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Daily repetitive high frequency transcranial magnetic stimulation of primary motor cortex for malignant neuropathic pain

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Abstract

Background: Background: Neuropathic pain in cancer patients can arise as a consequence of cancer- directed therapy, such as surgery, radiotherapy and chemotherapy. Significant analgesic effects of repetitive transcranial magnetic stimulation (rTMS) have been found in several studies of patients with chronic pain of various origins.

Objectives: to assess the efficacy of daily 10 sessions of rTMS on primary motor cortex in patients suffering from malignant neuropathic pain.

Material and methods: Thirty four patients were included in the study. They are divided randomly into 2 groups (17 patients for each) using closed envelop as real rTMS group and sham group. Real rTMS over the hand area of motor cortex (20 Hz, 10 trains with inter train interval 30 second with total pulses 2000, intensity 80% of motor threshold) every day for ten consecutive days (5 days/week) and the coil elevated and angled away from the head as sham stimulation. Patients were evaluated by verbal descriptor scale (VDS), visual analog scale (VAS), Leeds assessment of neuropathic symptoms and signs (LANSS) and Hamilton rating scale for depression (HAM-D) at the baseline, after 1st, 5th, 10th session, 15 day and 1 month after end of sessions.

Results: There was no significant difference between true and sham groups in the duration of illness, VDS, VAS, LANSS scores at the base line. VAS, VDS and LANSS scores of the patients who received real rTMS decreased more over the course of the treatment through the different points of follow-up than those who received sham stimulation but not after one month follow up.

Conclusion: The results confirmed that 10 sessions rTMS over the motor area can induce pain relief in malignant neuropathic pain for at least 15 days but the effect cannot be maintained after one month.

Key words: Motor cortex, rTMs, neuropathic pain, analgesia.

Background

Neuropathic pain in cancer patients may arise from several mechanisms. It may result from compression of the nerve or direct infiltration by the growing tumor, or secondarily from changes in the neuronal media resulting from cancer growth or from the resulting inflammatory response such as tissue pH (acidosis), release of tumor algogens or circulating chemokines and cytokines(1). These inflammatory events in cancer-neuropathy are likely to be more common and important than in other neuropathies; in these an acute tissue response subsides leaving restricted neuropathic mechanisms within peripheral nerve and the central nervous system. In addition to cancer-induced inflammation, debilitated patients are more likely to have secondary infections such as Herpes-Zoster, bacterial or fungal infections, which may lead directly to neuropathic damage, or additional hypersensitivity (2).

Neuropathic pain can also arise as a consequence of cancer- directed therapy, such as surgery, radiotherapy and chemotherapy (3). Drugs such as paclitaxel, vincristine and cisplatin have been widely reported to produce sensory neuropathies, evoking tingling sensations, or numbness in the distal extremities consistent with a glove and stocking distribution (3,4). Surgical interventions such as mastectomy, or debulking tumors often results in deafferentation pain. Patients post-mastectomy report a constellation of symptoms including pain or discomfort in the chest wall, surgical scar, upper arm and shoulder, which may be suggestive of intercostobrachial nerve damage and phantom breast sensations (5). Finally, radiation-induced fibrosis can injure peripheral nerves (e.g. fibrosis of brachial plexus)

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causing chronic neuropathic pain that begins months to years following treatment (2).

Significant analgesic effects of rTMS have been found in several studies of patients with chronic pain of various origins as central neuropathic pain (poststroke pain(6), spinal cord injury(7), thalamic pain(7)) and peripheral neuropathic pain as trigeminal neuralgia(6), phantom limb pain(8) and brachial plexus injery(7). Primary motor area (M1) stimulation at high frequency was shown to reduce pain scores by 20 to 45% after active stimulation and by less than 10% after sham stimulation(9). The 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 every day for several weeks (9).

The short term effect of rTMS as well as long term (cumulative) effect on non-malignant neuropathic pain was studied but not in malignant neuropathic pain as we know; for this we designed this multisession study to assess the efficacy of daily 10 sessions of high frequency rTMS at the primary motor cortex in patients suffering from malignant neuropathic pain.

Methods

Patients:

This study was conducted at pain clinic of South Egypt Cancer Institute, Assiut University and the department of neuropsychiatry, Assiut University Hospital in the period between 2010 and 2013. All patients within age group 18-65 years with malignant neuropathic pain resistant to medical treatment for at least 2 months or associated with significant adverse effect from medication was 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 were included in the study. They are divided randomly into 2 groups (17 patients in each) using closed envelops as real rTMS group and sham (control) group. In real group, the mean age of the studied patients was 47±9.2 years, (1 male and 16 female) with mean duration of illness was 15.4±15.9 months. Two of them didn't complete the study as one lost in follow up and other developed medical complication after the 10th session.9 had right cancer breast, 5 had left cancer breast, 1 had soft tissue sarcoma in the right upper limb, 1 had giant cell glioma of right radial nerve and 1 had left femoral nerve injury after femoral after femoral mass removal. 10 patients were under chemotherapy and 7 were under radiotherapy. In sham group, the mean age of the studied patients was 48±9.7 years, (2 male and 15 female) with mean duration of illness was 16.8±16.3 months. Two patients also didn't complete the study as they lost in follow up after 5th session. 8 had right cancer breast, 7 had left cancer breast, and 2 had soft tissue sarcoma in the right lower limb. 8 patients were under chemotherapy and 9 were under radiotherapy.

Preparation:

The patient set in a comfortable chair and was asked to relax as much as possible. Electromylography (EMG) recording from contralateral abductor digiti minimi (ADM) muscle was acquired with silver-silver chloride surface electrodes, using a muscle belly-tendon set –up, with a 3 cm diameter circular ground electrode placed on the wrist. A Magstim Super Rapid (dual PSU) was used to collect signal (A Magstim Super Rapid (dual PSU), Magstim Ltd, USA). An electromyography was used to collect the signal. EMG parameters included a bandpass of 20-1000 Hz and a recording time window of 200 ms. TMS was performed with a commercially available 90 mm figure of eight coil.

Determination of resting motor threshold:

First we determine the optimal scalp location from which TMS evoked motor potentials of greatest amplitude in the ADM. We use constant suprathreshold stimulus intensity and move 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 45ºangle from the mid-sagittal line (10). Single pulse TMS is 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) is defined as the minimal intensity required eliciting motor evoked potentials of 50 μV peak to peak amplitude in five out of 10 consecutive trials (11). The optimal scalp location and coil orientation was marked using a permanent red marker to reuse for daily rTMS.

Repetitive transcranial magnetic stimulation:

Real-rTMS involved applying a train of rTMS once per minute for 10 minutes. Each train consist of 200 pulses with inter train interval 30 seconds at 20 Hz and 80% RMT (total duration 10s) applied through a figure of eight coil over the identified motor cortical area corresponding to the hand of painful side. The treatment was repeated every day for 5 consecutive days in week for two week (10 sessions) with total pulses 2000. Sham-rTMS was applied using the same parameters but with the coil elevated and angled away from the head to reproduce the same of subjective sensation of rTMS and yet to avoid induction of current in the brain (12). However, since none of the patients have experienced rTMS previously they will be unaware of which stimulation is real and which is sham. During the rTMS, all patients will wear earplugs to protect ears from the acoustic artifact associated with the discharge of stimulation coil.

Follow up:

Patients were followed up after the first, fifth and tenth rTMS session, and 1 month after the last session, using VDS, VAS, LANSS and HAM-D scales. The measurements were done by a blind assessor without knowing the type of stimulation given.

Data analysis:

Pain level was assessed at the baseline, first, fifth, tenth, 15 days after the end of sessions and one month after the end of sessions using the VDS, VAS, and LANSS for all patients included in the study. HAM-D

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was also measured. The values of each group of patients for each scale were analyzed separately by one way ANOVA repeated measure analysis. Two way ANOVA repeated measure of analysis to assess the interaction between groups (time "pre, 1st, 5th, 10th, 15 days after stimulation and after one month" X group "real &sham"). Post hoc T- tests were used to assess interaction between groups at different point of assessment and between the baseline assessment and different point of assessment. The Greenhouse-Geisser correction of degrees of freedom was used when necessary to correct non-spherity of the data. The percentage of reduction of each scale was calculated after the 10th session of stimulation by Mann-Whitney test as scale at 10th day- prestimulation score X 100/prestimulation score. The percentage of reduction after one month of stimulation was calculated as scale after one month of stimulation- prestimulation score X 100/ prestimulation score.

Results

There were no differences between both groups as regard to demographic and clinical data of the studied patients in both groups as seen in table (1).

No difference in baseline assessment between both groups as regard to the baseline assessment in different scales used as seen in table (2)

There was significant improvement of VDS all over the course of rTMS and follow up for each group separately and these effects were more pronounced in the real group than the sham group (p value was 0.00001 in real group and in sham group was 0.0001). Two way ANOVA repeated measure analysis (time X group) was p value 0.0001. Table (3) and figure (1) shows that verbal descriptor pan scale score of patient who received real rTMS decreased significantly through the different point of assessment after the 5th ,10th and 15 days after the end of sessions but not maintained to 1 month follow up in the same degree than those patients who received sham rTMS. The same results was reported in VAS score as seen in table (4) and figure (2) and LANSS score as seen in table (5) and figure (3). Also the same changes occur in HAM-D as seen in table (6) and figure (4). The percentages of reduction were measured after the 10th session and 1month after the end of rTMS sessions in all scales used in the study as seen in table (7). We found significant reduction in all the scale after 10th session in real group than sham group; however these effects were not seen in 1 month after the end of stimulation except in LANSS and HAM-D.

Table 1: Demographic and clinical data of studied patients with neuropathic pain

	Real Group (n= 17)	Sham Group (n= 17)	P value
Age: mean ± SD	47.0 ± 9.2	48.0 ± 9.7	0.769
Sex: (male: female)	1 : 16	2 : 15	0.545
Diagnosis			
• Rt cancer breast	9	8	0.732
• Lt cancer breast	5	7	0.473
• Soft tissue sarcoma in rt upper limb	1	0	1.000
• Soft tissue sarcoma in rt lower limb	0	2	0.466
• Giant cell glioma of rt radial nerve	1	0	1.000
• Lt femoral nerve injury after femora mass removal	1	0	1.000
Site of pain:			
• Axilla	9	10	0.730
• Arm	6	5	0.714
• Lower limb	2	2	1.000
Character of pain:			
• Burning	9	9	1.000
• Numbness	6	5	0.714
• Stitching	2	3	0.628
Patients were under:			
• Chemotherapy treatment	10	8	0.545
• Radiotherapy treatment	7	9	
Duration of illness (months):	15.4 ± 15.9	16.8 ± 16.3	0.809

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Table (2): Baseline assessments of both groups in the studied patients

	Real group Mean ±SD	Sham group Mean ±SD	P -value
Verbal descriptor pain scale	4.7±0.8	4.6±0.9	NS
Visual analog scale (VAS)	6.3±0.5	6.1±0.6	NS
Hamilton rating scale for depression	13.3±1.9	13.5±1.5	NS
Leeds assessment of neuropathic symptoms and signs (LANSS)	16.7±2.49	16.4±2.9	NS

Table (3): Verbal descriptor scale (VDS)

	Prestimulation mean±SD	1st d of stim Mean ±SD	5thd of stim Mean ±SD	10thd of stim Mean ±SD	15 d after stim Mean ±SD	1m after stim Mean ±SD	One way ANOVA repeated measure analysis (Time)	Two way ANOVA repeated measure analysis (Time X group)
Real group	4.7±0.8	4.7±0.8	3.6±0.7	2.3±0.8	2.5±0.9	3.2±0.6	0.00001	P=0.0001 F=47.09
Sham group	4.6±0.9	4.6±0.9	3.8±0.8	3.5±0.6	3.5±0.7	3.6±0.7	0.0001	Df=1.89 (54.8)
Two way ANOVA repeated measure analysis at different point of assessment (Time X group		NS	0.0001	0.0001	0.32	0.005		
Two way ANOVA repeated measure analysis with the baseline time (Time X group)		1.000	0.000	0.000	0.000	0.000		

Table (4): Visual analog scale (VAS)

	Prestimulation mean±SD	1st d of stim Mean ±SD	5thd of stim Mean ±SD	10thd of stim Mean ±SD	15 d after stim Mean ±SD	1m after stim Mean ±SD	One way ANOVA repeated measure analysis (Time)	Two way ANOVA repeated measure analysis (Time X group)
Real group	6.3±0.5	6.3±0.5	5.3±0.6	3.9±1.3	4±1.2	4.8±0.9	0.00001	P=0.0001 F=8.07
Sham group	6.1±0.6	6.1±0.6	5.3±0.7	5.13±0.6	5±0.8	5.13±0.63	0.0001	Df=2.05 (57.5)
Two way ANOVA repeated measure analysis at different point of assessment (Time X group		NS	0.0001	0.001	0.27	0.016		
Two way ANOVA repeated measure analysis with the baseline time (Time X group)		1.000	0.000	0.000	0.000	0.000		

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Table (5): LANSS pain scale

	Prestimulation mean±SD	1st d of stim Mean ±SD	5thd of stim Mean ±SD	10thd of stim Mean ±SD	15 d after stim Mean ±SD	1m after stim Mean ±SD	One way ANOVA repeated measure analysis (Time)	Two way ANOVA repeated measure analysis (Time X group)
Real group	16.7±2.49	16.6±2.35	15.33±2.6	13.1±2.54	12.9±2.26	13.7±2.93	16.7±2.49	P=0.018 F=2.83
Sham group	16.4±2.9	16.4±2.8	15.6±2.3	14.9±2.12	14.5±1.76	15.1±2.13	16.4±2.9	Df=2.5 (70.4)
Two way ANOVA repeated measure analysis at different point of assessment (Time X group		NS	0.0001	0.006	0.27	0.013		
Two way ANOVA repeated measure analysis with the baseline time (Time X group)		0.787	0.000	0.000	0.000	0.000		

Table (6): Hamilton rating scale for depression

	Prestimulation mean±SD	1st d of stim Mean ±SD	5thd of stim Mean ±SD	10thd of stim Mean ±SD	15 d after stim Mean ±SD	1m after stim Mean ±SD	One way ANOVA repeated measure analysis (Time)	Two way ANOVA repeated measure analysis (Time X group)
Real group	13.3±1.9	13.3±1.9	11.1±1.4	10±1.8	10.06±1.8	11.1±1.8	0.0001	P=0.007 F=4.85
Sham group	13.5±1.5	13.6±1.45	12.4±1.5	12±1.4	12.05±0.88	12.3±0.8	0.001	Df=2.3.7 (66.37)
Two way ANOVA repeated measure analysis at different point of assessment (Time X group		NS	0.037	0.006	NS	0.063		
Two way ANOVA repeated measure analysis with the baseline time (Time X group)		0.326	0.000	0.000	0.000	0.000		

Table (7): Percentage of reduction of all scales used in the study

	Verbal descriptor scale (VDS)			Visual analog scale (VAS)			LANSS scale			Hamilton rating scale for depression (HAM-D)		
	real	sham	p-value	real	sham	p-value	real	sham	p-value	Real	sham	p-value
After 10th session	49.11 ± 18.99	22.78 ± 13.51	0.000	36.67 ± 18.44	15.94 ± 10.03	0.001	21.88 ± 9.37	7.72 ± 12.08	0.001	24.35 ± 10.18	10.63 ± 11.85	0.001
1 m after end of sessions	30.89 ± 14.77	20.78 ± 18.15	0.105	22.70 ± 16.32	15.94 ± 10.03	0.182	18.23 ± 9.99	7.37 ± 11.64	0.011	15.72 ± 9.07	7.96 ±10.44	0.038

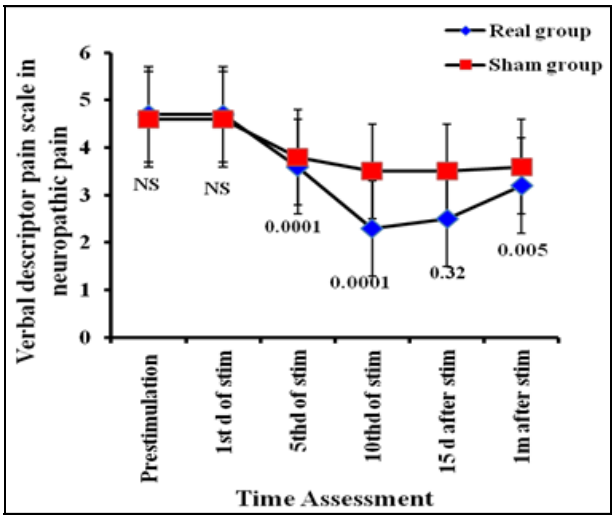

Figure (1): verbal descriptor scale (VDS)

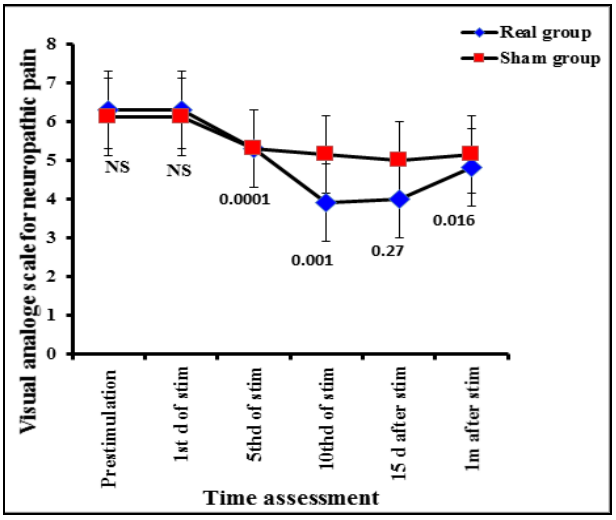

Figure (2): visual analog scale

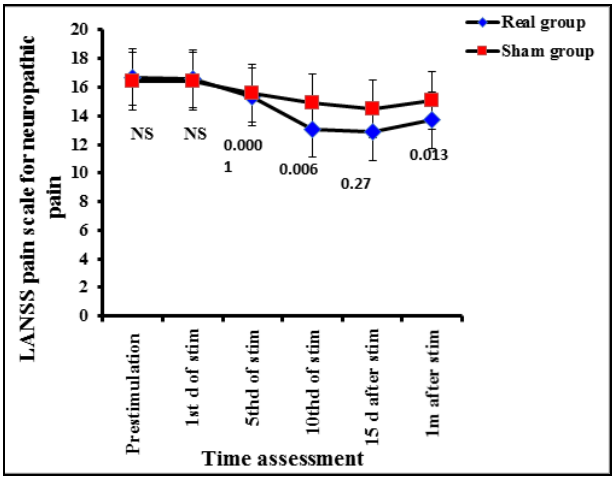

Figure (3): LANSS pain scale

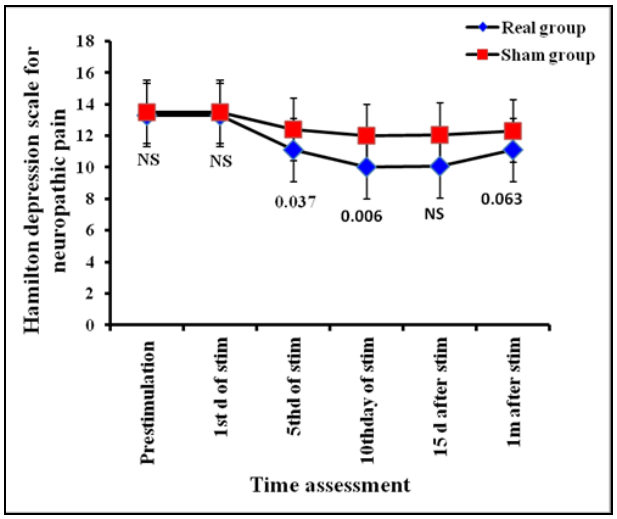

Figure (4): Hamilton rating scale for depression

Discussion

Epidural electrical motor cortex stimulation has been reported to ameliorate symptoms in some patients with intractable chronic pain of central and peripheral origin(13). However, 30% of operated patients fail to respond so that there is need to develop predictive tool to select patients for treatment(14). TMS is a relatively new technology that offers the possibility of testing whether patients will response to direct cortical stimulation by measuring their response to a period of non-invasive cortical stimulation. Repetitively TMS appears to stimulate motor cortex in way similar to that produced by epidural stimulation(15), and can transiently reduce pain in some groups of patients with neuropathic pain(16). Rather than isolated therapy, rTMS should be considered as an add-on treatment, combined with drugs and physiotherapy, to increase the speed and the extent of therapeutic response. This type has been already evaluated in the treatment of depression and stroke rehabilitation(17).

The first study of rTMS in chronic pain was done by Lefaucheur and colleagues in 2001. They did a placebo-controlled study in 18 patients with intractable neurogenic pain and showed that 10 Hz rTMS of the motor cortex induced substantial pain relief (as assessed by visual analogue scale) as compared with sham rTMS(16). 3 years later, the same group confirmed their previous results in a similar study with a larger sample size of 60 patients with intractable central pain(7). Khedr and her colleagues showed that multiple consecutive sessions of rTMS are associated with substantial pain relief in trigeminal neuralgia and central poststroke pain as the percentage of VAS reduction in both real group was 40% compared to the baseline and pain decrease still reduced to weeks after end of sessions(6). Also in complex regional pain syndrome (CRPS) type I, two controlled studies concerning a total of 33 patients showed a significant reduction of pain intensity over a short follow up period after sessions of high frequency rTMS delivered to M1(18,19).

Rollnik and Pridmore's(20) protocol including only one patient with phantom pain and Irlbacher et al.'s study(8) included 14 patients with phantom pain. Both

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reported significant reduction in pain score and second author reported no long-term analgesic effect on rTMS as they used low stimulation frequency (1 and 5 Hz) in comparison to Ahmed et al.' study(21) as they used 20 Hz on larger number of patients they found pain reduction in VAS in the real group decreased by 55% at the end of fifth session, after 1 and 2 month follow up.

The results of our study suggest that rTMS at 20 Hz given every day for 10 sessions can reduce pain rating in patients with malignant neuropathic pain after the end of tenth session and lasts for at least 2 weeks after end of sessions with loss of this effect after one month follow up. This was parallel to other studies on different types of neuropathic pain rather than malignant neuropathic pain. In 2001 Lefaucheur et al. (16) demonstrated that rTMS was able to relieve neuropathic pain when administered over M1 at 10 Hz but not at 0.5 Hz. Andre ´-Obadia et al.(22) also showed that rTMS provided better alleviation of pain at 20 Hz than at 1 Hz and Saitoh et al. (23) found that 10Hz rTMS was more effective than 5Hz rTMS, whereas 1Hz rTMS did not produce significant effects.

In the present study, there were no significant effects on verbal descriptor pain rating scale, VAS or LANSS scores after the first session as the effects built up rather slowly, but quit clear when tested immediately after the 5th session and much greater than the placebo effect of sham stimulation. This is consistent with Lefaucheur et al. (16) original observation that pain relief after a single session was optimal two to four days after rTMS. Pleger et al.(18) recorded some pain relief 30 seconds after rTMS, but this intensified after 45 minutes. The same was seen in Ahmed et al.(21) as they found no significant effect after the first session of rTMS. Since we assessed pain immediately after the first session, we may have missed the time of optimal response. However, by day 5, the effects were clear. Another explanation for the absence of significant pain relief after the first session could be related to the duration of the session in the present study, which was 10 minutes the same in Khedr et al.(6) study as compared with 20 minutes used in some of previous studies(7,24).

Our study shows the analgesic effect reaches the maximum after the end of tenth session and persists for 2 weeks after the end of sessions but not maintained after one month beyond the time of stimulation after rTMS. The same results were reported by Khedr et al.(6) in 2 weeks follow up, Passard et al.(25) in 60 days follow up as they found that the analgesic effect of rTMS continued for 15 days after end of sessions but was not after 30 and 60 days, and also Hosomi et al.(26) demonstrate the positive short term analgesic effect but no cumulative effect on 29 days follow up. However, this was different from Ahmed et al.(21) found that the analgesic effect still present in 1 month and 2 months follow up.

In our study the percentage of reduction in VAS in real group after the 10th session was 36.67 ± 18.44 than the sham group 15.94 ± 10.03 which was statistically significant (p value 0.001). However, these effect was not seen after one month as the percent of reduction in real group was 22.70 ± 16.32 and in sham group was 15.94 ± 10.03 and p value was 0.182. This results come in near to the previous meta-analysis of high frequencies rTMS on primary motor area (M1) for neuropathic pain calculated effect sizes corresponding to a pain reduction on a VAS as Lefaucheur and his colleague reported better results using stimulation of the motor cortex region adjacent to that corresponding to the painful site(27). Khedr et al.(6) found that the main degree of pain reduction was 45% and in Ahmed et al.(21) was 55%. However,it was 12% in Leung et al.(28), 13.7% in O'Connell et al.(29) and 19.7% in Hosomi et al. study(26). The possible explanation as the analgesic effect was not maintained for one month duration or more, may be the nature of malignant disease which is rapidly progressive.

In this study we assessed the Hamilton rating scale for depression in patients studied with neuropathic pain, and we found that there was significant reduction in real group after the 10th session was 24.35 ± 10.18 than the sham group 10.63 ± 11.85 and p value 0.002. Also, these effect was seen after one month as the percent of reduction in real group was 15.72 ± 9.07 and in sham group was 7.96 ± 10.44 and p value was 0.038. O'Reardon et al. reported significantly better clinical results in an active rTMS group in comparison to the sham group, as measured by the Hamilton Rating Scale for Depression (HAM-D) scale and the Montgomery Asberg Depression Rating Scale (MADRS)(30). However, Hosomi and his colleague founded no effect on Beck depression inventory (BDI)(26).

It has been suggested that the underlying pathophysiology of NP is associated with plastic changes and dysfunction of extensive neural circuits in the central nervous system, involving various structures related to pain perception, and with an affective-emotional component(28). The possible mechanisms of action of pain relief following the stimulation of M1, either EMCS or rTMS, are considered to be modulation of neural activity in these structures(27). The process of pain relief obtained by rTMS or EMCS is assumed that the stimuli act locally within M1, representing an entry port point, and modulates the above remote, deep brain structures through the subcortical fibers, increase in the cerebral blood flow in the ipsilatral thalamus, orbitofrontal and cingulate gyri and in upper brain stem during motor cortex stimulation(13,27,31). These hypotheses of cerebral modulation in the various central nervous system structures could explain the effects of rTMS lasting more than 60 min(26).

The mechanisms underlying the analgesic effects elicited by transcranial cortical stimulation of motor cortex are not fully understood yet and the exact nature of the involved pathways remains hypothetical. Raij et al. suggested that in chronic pain there was defective inhibition of M1 lead to pain perception so 20 Hz rTMS restored these defective mechanism and analgesia(32). Others reported that rTMS may increase central nervous system opioids, Maarrawi et al. reported that motor cortex stimulation (MCS) may induce release of endogenous opioids in brain structures involved in the processing of acute and chronic pain(33). Amassian et al. suggested that analgesic effects of rTMS in phantom pain were delivered by increase in the endogenous beta-endorphin release(34). Töpper et al. found that opiate antagonist naloxone abolished the rTMS-induced pain relief which was taken as evidence that the analgesic effect of rTMS acted via the release of endorphins(35). Borckardt et al. also found that a single session of high-frequency rTMS applied immediately after gastric bypass

surgery at 10 Hz over the left DLPFC for a total of 4000 pulses was associated with a 40% reduction in total morphine use during the first 2 days after surgery. This reduction corresponded to the effect of active rTMS minus that of sham stimulation(36,37).

Conclusion

The use of 10 sessions rTMS of 20Hz over the primary motor cortex area can have a beneficial reduction of pain score in malignant neuropathic pain patients and the maximum effect was apparent after the end of 10 sessions and this effect is maintained for 2 weeks follow up after the end of sessions, however this effect is decreased in one month follow up after the end of sessions.

Conflict of Interests

The authors declare that they have no conflict of interests.

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