles, resulting in measurable motor evoked potentials (MEP). This

technique has been also used for evaluation of changes in excitability of cortical neurons resulting from application of different transcranial stimulation methods.

Repetitive TMS (rTMS) has been developed as a diagnostic tool as well. It was observed that the magnetic pulses have a long term neuromodulation effect. This led to a development of more powerful TMS generators capable of delivery of multiple pulses within short time — the rTMS. Empirically, rTMS has been further subdivided to low- (rates below 1 Hz) and high-frequency (rates above 5 Hz) rTMS. Experimental evidence has revealed that rTMS with repetition rates below 1 Hz causes cortical inhibition and on the other hand rTMS trains above 5 Hz have opposite effect. In order to increase efficiency of the high-frequency rTMS a repeated individual pulses have been substituted with groups of pulses, or — the bursts. In a variant of rTMS, a theta-burst stimulation (TBS), the bursts of two or more pulses with intra-burst rate up to 50 Hz and inter-burst frequency of approximately 5 Hz are used. Although there is an evidence about increased efficiency, concerns about safety of the method arose. One of the limitations of current technology is that rTMS does not affect the deeper structures of the brain, but it is known that rTMS significantly involved in changing the perception of pain.

rTMS as a clinical tool is a very gentle, non-invasive method and the demonstration of the success of this treatment is a major step to non-invasive methods of pain therapy. This method is able to induce changes in the central nervous system at the cellular level including changes at ionic and metabolic level (Fricova et al., 2013; Fregini et al., 2007). In psychiatric disorders, the therapeutic effect of rTMS was confirmed mainly in the treatment of depression, and in negative symptoms of schizophrenia. In case of auditory hallucinations and posttraumatic stress disorder (PTSD) the same level of evidence for benefit of rTMS also exists (Lefaucheur et al., 2014; Rokyta and Fricova, 2012). In October 2008 the rTMS method was approved by FDA in the United States for the treatment of patients with unipolar

depression who are refractory to pharmacological treatment. In patients with Parkinson's disease, dystonia neurological stimulation was neurological stimulation used as well as in patients with tics, stuttering, tinnitus, seizures or epilepsy, or functional disorders of aphasia after a stroke.

rTMS showed prolonged therapeutic effect by reduction or elimination of chronic pain (Lefaucheur et al., 2014; O'Connell et al. 2014). Moreover recent studies suggest (Fricova et al. 2013) the involvement of the peripheral and central nervous system as a possible mechanism in the pathophysiology of atypical odontalgia. Besides, the pain became a test for the application of electrical stimulation of the brain's motor cortex (MCS) and subsequently it was shown in some cases rTMS had prolonged therapeutic effect including reduction and sometimes even complete elimination of chronic pain. We decided to check on the patient cohort the effect of this method mainly because we have our own experience with MCS. For the treatment of pain syndromes rTMS was used mainly by French neuroscientist (Lefaucheur et al. 2014, 2012, Andre-Obadia et al., 2014). In the Czech Republic these techniques were firstly used by members of our research group in 2009 (Fricová, Rokyta, Klírová, Kohútová, Novák and Masopust). Nevertheless our research team began using the method of rTMS in the treatment of chronic orofacial pain 6 years ago (on about 70 patients).

In our study, intermittent iTBS, compared with the sham, showed significant improvement in subjective evaluation of pain after stimulation, but not at the end of two-week follow-up. These results indicate that the only a single session was not enough for long lasting effect of the treatment and that the absence of other sessions represents a substantial limitation of our study. Since we implemented only two post-session measurements we are unable to specify duration of effect of TBS on pain. More frequent assessment during follow up would be preferable. Regarding the quantitative sensory testing (QST), we failed to find any significant

difference between iTBS and sham. Our findings demonstrate that iTBS of M1 transiently provides transient and modest subjective pain relief in chronic orofacial pain.

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Table 1 Baseline demographic and clinical data

	Group A (N=10)	Group S (N=9)	p value
Age: years	55.5±12.7	59.3±14.9	0.60 ¹
Sex: F/M	6/4	6/3	1.00 ²
VAS baseline	5.9±1.6	6.0±1.2	0.78 ³
BDI baseline	4.9±4.2	6.1±4.0	0.45 ³
BAI baseline	5.2±3.0	8.6±9.9	0.66 ³

Abbreviations: A: group with active iTBS; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; F: female, M: male, S: group with sham imTBS; VAS: Visual Analogue Scale.

Data are shown as a mean and standard deviation or as a number of cases.

¹ Unpaired t-test; ² Fisher's exact test; ³ Mann-Whitney U test

Table 2 VAS and QST scores

	Group A (N=10)	Group S (N=9)
VAS before	5.9±1.6	6.0±1.2
VAS after	3.4±1.7	5.7±1.3
VAS week 2	5.0±2.0	5.8±1.8
Thermal Aff before	60.4±8.4	57.0±8.8
Thermal Aff after	60.0±7.2	58.2±9.4
Thermal Aff week 2	58.8±8.3	60.4±10.4
Tactile Aff before	2.4±0.6	1.8±0.3
Tactile Aff after	2.2±0.7	1.9±0.4
Tactile Aff week 2	2.1±0.8	2.0±0.5

Abbreviations: A: group with active iTBS; S: group with sham imTBS; VAS: Visual Analogue Scale. QST: Quantitative Sensory Testing. Thermal Aff: thermal sensation in the affected facial area. Tactile Aff: tactile (touch) sensation in the affected facial area.

Data are shown as a mean and standard deviation.

Figure 1 The difference between intermittent TBS (iTBS) and intermediate TBS (imTBS) (adapted from Huang et al. 2005)

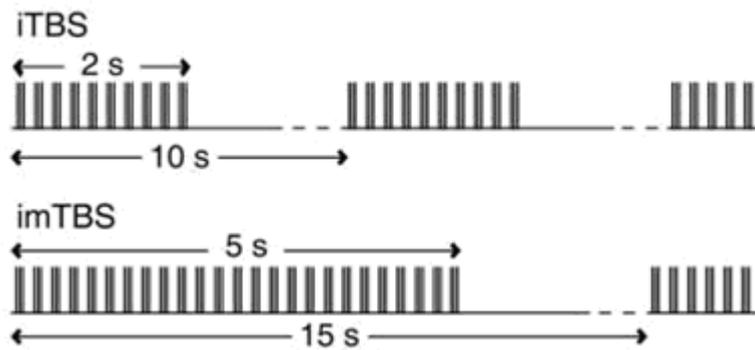
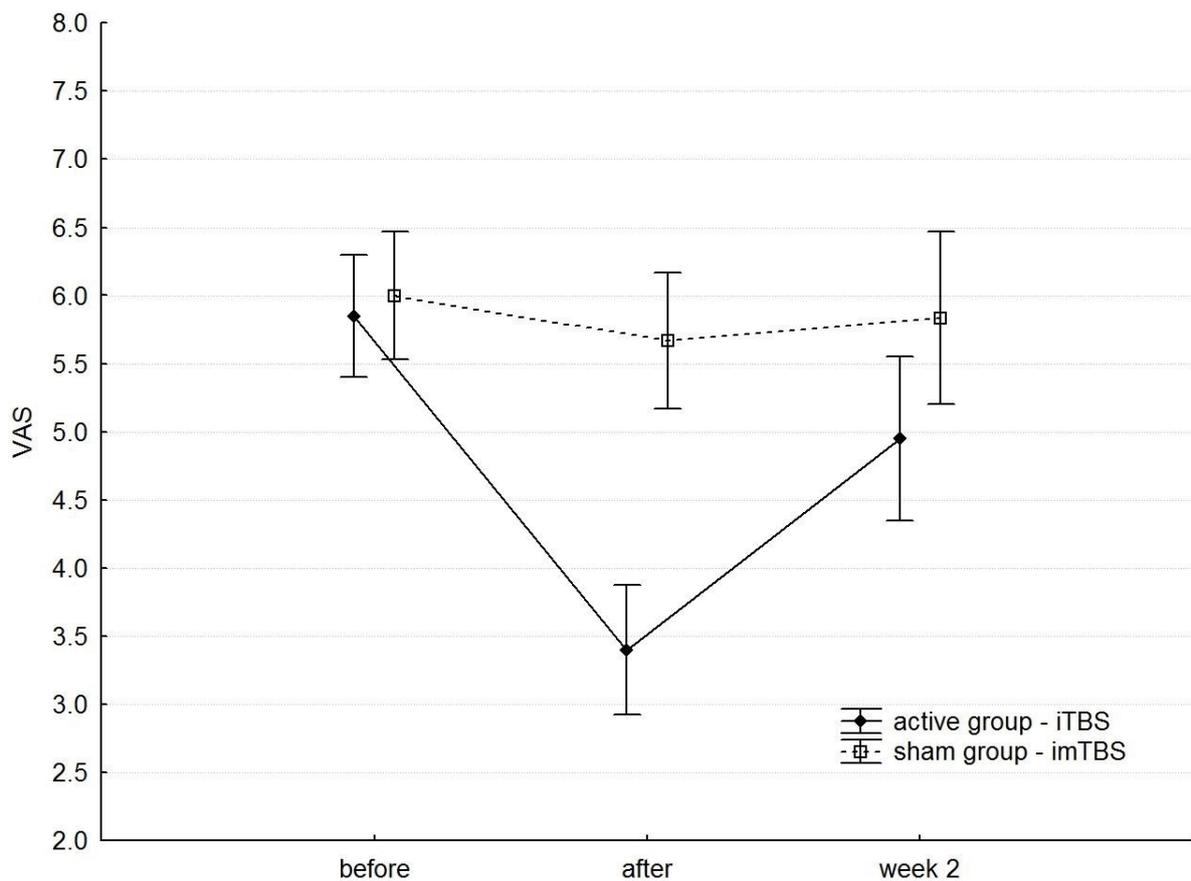


Figure 2 Immediate and delayed effect of TBS in terms of VAS score change



Abbreviation: VAS: Visual Analogue Scale; iTBS: intermittent theta burst stimulation; imTBS: intermediate theta burst stimulation.