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Effect of Repetitive Transcranial Magnetic Stimulation on Malignant Visceral Pain

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Abstract Background and objectives. To assess the efficacy of 10 sessions (once daily for 10 days) of repetitive transcranial magnetic stimulation (rTMS) on primary motor cortex (M1) in patients suffering from malignant visceral pain. Materials and methods. Thirty four patients were included in the study. They were divided randomly into two groups (17 patients for each, using closed envelopes): real rTMS (20 Hz, 10 trains with intertrain interval of 30 s with total pulses 2,000, intensity 80% of motor threshold) and sham rTMS (coil elevated and angled away from the head). Stimulation was applied over M1 every day for ten consecutive days. Patients were evaluated using a verbal descriptor scale (VDS), visual analog scale (VAS), and Hamilton rating scale for depression (HAM-D) at baseline; after the 1st, 5th, and 10th sessions; and then at 15 days and one month later after the end of the treatment sessions. Serum human dynorphin (Dyn) was measured at baseline, and after the 5th and 10th sessions. Results. Fifteen patients from each group completed the study. There was no significant difference between real and sham groups in the duration of illness, or any rating scales at baseline. Compared with the sham group, the VAS/VDS scores decreased more in patients who received real rTMS over the course of the treatment and at 15 days follow-up than in those who received sham stimulation. Scores were the same at one month follow-up. There were no significant changes in serum human Dyn in either group. Conclusion. The results confirm that 10 sessions of rTMS over the M1 can induce pain relief in malignant visceral pain for at least 15 days but the effect is not maintained at one month.

Keywords VAS; VDS; visceral pain; malignancy; rTMS; motor cortex; analgesia

1. Introduction

Chronic abdominal visceral pain (CAVP) is one of the most frequent and debilitating disorders in the general population, critically impacting economy and quality of life [1]. Our understanding of the etiology, pathophysiology, and natural history of chronic abdominal pain has significantly increased in the past decade, in part because of the new tools to investigate the nervous system [2]. For instance, the development of novel, neuroimaging tools has provided new insights into the brain dysfunction associated with CAVP. Recent data show that this disorder might be associated with a dysregulation at multiple levels of the so-called “brain-gut axis” [3], involving both the central nervous system (CNS) and the peripheral nervous system (PNS). Functional magnetic resonance imaging (FMRI) and positron emission tomography (PET) have allowed mapping of the visceral pain matrix which is unlike somatic sensation represented in secondary somatosensory cortex (SII). However, as with somatic sensation, the insula, anterior cingulate cortex, and the prefrontal cortex mediate the affective and cognitive part of visceral pain [4]. It is critical to understand the pathophysiology of CAVP in order to develop effective treatment targets for this disease. Therefore, approaches aimed at the modulation of the nervous system, rather than the ones interfering with the inflammatory pathways, may be more effective for chronic pain treatment. We propose that noninvasive central nervous system stimulation, with transcranial magnetic stimulation (TMS), might be a novel therapeutic option for CAVP.

Primary motor cortex (M1) itself is seen as a focal entry port point to a distributed pain system that can modulate activity in remote deep-brain structures through its subcortical projections, and increase cerebral blood flow in the ipsilateral thalamus, the orbitofrontal and cingulate gyri, and the upper brain stem [5,6,7]. Upregulation of motor cortex excitability might therefore modulate pain perception through indirect effects on neural networks in pain-modulating areas, such as thalamic nuclei, as suggested by neuroimaging [5]. The effect on pain may also be mediated by changes in beta-endorphin levels, which have been reported to be increased after repetitive transcranial magnetic stimulation (rTMS) as measured...
directly in serum as in the studies of de Andrade et al. [8] and Ahmed et al. [9] or indirectly as in the study of Taylor et al. [10] who found that naloxone pretreatment could reduce the analgesic effect of rTMS, consistent with involvement of beta-endorphin.

In the light of this, many studies have provided evidence for the efficacy and mechanisms of action of invasive and noninvasive motor cortex stimulation [11,12]. It has also been regularly observed that, even in cases of bilateral or midline pain, stimulation on only one side of the brain is sufficient to modulate pain bilaterally [13]. Thus, Hirayama et al. showed that relief of neuropathic pain was observed only when targeting M1, but not other areas [14]. Louppe et al. [13] previously reported a beneficial analgesic effect of motor cortex stimulation with rTMS in two cases of non-cancer pelvic pain [13]. Denis et al. [15] reported the first case of a patient in whom pelvic pain due to adenocarcinoma of the rectum was markedly improved by a series of five sessions of rTMS of the motor cortex.

The precise location and pattern of stimulation has varied somewhat between studies. A 2010 Cochrane systematic review concluded that higher stimulation frequencies (> 5 Hz), greater numbers of stimuli (> 500), and multiple sessions (> 1) yielded better results [16]. André-Obadia et al. [17] also showed that rTMS was more effective in reducing pain when applied at 20 Hz than at 1 Hz, and Saitoh et al. [18] found that 10 Hz rTMS was more effective than 5 Hz rTMS, while 1 Hz rTMS had no significant effects. A study of low-frequency rTMS over somatosensory areas has been performed in patients suffering from chronic pancreatitis [19]; whereas high-frequency rTMS over motor cortex was applied to treat pelvic pain due to rectal adenocarcinoma [15] and another for noncancer pelvic pain [13]. Finally, it should be noted that therapeutic applications of rTMS in pain syndromes are limited by the short duration of the induced effects, but prolonged pain relief can be obtained by repeating rTMS sessions everyday for several weeks [20].

Based on all of the above-mentioned data, we hypothesized that repeated sessions of high-frequency rTMS over M1 would relieve malignant visceral pain, and therefore we conducted a preliminary trial to test the acceptability of this form of treatment in cases of malignant visceral pain. Patients attended 10 sessions of high-frequency rTMS delivered to the M1. Pain was assessed by changes in the verbal descriptor scale (VDS) [21] and visual analogue scale (VAS) [22]; any changes in depressive symptoms were evaluated using the Hamilton rating scale for depression (HAM-D) [23]. In addition, we tested whether any of the effects was related to changes in the level of dynorphin (Dyn).

2. Materials and methods

2.1. Patients

This study was conducted at the pain clinic of the South Egypt Cancer Institute, Assiut University and the Department of Neuropsychiatry, Assiut University Hospital in the period between January 2010 and January 2012. All patients within the age group 18–65 years with malignant visceral pain resistant to medical treatment for at least two months or associated with significant adverse effect from medication were involved in this study. We excluded patients with intracranial metallic devices or with pacemakers or any other device. We also excluded those with extensive myocardial ischemia, unstable angina, and those known to have epilepsy.

Thirty four patients with visceral pain were recruited and allocated into one of two groups (1:1 ratio) using closed envelopes randomization (real rTMS group and sham rTMS group). Figure 1 shows the flow chart of patients through the course of the study. In the real group, the mean age of the patients was 51 ± 9.7 years, (10 males and seven females) with mean duration of illness 15 ± 19.6 months. Two of them did not complete the study as they died after the 5th session. Four patients had cancer of the pancreas, seven had hepatocellular carcinoma/or hepatic focal lesion, two had gall bladder carcinoma, one had cancer stomach, two had non-Hodgkin lymphoma (NHL), and one had metastatic peritoneal mesothelioma. Regarding the site of visceral pain, nine patients had right hypochondrium pain, five had left hypochondrium pain, and another three had epigastrium pain. Nine patients were under chemotherapy and eight were under radiotherapy. As regards the sham group, the mean age of the patients was 57.8 ± 3.9 years, (eight males and nine females) with a mean duration of illness 12.3 ± 14.9
months. Five patients had cancer head of the pancreas, six
had hepatocellular carcinoma/or hepatic focal lesion, two
had gall bladder carcinoma, one had cancer esophagus, two
had cancer stomach, and one had NHL. Regarding the site
of visceral pain, eight had pain at right hypochondrium,
six at left hypochondrium, and three at the epigastrium. Nine
patients were under chemotherapy and eight were under
radiotherapy. All patients were asked not to change their
analgescic regimen through the course of the study. All of
them were under the same regimen: tramadol hydrochloride
100 mg twice daily, scopolamine 20 mg three times per day,
and amitriptyline 25 mg twice daily.

At the baseline assessment of pain, intensity was
assessed using VDS and VAS; HAM-D was applied in both
real and sham groups. Blood samples were withdrawn from
patients with visceral pain to assess the serum human Dyn
at baseline.

Assiut Medical School Ethical Review Board approved
the study. Written informed consent was obtained from all
of the subjects after describing the nature of the intervention
and the possibility of receiving sham stimulation.

2.2. Preparation
The patient was set in a comfortable chair and asked to relax
as much as possible. Electromyography (EMG) recording
from contralateral abductor digiti minimi (ADM) muscle
was acquired with silver-silver chloride surface electrodes,
using a muscle belly-tendon setup, with a 3 cm diameter cir-
cular ground electrode placed on the wrist. A Nihon Kohden
Machine model 9400 (Japan) was used to collect the signal.
EMG parameters included a bandpass of 20–1000 Hz and
a recording time window of 200 ms. Transcranial magnetic
stimulation (TMS) was performed with a commercially
available 90 mm figure-of-eight coil connected to Magstim
Super Rapid magnetic stimulator (Whitland, Wales, UK).

2.3. Determination of resting motor threshold
First, we determined the optimal scalp location from which
TMS evoked motor potentials of greatest amplitude in the
ADM. We used constant suprathreshold stimulus intensity
and moved the figure-of-eight coil systematically in 1 cm
steps to determine the scalp position from TMS evoked
motor potentials of maximum peak-to-peak amplitude in
the target muscle. The coil was positioned tangentially to
the scalp and oriented so that the induced electrical currents
will flow approximately perpendicular to the central sulcus,
at 45° angles from the midsagittal line [24]. Single pulse
TMS was then delivered to the optimal location starting at
suprathreshold intensity and decreasing in steps of 2% of
the stimulator output. Relaxation and EMG signals were
monitored for 20 ms prior to stimulation. The resting motor
threshold (RMT) was defined as the minimal intensity
required for eliciting motor evoked potentials of 50 µV
peak-to-peak amplitude in five out of 10 consecutive
trials [25]. The optimal scalp location and coil orientation
was marked using a red marker to reuse for daily rTMS.

2.4. Randomization (parallel design)
Group allocations (real or sham with ratio 1:1) were placed
in serially numbered opaque closed envelopes. Each patient
was placed in the appropriate group after opening the corre-
sponding sealed envelope.

2.5. Repetitive transcranial magnetic stimulation (rTMS)
Real-rTMS is involving a train of rTMS once per minute
for 10 min. Each train consists of 200 pulses at 20 Hz and
80% RMT (total duration 10 s) applied through a figure-
of-eight coil. Motor cortical stimulation was given on the
contralateral side of pain so patients with right hypochon-
drium received stimulation on the left-hand area and vice
versa. Patients with epigastric pain received stimulation on
the dominant hemisphere (left hemisphere).

The treatment was repeated every day for five consecu-
tive days/week for two weeks (the total number of sessions
given was 10 sessions). Sham rTMS was applied using the
same parameters, but with the coil held so that the edge was
in contact with the head while the remainder was rotated
90°away from the scalp in the sagittal plane to reproduce the
noise of the stimulation as well as some of its local sensa-
tion. However, since none of the patients have experienced
rTMS previously, they were unaware of which stimulation
was real and which was sham. During the rTMS, all patients
wore earplugs to protect ears from the acoustic artifact asso-
ciated with the discharge of stimulation coil.

2.6. Sample collection
The blood samples were withdrawn from all studied
patients. Serum was separated from all samples. Three
samples were withdrawn: the first sample was taken before
the 1st session, the second sample was taken one hour after
the end of the 5th session of rTMS, and the third sample
was withdrawn one hour after the end of the 10th session
of rTMS. The samples were left at room temperature for
10–20 min, centrifuged for 20 min at the speed of 2000–
3000 rpm, and then the serum was removed and stored at
−20 °C until the beginning of the work.

2.7. Determination of serum human Dyn level
Human Dyn ELISA kit (Glory Science Co., TX, USA)
was used in the measurement of the serum level of Dyn.
Measurement of Dyn was performed using Evolis system
(Bio-Rad, CA, USA). Enzyme-linked immunoassay was
performed as manufacturer instructions. The concentration
of Dyn in the samples was determined by comparing
the optical density (OD) of the samples to the standard
curve which was obtained by plotting the standard density
using six standard samples with different concentrations
Table 1: Demographic and clinical data of studied patients with visceral pain.

<table>
<thead>
<tr>
<th></th>
<th>Real group (n = 17)</th>
<th>Sham group (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean ±SD</td>
<td>55.0 ± 9.7</td>
<td>57.8 ± 3.9</td>
<td>.12</td>
</tr>
<tr>
<td>Sex: male/female</td>
<td>10/7</td>
<td>8/9</td>
<td>.732</td>
</tr>
<tr>
<td>Duration of illness: (months)</td>
<td>15.0 ± 19.6</td>
<td>12.3 ± 14.9</td>
<td>.667</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer pancreas</td>
<td>4</td>
<td>5</td>
<td>.827</td>
</tr>
<tr>
<td>Hepatocellular carcinoma/or hepatic focal lesion</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Gall bladder cancer</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cancer esophagus</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cancer stomach</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma (NHL)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metastatic peritoneal mesothelioma</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patients were under:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy treatment</td>
<td>9</td>
<td>10</td>
<td>.730</td>
</tr>
<tr>
<td>Radiotherapy treatment</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Site of pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hypochondrium</td>
<td>9</td>
<td>8</td>
<td>.928</td>
</tr>
<tr>
<td>Left hypochondrium</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Epigastric</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Verbal descriptor scale (VDS)</td>
<td>4.8 ± 0.76</td>
<td>4.8 ± 0.83</td>
<td>.81</td>
</tr>
<tr>
<td>Visual pain scale (VAS)</td>
<td>6.4 ± 0.5</td>
<td>6 ± 0.65</td>
<td>.073</td>
</tr>
<tr>
<td>Hamilton rating scale for depression (HAM-D)</td>
<td>13.5 ± 1.64</td>
<td>13.7 ± 1.16</td>
<td>.61</td>
</tr>
<tr>
<td>Character of pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dull aching</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Stabbing</td>
<td>3</td>
<td>4</td>
<td>.635</td>
</tr>
<tr>
<td>Heaviness</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Colicky</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

as horizontal axis and the vertical axis to the obtained OD value.

2.8. Follow-up measures

Measurements were done before and after the 1st, 5th, and 10th sessions, then at 15 days and one month later, with all rating scales: VDS, VAS, and HAM-D. The measurements were done by a blind assessor without knowing the type of stimulation applied. During the follow-up, seven patients of the real group asked to decrease the dose of tramadol hydrochloride to be 50 mg twice/day after the 10th session, and eight patients of sham group asked to increase the dose of tramadol to be 150–200 mg twice/day.

2.9. Outcomes

The primary outcome was pain relief on the VAS after the 10th session and one month later, and the secondary outcomes were pain and depression reduction on VDS and HAM-D after the 10th session and one month later. Serum human Dyn level was assessed at baseline, and after the 5th and 10th treatment sessions.

2.10. Data analysis

Pain level was assessed at baseline, 1st, 5th, and 10th sessions then at 15 days and one month after the end of sessions using the VDS and VAS. HAM-D was also measured.

The values of each group of patients for each scale were analyzed separately by one-way repeated measures analysis of variance (ANOVA). Two-way repeated measures ANOVA was used to assess the interaction between groups (Time “pre, 1st, 5th, 10th, 15 days after stimulation and after one month” × Group “real & sham”). Post-hoc t-tests were used to assess interaction between groups at different points of assessment. The Greenhouse-Geisser correction for degrees of freedom was used when necessary to correct for nonsphericity of the data. The percentage of reduction in each scale was calculated after the 10th, 15 days, one month after the end of stimulation as (((prestimulation score – poststimulation score) × 100)/prestimulation score) and then compared the two groups using the Mann-Whitney test.

3. Results

Demographic/clinical data and different rating scales of pain assessment are demonstrated in Table 1. Figure 2 illustrates the effect of treatment on the main VAS and secondary outcome measures (VAS and HAM-D), showing how scores at baseline changed over the following month. A two-way repeated measures ANOVA with TIME (pre, after 1st, 5th, 10th, and 15 days and one month later) and GROUP (real or sham) as main factors showed a significant TIME × GROUP interaction for VDS [P =
Figure 2: The figure shows changes in the VDS (a), the VAS (b), and the HAM-D (c) in patients with malignant visceral pain at six points of assessment. The first one was prior to commencing rTMS treatment (prestimulation). The second was after the 1st session (post-1st session). The third was after the 5th session (post-5th session), the fourth was after the 10th session of stimulation (post-10th session), the fifth and sixth assessment points were at 15 days and one month after the end of stimulation sessions. Data are expressed as mean ± standard deviation. The significant percent changes (((prestimulation – poststimulation) × 100)/prestimulation) between groups appeared at different points of assessment in comparison to baseline assessment. These were seen mainly after the 5th and 10th sessions for the three rating scales as well as at 15 days after the end of sessions for VDS only.

.008, $F = 4.42$, df = 2.7 (77.7), VAS [$P = .049$, $F = 2.7$, df = 2.76 (80)], but not for HAM-D [$P = .97$, $F = 2.59$, df = 2.17 (60.76)]. This indicates that the effect of treatment differed in the two groups on the VAS and VDS but not on the HAM-D. We then used a one-way ANOVA to examine the effect of TIME on the data from each group separately. There was a significant effect of time in both groups in all rating scales ($P = .001$); see Table 2. Thus both real and sham treatments tended to reduce symptoms. However, the effects were greater with real stimulation in the VAS and VDS, particularly at the end of treatment and at 15 days follow-up. The results of individual $t$-test comparisons between groups at each time point in comparison to the baseline assessment are shown in Table 2 and Figure 2. In general, there was no effect of real rTMS after the first treatment session. A difference with sham group gradually appeared over the course of treatment, but was no longer present after one month.
Neuroenterology

The serum human Dyn level shows no significant difference between patients with visceral pain treated with real rTMS and sham rTMS \( [P = .77, F = 0.184, df = 1.49 (34.43)] \), as seen in Figure 3.

4. Discussion

Previous studies of rTMS in patients with chronic neuropathic pain have considered the immediate analgesic effect of single session [26]. Our group was the first to consider repeated sessions over a five-day period in patients with neuropathic pain with long lasting effects [27]. The present study is an indicator for the first time that rTMS of motor cortex may also be effective in patients with malignant visceral pain due to different pathology. The rationale to choose 10 sessions of rTMS in order to obtain more sustained pain relieve was for that most of the previous studies found that repeated sessions have a cumulative and long-term effect on relieving pain [9,27,28].

These results are consistent with those of recent work showing a significant reduction in pain after real rTMS applied to sensory cortex SII that lasted for three weeks [20].

Also, a case report has shown that rTMS applied to motor cortex was associated with a significant reduction in pain intensity in cancer head of the pancreas [15].

Interestingly, the effect of rTMS in our patients for 10 days of stimulation could produce improvement in pain scale up to two weeks, which is also reported in patients with chronic pancreatitis by a study of Fregni et al. [20]. These data suggest that rTMS at the motor cortex and sensory cortex SII can induce long lasting changes in pain intensity due to visceral pain. rTMS can modulate the activity of brain structures involved in pain perception changes in cortical inhibitory mechanism of pain.

Table 2: Rating scales of patients with visceral pain in studied groups (15 patients for each group).

<table>
<thead>
<tr>
<th>Rating scales</th>
<th>Pre session</th>
<th>1st day</th>
<th>5th day</th>
<th>10th day</th>
<th>2 weeks</th>
<th>1 month</th>
<th>Repeated measure analysis one ANOVA (each group separately)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Verbal descriptor scale</td>
</tr>
<tr>
<td>Real group</td>
<td>4.86 ± 0.8</td>
<td>4.87 ± 0.83</td>
<td>3.83 ± 0.8</td>
<td>3.13 ± 0.9</td>
<td>2.93 ± 1</td>
<td>3.4 ± 0.7</td>
<td>df = 1, F = 12.8, P = .0001</td>
</tr>
<tr>
<td>Sham group</td>
<td>4.8 ± 0.7</td>
<td>4.8 ± 0.7</td>
<td>4.27 ± 0.5</td>
<td>3.8 ± 0.8</td>
<td>3.73 ± 0.7</td>
<td>3.7 ± 0.6</td>
<td>df = 1, F = 13.9, P = .0001</td>
</tr>
<tr>
<td>P-value between</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline and each point</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Real group</td>
<td>P = .81</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td></td>
</tr>
<tr>
<td>Sham group</td>
<td>P = .973</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td>df = 1,</td>
<td></td>
</tr>
<tr>
<td>P-value between</td>
<td></td>
<td></td>
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<tr>
<td>baseline and each point</td>
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<td></td>
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</tr>
<tr>
<td>Real group</td>
<td>F = 1.9,</td>
<td>F = 12.8,</td>
<td>F = 10.3,</td>
<td>F = 8.8,</td>
<td>F = 1.8,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham group</td>
<td>F = .33</td>
<td>P = .005</td>
<td>P = .003</td>
<td>P = .006</td>
<td>P = .190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value time × group</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Visual analogue scale

| Real group    | 6.4 ± 0.5  | 6.33 ± 0.6 | 5.13 ± 0.7 | 4.47 ± 1  | 4.73 ± 1 | 5.2 ± 0.9 | df = 1, F = 11.6, P = .0001                     |
| Sham group    | 6 ± 0.7    | 6 ± 0.7    | 5.33 ± 0.8 | 5.1 ± 1   | 5.13 ± 0.7 | 5.13 ± 0.4 | df = 1, F = 9.2, P = .004                      |
| P-value between |            |         |         |          |         |         |                                                   |
| baseline and each point |            |         |         |          |         |         |                                                   |
| Real group    | P = .973   | df = 1,   | df = 1,  | df = 1,  | df = 1,  | df = 1,  |                                                   |
| Sham group    | P = .33    | P = .005  | P = .01  | P = .053  | P = .24  |                                                   |
| P-value time × group |            |         |         |          |         |         |                                                   |

Hamilton rating scale for depression

| Real group    | 13.47 ± 1.6 | 13.47 ± 1.6 | 12.13 ± 2.2 | 11.2 ± 2.2 | 11.47 ± 2.2 | 11.73 ± 2.1 | df = 1, F = 11.5, P = .0001                     |
| Sham group    | 13.73 ± 1.2 | 13.73 ± 1.2 | 13.27 ± 1.5 | 12.47 ± 1.5 | 12.2 ± 1.4 | 12.2 ± 1.4 | df = 1, F = 13.5, P = .0001                     |
| P-value between |            |         |         |          |         |         |                                                   |
| baseline and each point |            |         |         |          |         |         |                                                   |
| Real group    | P = .61    | df = 1,  | df = 1,  | df = 1,  | df = 1,  | df = 1,  |                                                   |
| Sham group    | F = 1.6,   | F = 4.7,  | F = 5.45, | F = 0.8,  | F = 0.2,  |                                                   |
| P-value time × group |            |         |         |          |         |         |                                                   |

Visual analogue scale

| Real group    | 2.768 ± 1.0 | 2.729 ± 0.9 | df = 2.768, F = 4.423, P = .008 |

Figure 3: The figure shows serum human Dyn level in studied patients with visceral pain at three points of assessment for the two groups of patients. The first was prior to commencing rTMS treatment (prestimulation). The second after the end of the 5th session (5th day of stimulation), and the third was after the 10th session of stimulation (10th day of stimulation). Data expressed as mean ±SD. There are no significant changes in the serum level of Dyn neither in real group nor in the sham group.
metabolic correlation in patients with chronic visceral pain and brain stimulation showed that changes in the baseline levels of glutamate (magnetic resonance spectroscopy) were negatively correlated with pain response [20].

The lack of sustained effect could be due to disease progression as these conditions progress much more rapidly than the other types of pain that have been studied before that had longer lasting effects. In addition, the neuromodulatory effect could weaken more rapidly in this type of cancer than in other types of pain. This could be a consequence of their drug treatment which in most cases included scopolamine, an anticholinergic. It is known that these drugs can interfere with synaptic plasticity; see recent review by Ziemann et al. [29].

The possible mechanisms of action and the duration of pain relief following the stimulation of M1, by rTMS, are considered in the review by Lefaucheur and colleagues [6] and Hosomi et al. [30]. The consequence may be to change the levels of central nervous system opioids. Maarrawi et al. [11] reported that motor cortex stimulation may induce release of endogenous opioids in brain structures involved in the processing of acute and chronic pain [11]. Töpper et al. [31] found that the opioid antagonist naloxone abolished the rTMS-induced pain relief, which was taken as an evidence that the analgesic effect of rTMS acted via the release of endorphins. Ahmed et al. [9] found an elevation of serum beta-endorphin concentration after five sessions of 20 Hz rTMS over the left-hand area of motor cortex in 17 patients with chronic phantom pain. However, serum human Dyn level was measured in the present study and we found that there was no significant interaction between real and sham groups in tested patients with visceral pain. Thus, is Dyn involved in rTMS analgesia? It seems from these data that it may not be and measuring of serum Dyn is unreliable. However, the depressant effect of Dyn and kappa-opioid receptor agonist has been proved [10] and furthermore several studies have shown that reduced activity in the kappa-opioid receptor system may be effective in treatment of depression [32,33]. Lee et al. found that rTMS over the right dorsolateral prefrontal cortex (DLPFC) or left motor cortex could have an antidepressant and pain modulating effect in patients with fibromyalgia [34]. This study speculates that changes reported by rTMS a sort of balance dynorphin could be joined with changes in endogenous opioid peptide. Perhaps, a larger sample size and concomitant measure of beta-endorphin as well can solve this issue.

5. Conclusion

The use of 10 rTMS sessions of 20 Hz over the primary motor cortex area can have a beneficial reduction of pain score in malignant visceral pain patients and the maximum effect was apparent after the end of 10 sessions. This effect is maintained for two weeks follow-up after the end of sessions, however, it is no longer present after one month of the end of treatment sessions.

Conflict of interest  The authors declare that they have no conflict of interest.

References


