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ORIGINAL ARTICLE

Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex

J.P. Lefaucheur*, X. Drouot, J.P. Nguyen

Service de physiologie–explorations fonctionnelles, service de neurochirurgie, hôpital Henri-Mondor, Assistance Publique – Hôpitaux de Paris, Inserm U421, faculté de médecine, 51, avenue de-Lattre-de-Tassigny, 94010 Créteil, France

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Summary – The chronic electrical stimulation of a motor cortical area corresponding to a painful region of the body, by means of surgically-implanted epidural electrodes is a validated therapeutical strategy to control medication-resistant neurogenic pain. Repetitive transcranial magnetic stimulation (rTMS) permits to stimulate non-invasively and precisely the motor cortex. We applied a 20-min session of rTMS of the motor cortex at 10 Hz using a 'real' or a 'sham' coil in a series of 14 patients with intractable pain due to thalamic stroke or trigeminal neuropathy. We studied the effects of rTMS on pain level assessed on a 0–10 visual analogue scale from day 1 to day 12 following the rTMS session. A significant pain decrease was observed up to 8 days after the 'real' rTMS session. This study shows that a transient pain relief can be induced in patients suffering from chronic neurogenic pain during about the week that follows a 20-min session of 10Hz-rTMS applied over the motor cortex. © 2001 Éditions scientifiques et médicales Elsevier SAS

interventional neurophysiology / pain / repetitive transcranial magnetic stimulation / thalamic stroke / trigeminal neuropathy

Résumé – Neurophysiologie interventionnelle dans le contrôle de la douleur : la durée du soulagement de la douleur après la stimulation magnétique transcranienne répétitive du cortex moteur. La stimulation électrique chronique de l'aire motrice corticale correspondant à une zone corporelle douloureuse, au moyen d'électrodes épidurales implantées chirurgicalement, est une stratégie thérapeutique validée pour contrôler les douleurs neurogènes résistantes aux médicaments. La stimulation magnétique transcranienne répétitive (SMTr) permet de stimuler le cortex moteur de façon non invasive et précise. Nous avons appliqué une séance de SMTr du cortex moteur à 10 Hz pendant 20 min, au moyen d'une bobine réellement efficace ou d'une bobine « placebo », chez 14 patients souffrant de douleurs résistantes au traitement médicamenteux et liées à un accident vasculaire thalamique ou à une neuropathie trigéminale. Nous avons évalué les effets de la SMTr sur le niveau de douleur estimé sur une échelle visuelle analogique échelonnée entre 0 et 10, du 1er au 12e jour suivant la séance de SMTr. Une réduction significative de la douleur fut observée jusqu'au 8e jour suivant la SMTr « réelle ». Cette étude montre qu'un soulagement de la douleur peut être obtenu chez des patients

*Correspondence and reprints: Service de physiologie–explorations fonctionnelles, hôpital Henri-Mondor, 51, avenue de-Lattre-de-Tassigny, 94010 Créteil, France. Tel.: 33 1 49 81 26 94; fax: 33 1 49 81 46 60.
E-mail address: jean-pascal.lefaucheur@hmn.ap-hop-paris.fr (J.P. Lefaucheur).

souffrant de douleurs neurogènes chroniques tout au long de la semaine qui suit une SMTr du cortex moteur appliquée pendant 20 min à 10 Hz.

accident vasculaire thalamique / douleur / neuropathie trigéminale / neurophysiologie interventionnelle / stimulation magnétique transcranienne répétitive

Electrical neuromodulation is defined as the treatment of neurological diseases by the chronic electrical stimulation of nervous structures. Such a therapeutical strategy was shown to be effective to control intractable pain resistant to drug treatment. The main targets of electrical neuromodulation for pain are the peripheral nerves, the spinal cord (dorsal columns) [8], various deep brain structures (mainly the thalamic sensory nuclei) [9] and the motor cortex (precentral gyrus) [32]. Motor cortex stimulation appears to be one of the most promising type of neuromodulation to treat drug-resistant neurogenic pain of the face or the limbs due to central or peripheral nerve lesion [10, 18, 19, 21, 22, 33]. However, this procedure requires the surgical implantation of epidural electrodes and of a pulse generator. The treatment is costly and invasive, which limits its indication.

Since the 80s, the human motor cortex can be stimulated non-invasively by means of transcranial magnetic stimulation (TMS) [1]. The maximal frequency reached by the first generation of TMS machines was 0.2 Hz (one magnetic pulse every 5 s) and TMS was applied to study the conduction times in the pyramidal tract [11]. More recently new stimulators have been developed that permit stimulations at various rates (up to 30 or 40 Hz at least) [35]. By means of repetitive transcranial magnetic stimulation (rTMS), it became possible to modify the excitability of a targeted cortical region [2]. Preliminary and controversial therapeutical applications of rTMS have been reported in various neuropsychiatric diseases, such as movement disorders (Parkinson disease and focal dystonia) [23, 29], epilepsy [31], depression [5, 6, 12, 17, 24] and schizophrenia [7]. Regarding the application of rTMS in chronic pain, results are in waiting [27]. One study has shown the efficacy of repetitive magnetic stimulations to relieve musculoskeletal pain by applying the stimulation directly over a painful limb [28], but we first showed that a transient pain relief could be obtained by high frequency rTMS over the motor cortical area corresponding to a painful region of the body [13, 14]. We have applied the rTMS technique to control medication-resistant neurogenic pain in the same design as the neurosurgical procedure of motor cortex stimulation. We found that neurogenic pain of various origins, assessed on a visual analogue scale, could be relieved just after a 20-min session of rTMS of the motor cortex performed at 10 Hz [3]. In this study, we show that the daily pain scores could be reduced significantly for 8 days after one session of 10Hz-rTMS in patients with chronic intractable pain related to a thalamic stroke or a trigeminal neuropathy.

PATIENTS AND METHODS

The study included 14 right-handed patients, eight females and six males, aged 34 to 80 years (mean 57.2 years). None had history of seizures. The patients presented chronic, drug-resistant, unilateral pain and were referred to our hospital to be treated by implanted motor cortex stimulation. The pain was due to a thalamic stroke (infarction or haemorrhage) ($n = 7$) or a trigeminal neuropathy (with past history of surgery in the trigeminal territory or thermocoagulation of the trigeminal ganglion) ($n = 7$). In the cases of thalamic stroke, the pain predominated in the distal upper limb.

Two different sessions of rTMS separated by 3 weeks at least were randomly performed in each patient. These two sessions were identical in their course. First, the pain was rated by the patient using the 0–10 visual analogue scale (VAS) ('day 0' value). Second, we determined the area of the motor cortex corresponding to the painful zone using the single-pulse programme of a Super-Rapid Magstim magnetic stimulator (The Magstim Co., Whitland, UK) and a 8-shaped coil (70mm Double Coil – 9925-00, The Magstim Co., Whitland, UK) held on the scalp. This area was identified as the site at which single-pulse TMS evoked contralaterally a motor potential of maximal amplitude in the painful zone, i.e. in the first dorsal interosseus muscle of the painful hand in patients with thalamic stroke and in the masseter muscle of the painful hemiface in patients with trigeminal neuralgia. The motor evoked potentials were recorded in these muscles using a standard EMG machine (Phasis II, EsaOte, Florence, Italy) and surface electrodes. This procedure allowed to be sure of stimu

lating over the anterior bank of the central sulcus [34]. Third, we determined the rest motor threshold, which was defined as the lowest stimulation intensity allowing to evoke motor responses in the targeted muscles greater than 50 μV peak-to-peak amplitude in five of ten trials with the patient at rest [24]. Fourth, rTMS was applied using the Super-Rapid Magstim magnetic stimulator and a 8-shaped coil centred over the motor cortex area corresponding to the painful zone. At this point, one of the following two protocols was randomly applied: (i) a series of 20 trains of 5 s in duration (55-s intertrain interval) at a stimulation rate of 10 Hz and at 80% of rest motor threshold intensity using a 'real' TMS coil; (ii) the same protocol using a 'sham' 8-shaped coil (Magstim Placebo Coil System 1730-23-00, The Magstim Co., Whitland, UK). The Magstim Placebo Coil System, which was designed and homologated not to have a stimulating effect on the cortex of the patient was preferred to the common method consisting in holding a 'real' TMS coil elevated and angled 45° tangentially to the scalp, which did not meet the criteria for an ideal 'sham' as reported recently [15]. Whatever the session, the 8-shaped coil was maintained steady the whole session long, tangentially to the scalp, in a postero-anterior direction.

Finally, the patients were instructed to rate their daily pain every evening at home from days 1 to 12 following the rTMS session. For this purpose, a book of 12 sheets with a VAS drawn on each sheet was given to the patients.

The respective effect of 'real' and 'sham' stimulations on pain level was studied by comparing statistically the daily pain scores measured on the VAS following the two types of rTMS session using the Wilcoxon signed rank test. A two-tailed *P*-value of less than 0.05 was considered significant.

Individual effects of rTMS on VAS scores were classified into four categories: excellent (reduction of the pain score by more than 80%), good (by 50 to 79%), fair (by 30 to 49%) and poor (by less than 30%) [22].

RESULTS

No adverse effects of rTMS were observed immediately after the session or the days after; in particular no seizures were induced.

Figure 1 presents the mean daily VAS scores following 'real' and 'sham' 10Hz-rTMS session in the entire series of 14 patients. A significant reduction of the daily VAS scores was found from days 1 to 8 after 'real' 10Hz-rTMS session compared to 'sham' stimulation (*P*-values ranged between 0.013 and 0.049). From days 9 to 12, the difference between the two conditions was no more significant (*P*-values ranged between 0.09 and 0.14). Considering the two subgroups, i.e. patients with thalamic stroke and patients with trigeminal neuropathy, it was impossible to yield significant results due to so few data points (7 patients in each subgroup), but a similar tendency of VAS score reduction following 'real' and not 'sham' 10Hz-rTMS was observed in both subgroups *(figure 1)*.

Regarding individual results, a significant pain relief, i.e. a reduction of VAS daily score by more than 30%, was observed in four of the seven patients in both subgroups following the 'real' 10Hz-rTMS session. Using the previously stated criteria [22], excellent or good pain relief was experienced by two patients with thalamic stroke (from days 1 to 5 and from days 1 to 12, respectively) and in four patients with trigeminal neuralgia (from days 4 to 12, from days 2 to 9, from days 2 to 7 and from days 1 to 3, respectively). In addition, two patients with thalamic stroke experienced a fair pain relief (from days 6 to 12 and from days 2 to 12, respectively). In contrast, we did not find any reduction of the VAS score by more than 30% following the 'sham' rTMS session.

DISCUSSION

This study shows for the first time that pain relief could last about a week after 10Hz-rTMS of the motor cortex in patients suffering chronic neurogenic pain of various origins. However, definitive conclusions could not be made considering separately the two types of pathologies assessed in this study, i.e. thalamic stroke and trigeminal neuropathy, due to the too small number of patients in each subgroup.

The lowest pain scores were observed between 2 and 4 days following the rTMS session, and thereafter, the VAS score increased progressively to reach ' sham' values. Even if it lasted 1 week, the duration of the pain relief induced by one session of 10Hz-rTMS was too short for a therapeutical application. Repeated sessions of rTMS might prolong the control of pain, and should be planned.

High-frequency rTMS, defined as stimulation rate over 1 Hz [36], is thought to excite the underlying cortex, although the results are variable between individuals [16]. The stimulation frequency used in chronic motor cortex neuromodulation ranges from 20

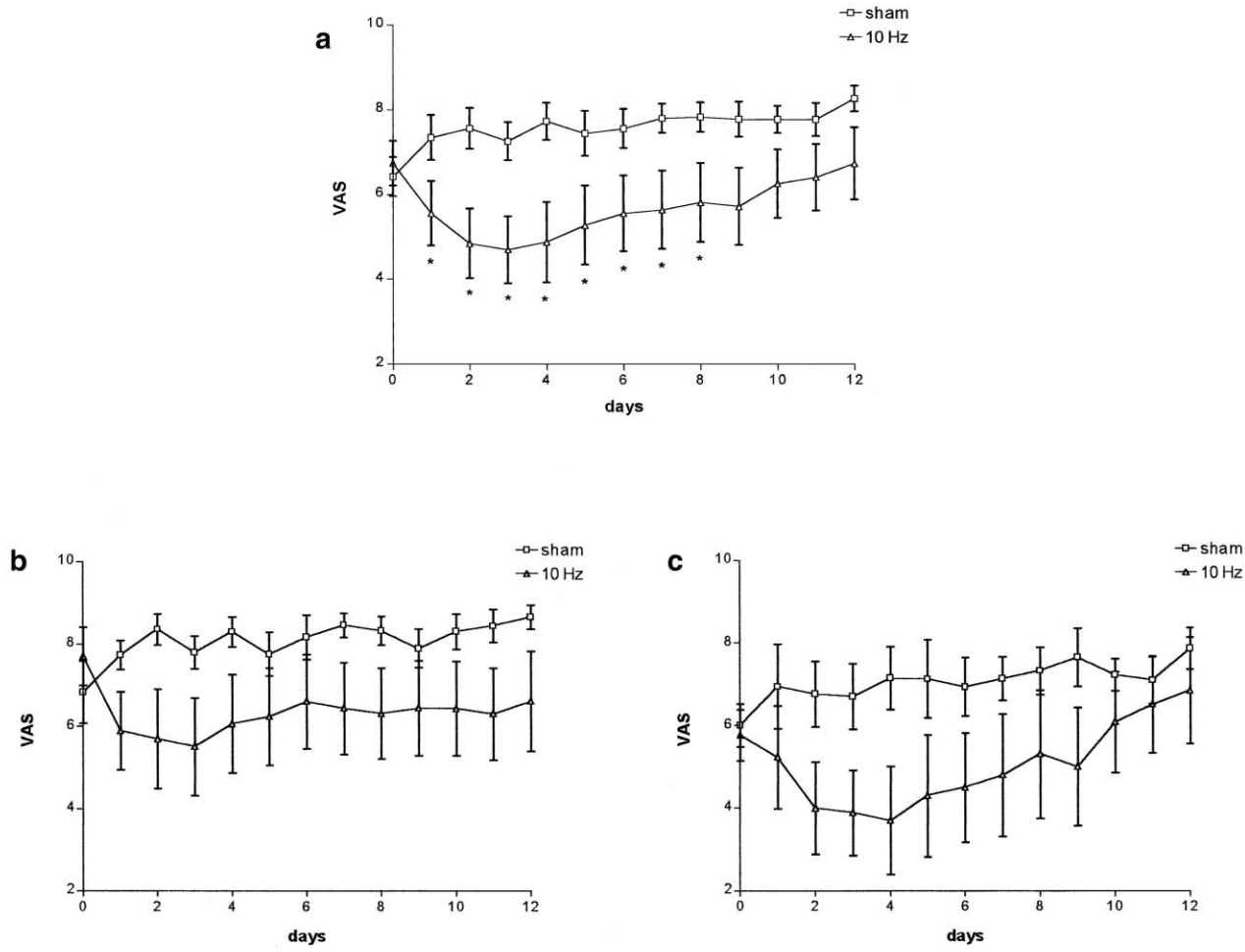

Figure 1. Daily pain scores (mean ± s.e.m.) assessed on the 0–10 visual analogue scale, before and from days 1 to 12 following a 'real' or a 'sham' 10Hz-rTMS session in the whole series of 14 patients with chronic pain (a). The effects of the two rTMS sessions were compared using the Wilcoxon signed rank test. *: $P < 0.05$. The lower graphs show the results observed in the two subgroups of patients, with thalamic stroke (b) or trigeminal neuropathy (c).

to 55 Hz [10, 18, 22] and may have similar effects as 10Hz-rTMS on cortex excitability [35]. Such a statement needs however to be confirmed on patients with chronic pain by studying higher rTMS frequencies, even if there are two limiting factors, one ethical and one technical. The ethical limitation is the increasing risk of inducing seizures in parallel with the increasing rate of stimulation [36]. The technical limitation is due to the heating of the coils. However, at present, cooled coils are available, that permit rTMS sessions at higher frequencies or intensities.

The ability of rTMS to induce a transient relief of chronic pain for about a week is supposed to be related to plastic changes induced in the central nervous system at the level of the structures involved in the generation or the modulation of pain. Experimental data need to be collected to support this hypothesis. The mechanisms of action of motor cortex stimulation for pain control remain poorly understood and the relatively easy and non-invasive use of rTMS technique to stimulate the motor cortex should help to delineate these mechanisms. Relevant data have been found in studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) [4, 25, 26]. These studies have shown that motor cortex neurostimulation increased the cerebral blood flow in the

thalamus ipsilateral to the stimulated motor cortex, in the orbitofrontal and anterior cingulate gyri, the anterior insula and the upper brainstem near the periaqueductal grey matter. Cingulate/orbitofrontal activation should participate in a modulation of the affective/emotional component of pain, while descending activation of the brainstem could inhibit the transmission of discriminative noxious information [4]. To our knowledge, the influence of the rTMS of the motor cortex on deep brain structure activity was not clearly established [30]. The combination of rTMS and PET techniques should allow a better understanding of the pathophysiological mechanisms underlying pain control induced by motor cortex stimulation.

But a first goal of rTMS application for pain relief should be the screening of patients for the indication of an implanted cortical neuromodulation [20], since about 30% of operated patients do not respond to the surgical procedure [18, 22]. Various screening tests have been proposed, based on the efficacy of drugs like morphine, propofol or barbiturate [20, 33] or on clinical examination [10], but validated selection criteria for suitable patients are lacking. A study of the usefulness of 10Hz-rTMS to predict the surgical outcome therefore appears warranted, but it has not been performed yet to our knowledge.

The management of chronic pain appears as a new and exciting field of development of rTMS technique, as it is the case for the treatment of psychiatric disorders [6, 7, 12]. To apply rTMS over the motor cortical area corresponding to a painful region of the body or to detect this area by an electrophysiological procedure during surgery for the implantation of epidural electrodes are two complementary aspects of "interventional clinical neurophysiology", a discipline increasingly involved in the management of chronic pain.

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