Prospective Evaluation

Is Life Better After Motor Cortex Stimulation for Pain Control? Results at Long-Term and their Prediction by Preoperative rTMS

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Background: A positive effect of motor cortex stimulation (MCS) (defined as subjective estimations of pain relief ≥ 30%) has been reported in 55 – 64% of patients. Repetitive magnetic cortical stimulation (rTMS) is considered a predictor of MCS effect. These figures are, however, mostly based on subjective reports of pain intensity, and have not been confirmed in the long-term.

Objectives: This study assessed long-term pain relief (2 – 9 years) after epidural motor cortex stimulation and its pre-operative prediction by rTMS, using both intensity and Quality of Life (QoL) scales.

Study Design: Analysis of the long-term evolution of pain patients treated by epidural motor cortex stimulation, and predictive value of preoperative response to rTMS.

Setting: University Neurological Hospital Pain Center.

Methods: Patients: Twenty patients suffering chronic pharmaco-resistant neuropathic pain. Intervention: All patients received first randomized sham vs. active 20Hz-rTMS, before being submitted to MCS surgery. Measurement: Postoperative pain relief was evaluated at 6 months and then up to 9 years post-MCS (average 6.1 ± 2.6 y) using (i) pain numerical rating scores (NRS); (ii) a combined assessment (CPA) including NRS, drug intake, and subjective quality of life; and (iii) a short questionnaire (HowRu) exploring discomfort, distress, disability, and dependence.

Results: Pain scores were significantly reduced by active (but not sham) rTMS and by subsequent MCS. Ten out of 20 patients kept a long-term benefit from MCS, both on raw pain scores and on CPA. The CPA results were strictly comparable when obtained by the surgeon or by a third-party on telephonic survey (r = 0.9). CPA scores following rTMS and long-term MCS were significantly associated (Fisher $P = 0.02$), with 90% positive predictive value and 67% negative predictive value of preoperative rTMS over long-term MCS results. On the HowRu questionnaire, long-term MCS-related improvement concerned "discomfort" (physical pain) and "dependence" (autonomy for daily activities), whereas "disability" (work, home, and leisure activities) and "distress" (anxiety, stress, depression) did not significantly improve.

Limitations: Limited cohort of patients with inhomogeneous pain etiology. Subjectivity of the reported items by the patient after a variable and long delay after surgery. Predictive evaluation based on a single rTMS session compared to chronic MCS.

Conclusions: Half of the patients still retain a significant benefit after 2 – 9 years of continuous MCS, and this can be reasonably predicted by preoperative rTMS. Adding drug intake and QoL estimates to raw pain scores allows a more realistic assessment of long-term benefits and enhance the rTMS predictive value.

The aims of this study and its design were approved by the local ethics committee (University Hospitals St Etienne and Lyon, France).

Key words: Neuropathic pain, chronic refractory pain, repetitive transcranial magnetic stimulation, rTMS, epidural motor cortex stimulation, MCS, quality of life, predictive value

Epidural motor cortex stimulation (MCS) for neuropathic pain was proposed in the early 1990s by Tsubokawa et al (1,2) and its efficacy has been supported by a number of clinical studies and systematic reviews (3-7). A positive effect of MCS (defined as subjective estimations of pain relief of at least 30%) (3) has been reported in 55 – 64% of the patients (3,4,6). These figures are, however, mostly based on subjective reports of pain intensity, and are not reported in the long term. Measures are usually obtained in hospital settings and performed by doctors, either the one who operated on the patient or a collaborator, implying the possibility of positive bias. Reports including quality of life (QoL) measures are more realistic towards reflecting the patient's status, but this kind of evaluation remains very rare. Two studies (8,9) performed a more detailed appraisal including the McGill Pain questionnaire, changes in drug consumption and evaluation of pain consequences on daily functioning up to one-year follow-up. While both studies described improvements in daily living activities and drug consumption, between-study inconsistencies were noted concerning the differential impact of MCS on sensory-discriminative and affective components of pain.

The interest for non-invasive procedures based on repetitive transcranial magnetic stimulation (rTMS) for chronic pain has increased steadily. This technique is proposed either as an ancillary treatment for drug-resistant pain or as a predictive factor of subsequent MCS efficacy (3,6,10,11). Since the first case-study reported by Migita and coworkers in 1995 (12), the effect of rTMS has often been considered as an aid to preoperative selection of good responders' to implanted stimulation. However, while several studies supported the predictive value of successful rTMS for subsequent MCS efficacy (11,13,14), good MCS analgesia was also reported in cases of ineffective rTMS (e.g. 14 out of 35 patients in [11]), thus limiting the predictive value of the procedure. In these studies, the correlation between rTMS and MCS results was performed at a single end-point, with less than a 3-year follow-up; it was based on pain scores exclusively and did not correlate preoperative rTMS effects with a comprehensive assessment of the global patient's status including QoL measures. Also, the possible bias induced by a purely intra-hospital evaluation (as compared by assessment from a third party) was never established. For all these reasons, the natural long-term evolution of pain relief after MCS, the predictive validity of rTMS, as well as the correlations between pain reduction and QoL, and between doctor and non-doctor pain assessment remain uncertain.

In this work we assessed the relation between preoperative pain relief using sham and real rTMS and the subsequent efficacy of MCS at short- (6 months) and long-term (6 years in average). To minimize operator bias, the long-term data collected were re-assessed through interviews by a third-party independent from all medical interventions, as well as by the patients' own evaluation of pain intensity, drug intake, and QoL. A recently developed QoL generic tool elaborated for chronic diseases (the "HowRu" scale [21]) is applied here for the first time to chronic neuropathic pain.

Methods

Patients

Twenty patients (mean age 54.3 ± 9.7; 9 women) suffering drug-resistant neuropathic pain received sham and 20Hz-rTMS 6 months before MCS. The decision to perform epidural MCS was taken independently of, and was not influenced by, rTMS results. Mean follow-up after MCS surgery was 6.1 ± 2.6 years. All patients gave their informed consent to this study and their clinical data are summarized in Table 1. One patient (Table 1: Nb 1) benefited from rTMS and MCS with regular visits to the surgical team up to 8 years after MCS but died from reasons unrelated to the pain-eliciting condition before the beginning of the phone survey. rTMS sham and active sessions order was defined randomly on a cross-over design. The aim of this study and its design have been approved by the local ethics committee (University Hospitals St Etienne and Lyon, France).

rTMS Procedure

Coil position and threshold determination

rTMS was performed in Lyon's University Hospital Pain Center (CETD) with a magnetic stimulator (MagPro X100, Medtronic) inducing biphasic pulses via an 8-shaped coil (cool-B65 butterfly shape coil Medtronic). Sham rTMS was delivered via a "placebo coil" able to reproduce the noise of the real coil (MCF-P-B65, Medtronic). Motor responses were recorded using a standard EMG machine and surface electrodes using the belly-tendon method (15).

The coil was positioned perpendicularly to the central sulcus, with postero-anterior orientation. Such orientation was perferred since it has proved more effective in terms of pain relief than latero-medial po-

Table 1. *Clinical data.*

Nb	Sex	Pain		Age*	Delay after surgery	Mean NRS
		Topography	Etiology		(months)	decrease
1	F	hemibody	CPSP (thalamic)	66	96	33.7
2	F	hemibody	CPSP (thalamic)	58	96	
3	F	hemibody	CPSP (thalamic)	30	96	
4	M	hemibody	CPSP (thalamic)	52	108	
5	M	hemibody	CPSP (thalamic)	59	84	
6	F	hemibody	CPSP (thalamic)	61	72	
7	M	hemibody	CPSP (thalamic)	56	84	
8	F	hemibody	CPSP (thalamic)	54	48	
9	F	hemibody	CPSP (thalamic)	48	24	
10	M	hemibody	CPSP (thalamic)	51	72	
11	M	lower limb	CPSP (medulla)	62	90	
12	M	lower limb	Spinal (cervical)	48	72	15.5
13	F	upper limb	Spinal (cervical)	54	24	
14	F	face	Trigeminal neuropathy	67	24	7.5
15	F	face	Trigeminal neuropathy	53	72	
16	M	face	Trigeminal neuropathy	67	84	
17	M	face	Trigeminal neuropathy	54	24	
18	M	upper limb	Peripheral (ulnar nerve)	46	96	16.7
19	M	upper limb	Peripheral (brachial plexus)	43	96	
20	M	upper limb	Peripheral (brachial plexus)	73	84	

NRS: Numerical Rating Scale. CPSP: Central Post-Stroke Pain. *Age at time of surgery

sitioning (16). We first determined the "motor cortical hotspot" at which a single TMS pulse evoked a contralateral motor evoked potential of maximal amplitude in a hand muscle (abductor digiti minimi). The optimal coil position was marked on an elastic cap that the patient wore during sham and active rTMS session. The coil was fixed on an adjustable arm, and its position was controlled repeatedly during the rTMS session to ensure stability of the stimulating locus. Motor threshold at rest was determined as the lowest intensity that produced 5 responses with peak-to-peak amplitude of at least 50 μV in 10 consecutive trials (17). Determination of the coil position and estimation of motor threshold were conducted immediately before each rTMS session, be it sham or active.

Experimental procedures

Active and sham stimulation procedures were applied in each patient, as follows (18):

Active, high-frequency rTMS included 20 consecutive trains of 80 stimulations each, delivered at 20 Hz and 90% of motor threshold, separated by inter-trains intervals of 84 seconds (i.e. a total of 1600 stimulations during a 26-minutes session).

Sham stimulation (placebo-rTMS) followed the same protocol as above, using a sham coil at identical frequency (20 Hz) as the real coil.

rTMS was delivered at high-frequency (20 Hz), since only stimulus rates > 5 Hz have proven to have analgesic effects in humans (3,13). Although epidural MCS for pain relief is commonly applied at still higher frequencies, rTMS frequencies up to 20 – 25 Hz have been so far thoroughly tested and found safe. Active and sham rTMS sessions were separated each other by at least 2 weeks, during which the patients completed a written subjective pain assessment every day (see below). This interval was chosen on the basis of the maximal remnant post-stimulation effects after a single rTMS session, which does not exceed a week (10,13,19).

SCM

One or 2 electrodes (Resume, Medtronic) with 4 stimulating contacts were placed over the dura through a fronto-parietal craniotomy under general

anesthesia. The central sulcus was located with 3D-MRI neuronavigation (using the preoperative MRI) and the reversal of the response of primary somatosensory area to median nerve stimulation (somatosensory evoked potential [SEP] N20-P20). Direct electrical stimulation of the motor strip followed to confirm primary motor area location and its precise somatotopy. The stimulation electrode was then placed over the motor cortex representation corresponding to the painful area, and connected to a subcutaneously implanted stimulator (Synergy or Prime–advanced Medtronic). The stimulation parameters were adapted in the postoperative stage to optimize the analgesic effects within a range of frequency between 25 and 50 Hz, intensity 1.5 – 4.5 V (always under the threshold of motor response and/or paresthesia), pulse width 60 μs and stimulation cycle "on" for 30 minutes and "off" for 90 minutes (20).

Clinical Evaluation

Assessment after rTMS

All patients were familiar with the conventional numerical rating scale (NRS) from 0 (no pain) to 10 (unbearable pain). During the 5 days preceding the first rTMS session, all patients estimated their pain by filling a standardized form, and the average of these 5 values served as reference. After the first rTMS session (randomly distributed sham or active session) each patient pursued a daily evaluation of pain intensity, by filling the same form each evening for 2 weeks. Ratings during the 5 days before the second rTMS session were averaged and served as reference for the effect of the next session. Thus, the analgesic effect of each session was compared to its own baseline, obtained at least 10 days after any previous intervention session to avoid carry-on effects. Drug intake (number of drugs and dosages) was also noted each day and the patient had the possibility to add free commentaries in his/her logbook.

In addition to NRS, a "Combined Pain Assessment" (CPA) aimed at clinical benefit (13,16) was performed based on 3 dichotomic questions regarding (a) changes in subjective pain intensity (increase vs. decrease of at least 10% relative to baseline), (b) increase or decrease of analgesic rescue drug intake (no change of background medication being authorized during the study), and (c) change in subjective QoL (improved vs. worsened). Each item was rated +1, 0, or –1 according to whether it indicated improvement, stability, or worsening, respectively. Thus, total scores ranged from -3 (definite worsening) to +3 (definite improvement). A given rTMS session was considered efficacious in the case of a positive score during the week that followed the session.

Clinical evaluation following MCS

Pain relief assessment during hospital visits

All patients benefited from hospital visits every time it was necessary and at least at 6 months, one year, and then each year for long-term survey. During them, NRS was systematically recorded and completed by other questions concerning tolerance of the device, modifications of medical treatment, and global QoL evolution. Using this information, the CPA was calculated after MCS with the same methodology as defined in above, save for the fact that changes in subjective pain intensity were considered significant only if they exceeded 30% relative to baseline.

Phone survey by a third party and written survey

A member of the team, who did not participate to the rTMS sessions or to the standardized pain evaluation, and independent from the surgical team too, collected the survey data. She contacted the 19 surviving patients by phone and presented them a questionnaire comprising 10 items, which assessed the subjective evolution of pain complaints in more detail than the standardized evaluation above (Table 2). The order of the questions and the terms used for each of them were the same for all the patients. Based on the questionnaire, the CPA was calculated for each patient after MCS with the same methodology as after rTMS. A simplified QoL scale, the HowRu, was added to the questionnaire (21). In a last question, the patient was asked whether he would agree to be operated if he had to decide again.

After responding by phone, the patients were informed that they would receive the same questionnaire by regular mail, and were asked to provide written answers that should be sent back to us. In the written form, both pain intensity and QoL were assessed through the patient's choice on a visual numerical scale and using "smiles" corresponding to the 4 different levels of quotation of the HowRu scale (21). All the 19 patients responded to the phone survey and 10 sent back the written questionnaire. For these 10 patients, 2-tailed paired t-tests revealed no significant difference between phone and written responses concerning NRS and QoL evaluations and phone and written data were significantly correlated (Spearman r = 0.84; 2-tailed P = 0.004). Thus further analysis of the results was done

Table 2. *Phone and written survey.*

Before the operation, you were treated with two sessions of repetitive magnetic transcranial stimulation (here the interviewer had sometimes to explain with more detail the rTMS procedure). In your memory, did these stimulations modify your chronic pain, at least during a few days?	YES	NO		
A few months later, you were operated upon, to implant a stimulator over the motor cortex: did you have any problem during (or immediately after) this surgery?	YES	NO		
Did the implanted stimulator significantly decrease your pain?	**YES**	**NO**		
o If yes, were some pain characteristics specifically modified?	YES	NO		
o Which ones?:				
Try to give a number between 0 and 10 to quantify your pain intensity:	**0 – 10**	**0 – 10**		
o Before surgery				
o After surgery				
Did you note a modification of your quality of life after surgery?	**YES**	**NO**		
Try to remember your state before operation, and rate accordingly the following items:	**None**	**A little**	**Quite a lot**	**Extreme**
1. Pain or discomfort (short label: discomfort)				
2. Feeling low or worried (distress)				
3. Limited in what I can do (disability)				
4. Dependent on others (dependence)				
Rate the same health-related items as you feel them after surgery (i.e. at this moment):	**None**	**A little**	**Quite a lot**	**Extreme**
1. Discomfort				
2. Distress				
3. Disability				
4. Dependence				
Was it possible to decrease your medical treatment after surgery?	**YES**	**NO**		
If you had to decide again, would you choose to be operated?	**YES**	**NO**		

on phone survey data obtained from the 19 patients studied.

Statistical Analysis

After checking the normal distribution of the data (Kolmogorov and Smirnov test), appropriate statistical tests were chosen in order to reveal potential significant differences or correlation between the different sets of results. Significance was accepted at $P < 0.05$. One–way ANOVA for repeated measures was used to compare NRS changes induced by sham vs active rTMS and to compare pain relief induced by rTMS vs MCS at mid- and long-term. In case of significant ANOVA results, the analysis was completed by post-hoc Tukey's multiple comparison tests. A 2-way repeated measures ANOVA, with "time" and "QoL subtypes" as within-subject factors, was performed to compare the 4 HowRu subscores before and after MCS. Pearson's product-moment test was used to analyze the correlation between pain scores obtained at 6 months and at longer term, and between the surgical and the phone surveys of long-term pain relief. Significance of the contingency tables constructed to compare CPA scores after rTMS and MCS was tested using Fischer's exact test.

Results

Active versus Sham rTMS

All patients received 2 rTMS sessions (one sham and one active) during the months preceding (MCS). Paired t-tests showed a significant reduction of pain scores (NRS) following active rTMS $t[19] = 4.0$; $P < 0.01$) but not sham rTMS. This corresponded to a subjective pain relief of 14.6% for active rTMS versus 2.9% for sham rTMS.

Pain Relief Scores After rTMS and MCS

MCS efficacy was evaluated at 6 months (MCS6) and then iteratively up to 6.1 ± 2.6 years following MCS (MCS ≥ 24). Values of subjective pain relief at the most recent visit were assessed separately by the surgeon and through phone interviews by a third party not involved

in the clinical follow-up (see Methods). As shown in Fig. 1 (upper right panel), the results of these 2 evaluations were very significantly correlated (Pearson's r = 0.9; $P < 0.001$). NRS values collected by the surgical team were used for subsequent analyses.

One-way repeated-measures ANOVA comparing pain ratings at baseline and following MCS at mid- and long term was highly significant ($F[2,19] = 3.6$; $P < 0.001$). Post-hoc Tukey's multiple comparison tests revealed a significant decrease in pain ratings following MCS relative to baseline pain reports, whatever the delay considered after MCS ($P < 0.001$ for both mid- and long-term, Fig. 1). Pain ratings at MCS6 and MCS > 24 were significantly correlated (Pearson's r = 0.79; $P < 0.001$) and no difference could be demonstrated between mean pain scores at mid- and long-term. On individual analysis, however, only 3 patients improved slightly with time, while 10 others slightly worsened (Fig. 1, lower right panel). No correlation was found between the delay after MCS and the level of pain relief.

Pain reduction scores were larger after MCS (at any time) than after rTMS (mean 37.2% and 28.9% for MCS vs 14.6% for rTMS). Despite their quantitative differences, the clinical effects of preoperative rTMS were significantly associated with those of MCS at 6 months ($\chi 2(1) = 5.7$; Fisher's exact test $P = 0.04$) but this association disappeared with long-term MCS efficacy.

Combined Assessment of Clinical Benefit

This CPA, associating changes in pain score, drug intake, and subjective QoL, was devised to dichotomize in a meaningful fashion patients with a good outcome (positive score) and those with globally bad results, using more robust criteria than simple unidimensional pain scores (see Methods). CPA scores following rTMS and long-term MCS were significantly associated ($\chi 2(1) = 6.53$; Fisher's exact test $P = 0.02$; Fig. 2). A good global score after noninvasive rTMS predicted subsequent long-term pain relief by MCS

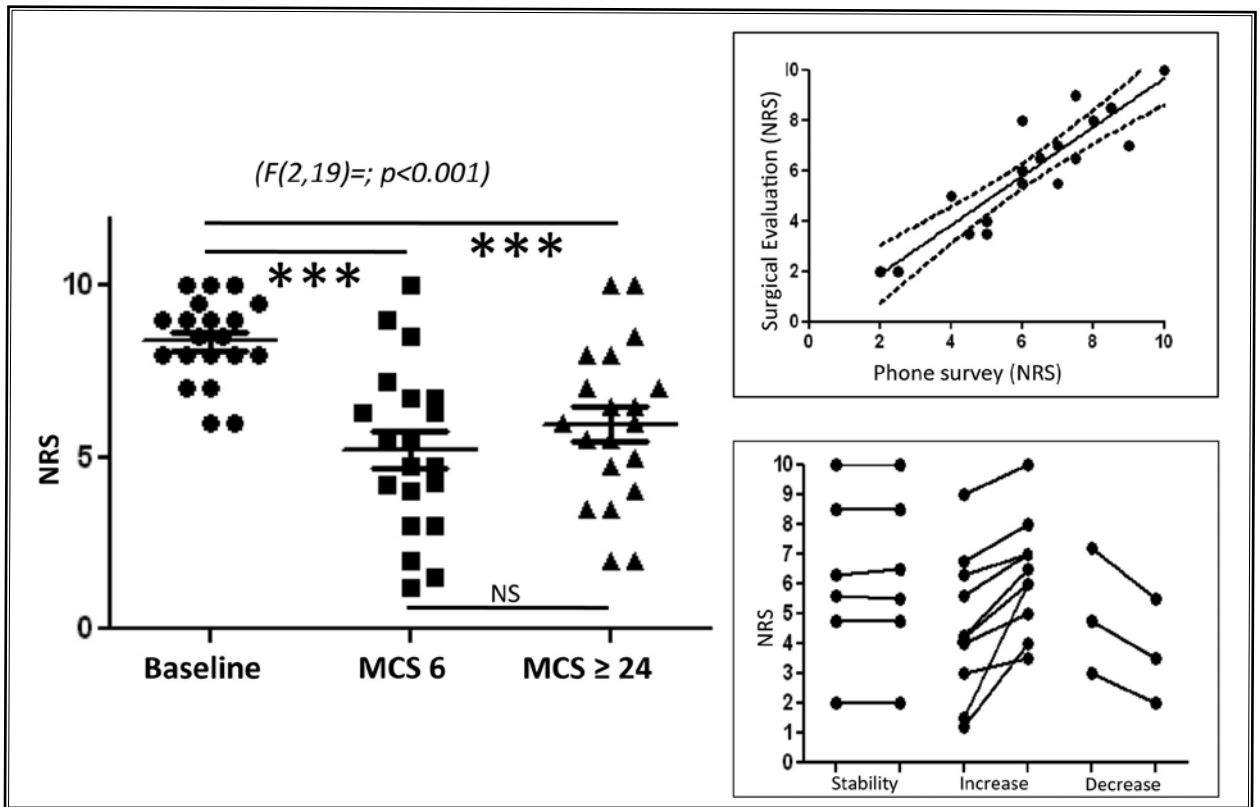

Fig. 1. Numerical pain intensity ratings (NRS) at baseline, and after MCS at mid- (MCS 6) and long-term (MCS ≥ 24). Pain ratings decreased significantly following MCS, at mid- and long-term. No significant difference was observed between the 2 end-points after MCS.
The framed upper panel shows the correlation between long-term pain ratings obtained by a phone survey (horizontal axis) and by the surgeon (vertical axis).
The framed lower panel shows individual short- and long-term pain ratings after MCS, according to the 3 possible evolutions.

with a 0.9 positive predictive value. The negative predictive value of unsuccessful rTMS over subsequent MCS was lesser, but still sizeable (0.67).

Phone Survey Using the HowRu Scoring

Analysis of the global HowRu scores indicated a significant improvement of long-term QoL after MCS (2-tailed paired t-test: t(18) = 3.6; P = 0.002) and the results of the HowRu questionnaire were correlated to those of the combined CPA score (Pearson's r = 0.66; P = 0.002).

A more detailed analysis of the changes for each QoL subtype was performed using 2-factor repeated measures ANOVA with 2 "time" (before vs after long-term MCS) and "QoL" axes (discomfort, distress, disability, and dependence) as within-subject factors. This analysis showed a main effect of time (F[1,18] = 12.3; P = 0.002), a significant effect of HowRu subtypes (F[3;18] = 4.51; P = 0.006) and no interaction. Fig. 3 illustrates the changes in different sub-scores of the HowRu questionnaire after long-term MCS. Following MCS, axes reflecting "pain-discomfort" (the physical dimension of pain) and "dependence" (the consequences of pain on autonomy for daily activities) significantly improved (paired t-test: t[18] = 3; P = 0.008 and t[18] = 2.9; P =0.009, respectively), whereas "disability" (work, home, and leisure activities) and "distress" (the psychological dimension of anxiety, stress, and depression) were not significantly modified.

Nine of 19 patients responded positively to the question: "should you have to decide now, would you accept surgery again?" While pain relief ratings did not significantly differ in both patients groups, their QoL improvement (HowRu) was significantly higher (t-test: t[17] = 4; P < 0.001) (Fig. 4).

Discussion

This work analyzed the natural long-term evolution of patients' satisfaction following surgically implanted MCS, and its possible prediction using preoperative rTMS. The clinical MCS effects were estimated not only by simple pain scores but also combining ratings of pain relief with objective (drug intake) and subjective (QoL) measures of satisfaction. In addition, a recently developed questionnaire for chronic diseases (the HowRu [21]) distinguished changes in physical discomfort, affective distress, disability, and dependence axes.

Preoperative active rTMS induced a significant analgesic effect compared to placebo (respectively 14.6% vs 2.9% pain relief). Effect magnitude was comparable

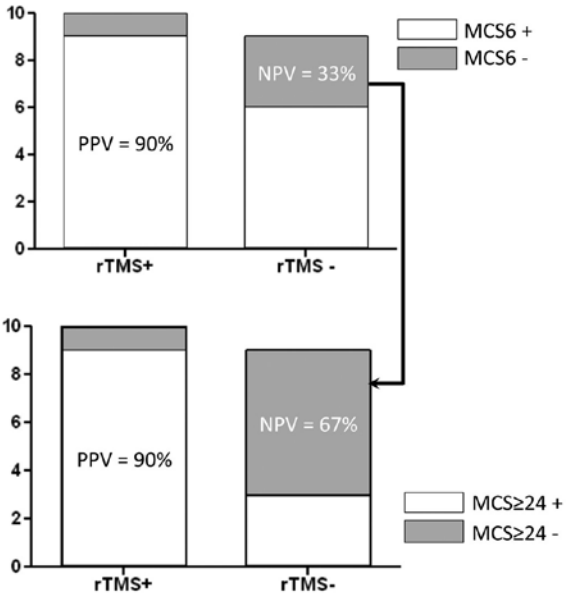

Fig. 2. *Predictive value of rTMS based on the evaluation of global clinical benefit.*
The positive predictive value of MCS effect remains stable and high (at 90%) in the long-term whereas the negative predictive value of rTMS increases with time, reaching 67% in the long-term: 3 patients unresponsive to rTMS responded only transiently to MCS.

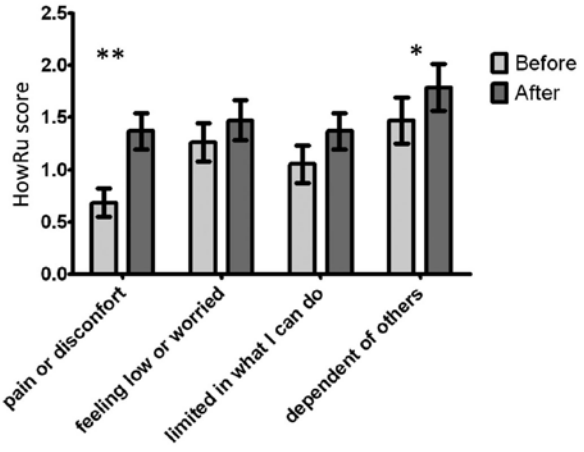

Fig. 3. *Comparison of QoL criteria of the HowRu scale before and after MCS.*
An increase of the HowRu score traduces an improvement of QoL.

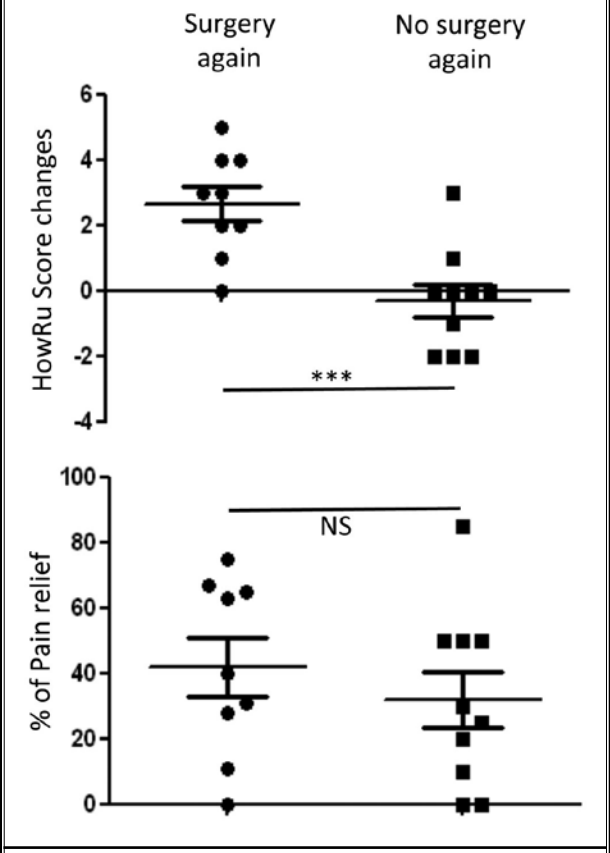

Fig. 4. *Influence of QoL on willingness to be operated on again.*
During the phone survey, the 19 patients were asked: "should you have to decide now, would you accept surgery again?" In the 9 patients who responded positively, QoL improvement (HowRu) was significantly higher (t-test: t(17) = 4; P < 0.001) than in the 11 remaining patients although pain relief ratings did not significantly differ between the 2 groups.

to that reported in most previous rTMS studies (3,11,22) although smaller than reports where pain relief was calculated on responders only (23). Pain reduction scores after MCS were significantly greater than those after non-invasive rTMS, at both the short and long term (37.2% and 28.9%, respectively).

The long-term evolution of analgesic MCS effect remains uncertain. Most previous studies reported a single evaluation, usually at one year (8,9,11,20). Nuti et al (20) compared MCS effects at 2 points (1 month and end-point 1 – 3 years) and did not observe a significant decrease of mean analgesia without specifying changes in individual patients. The present study provides the longest follow-up so far reported after MCS: although pain ratings at the short and long term (MCS6 and MCS > 24) remained significantly correlated, a slight decrease of MCS efficacy with time was noted in 10 patients on individual analysis (among them, those with maximal effect at 6 months), while only 3 patients improved with time (Fig. 1, lower right panel). Changes in pain relief were however not a linear function of post-operative delay. The small variations in pain relief between short- and long-term analyses did not reach significance. Overall, this study supports a good stability of MCS results over time at the group level, but such stability cannot be guaranteed in the individual patient. These results are nevertheless to be tempered regarding the limited cohort of patients included and suffering pain from inhomogeneous etiology.

Positive and Negative Predictive Value of Preoperative rTMS

Predictive value at long term of CPA (13,16) (associating NRS, QoL, and drug intake) performed better than raw pain scores. Thus, while raw pain scores after rTMS and MCS lost their correlation in the long term, CPA measures of clinical benefit did not (Fig. 2). A good predictive value of successful rTMS was acknowledged since the very first studies on this matter. Conversely, negative rTMS results were previously considered of no predictive use for MCS effect at one year (11,13). In this series, however, rTMS provided a sizeable negative predictive value of almost 0.7 on long-term MCS efficacy, provided that clinical effect was appreciated using not only numerical pain ratings, but also drug intake and QoL estimates. According to these data, lack of significant response to rTMS may significantly decrease (to less than one-third) the probability of MCS benefit in the long term and should question the use of such a treatment.

QoL Evaluation to Assess MCS Efficacy

Pain relief magnitude alone constitutes a very limited evaluation of clinical efficacy, particularly in the long term. This has been frequently acknowledged both in the context of MCS (e.g. (20), discussion page 49) and in other forms of neurostimulation (24). While a patient's attention may be focused on the potential analgesic effect during the first months after surgery, his/her self-evaluation is likely to be progressively tempered by a lack of improvement in everyday life quality. This was the main reason prompting us to include QoL measures to assess the long-term MCS benefits.

Few studies have included QoL criteria, and results are somewhat inconsistent (8,9). In our patients, QoL evaluation was attempted both via the CPA, which includes a simple question on global QoL status, and through a more comprehensive phone and questionnaire survey using the HowRu scale (21). Although the results of the CPA were correlated to those of the more detailed HowRu scale (r = 0.66), the CPA did not allow a separate assessment of different components that build up QoL. The HowRu scale, in contrast, suggested that QoL improvement concerned "discomfort" (physical dimension of pain), and "dependence" (consequences of pain on autonomy for daily activities) axes, whereas "distress" (anxiety, stress, depression) and "disability" (work, home, and leisure activities) items remained unchanged (Fig. 3). Although the results obtained through this approach are based on a retrospective evaluation of the preoperative status, they These results highlight nevertheless that pain relief after MCS is not always correlated with an improvement of other important QoL dimensions. The main difference between patients who would agree to be operated again and those who wouldn't concerned their QoL scores, independently of pain relief, supporting the fact that quality of life assessment is crucial.

Limitations

Our results are to be tempered regarding the limited number of patients included in the study, and the inhomogeneous etiologies of their pain. Results concerning long-term evolution after MCS deserve therefore being replicated so as to increase the sample size, even if such a long-term survey is always difficult to conduct on large cohorts. Another weakness of this study concerns QoL estimations, since long-term post-operative changes were assessed with respect to a retrospective evaluation of the preoperative status. It remains, however, that this first analysis strongly inclines to modifying medical practice, so that estimations of quality of life systematically completes pain intensity scores.

Conclusions

This series confirms the high positive predictive value of successful rTMS on the subsequent benefit from MCS. Further, it suggests that rTMS inefficacy may also have a substantial negative predictive value provided that QoL criteria are added to pain intensity scales. In the context of prospective longitudinal studies, evaluating both pain intensity and QoL every year after MCS appears important to appreciate reliably the stability of the long- lasting efficacy of the procedure.

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References

1. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl* 1991; 52:137-139.
2. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. *J Neurosurg* 1993; 78:393-401.
3. Cruccu G, Aziz T, Garcia-Larrea L, Hansson P, Jensen T, Lefaucheur J, Simpson B, Taylor R. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007; 14:952-970.
4. Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: Critical review of the literature. *J Neurosurg* 2009; 110:251-256.
5. Levy R, Deer TR, Henderson J. Intracranial neurostimulation for pain control: A review. *Pain Physician* 2010; 13:157-165.
6. Lima MC, Fregni F. Motor cortex stimulation for chronic pain: Systematic review and meta-analysis of the literature. *Neurology* 2008; 70:2329-2337.
7. Plow EB, Pascual-Leone A, Machado A. Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. *J Pain* 2012; 13:411-424.
8. Lefaucheur JP, Drouot X, Cunin P, Bruckert R, Lepetit H, Creange A, Wolkenstein P, Maison P, Keravel Y, Nguyen JP. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain* 2009; 132:1463-1471.
9. Nguyen JP, Velasco F, Brugieres P, Velasco M, Keravel Y, Boleaga B, Brito F, Lefaucheur JP. Treatment of chronic neuropathic pain by motor cortex stimulation: Results of a bicentric controlled crossover trial. *Brain Stimul* 2008; 1:89-96.
10. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurol* 2007; 6:188-191.
11. Lefaucheur JP, Menard-Lefaucheur I, Goujon C, Keravel Y, Nguyen JP. Predictive value of rTMS in the identification

of responders to epidural motor cortex stimulation therapy for pain. *J Pain* 2011; 12:1102-1111.

12. Migita K, Uozumi T, Arita K, Monden S. Transcranial magnetic coil stimulation of motor cortex in patients with central pain. *Neurosurg* 1995; 36:1037-1039; discussion 1039-1040.
13. Andre-Obadia N, Peyron R, Mertens P, Mauguiere F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin Neurophysiol* 2006; 117:1536-1544.
14. Canavero S, Bonicalzi V, Dotta M, Vighetti S, Asteggiano G, Cocito D. Transcranial magnetic cortical stimulation relieves central pain. *Stereotact Funct Neurosurg* 2002; 78:192-196.
15. Harvey A, Masland R. A method for the study of neuromuscular transmission in human subjects. *Bull Johns Hopkins Hosp* 1941; 68:81-93.
16. Andre-Obadia N, Mertens P, Gueguen A, Peyron R, Garcia-Larrea L. Pain relief by rTMS: Differential effect of current flow but no specific action on pain subtypes. *Neurology* 2008; 71:833-840.
17. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 1994; 91:79-92.
18. Andre-Obadia N, Magnin M, Garcia-Larrea L. On the importance of placebo timing in rTMS studies for pain relief. *Pain* 2011; 152:1233-1237.
19. Lefaucheur JP, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: Duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. *Neurophysiol Clin* 2001; 31:247-252.
20. Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, Mertens P. Motor cortex stimulation for refractory neuropathic pain: Four year outcome and predictors of efficacy. *Pain* 2005; 118:43-52.
21. Benson T, Sizmur S, Whatling J, Arikan S, McDonald D, Ingram D. Evaluation of a new short generic measure of health status: HowRu. *Inform Prim Care* 2010; 18:89-101.
22. Leo RJ, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: A review. *J Pain* 2007; 8:453-459.
23. Hosomi K, Saitoh Y, Kishima H, Oshino S, Hirata M, Tani N, Shimokawa T, Yoshimine T. Electrical stimulation of primary motor cortex within the central sulcus for intractable neuropathic pain. *Clin Neurophysiol* 2008; 119:993-1001.
24. Monhemius R, Simpson BA. Efficacy of spinal cord stimulation for neuropathic pain: Assessment by abstinence. *Eur J Pain* 2003; 7:513-519.