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The Effect of Transcranial Magnetic Stimulation on Pain Intensity and Opioid Use in Breast Cancer Patients and on Serum Beta-Endorphin Levels: A Randomized Controlled Trial

Nur Surya Wirawan¹, Noor Ramadhaniah¹, A. M. Takdir Musba¹, Muh. Ramli Ahmad¹, Alamsyah Ambo Ala Husain², Madonna Damayanthie Datu¹, Salman Ardi Syamsu³, Nilam Smaradania³

¹Department of Anaesthesiology, Intensive Care, and Pain Management, Medical Faculty, Hasanuddin University/Hasanuddin University Teaching Hospital, Makassar, Indonesia

²Department of Anaesthesiology, Intensive Care, and Pain Management, Medical Faculty, Hasanuddin University/Bhayangkara Hospital, Makassar, Indonesia

³Division of Oncology, Department of Surgery, Medical Faculty, Hasanuddin University/Hasanuddin University Teaching Hospital, Makassar, Indonesia

* Corresponding author: Nur Surya Wirawan

Department of Anaesthesiology, Intensive Care, and Pain Management, Medical Faculty, Hasanuddin University/Hasanuddin University Teaching Hospital, Makassar, Indonesia
Tel: +62- 811466603

E-mail: acoanestesi@yahoo.com

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ABSTRACT

Background: Cancer patients commonly experience pain. Advanced breast cancer patients experience pain due to the involvement of other structures, as well as due to the cancer treatment. Transcranial magnetic stimulation is a new non-invasive brain stimulation method for pain management. This treatment has been proven to decrease the visual analogue scale pain score and to increase the serum beta-endorphin level in other chronic pain patients. **Objective:** To study the effect of transcranial magnetic stimulation on pain intensity, opioid usage, and serum beta-endorphin levels in breast cancer patients.

Design: Prospective, randomized controlled trial.

Setting: University Hospital

Patients: Forty admitted and outpatient breast cancer patients, divided into groups P1 and P2.

Intervention: The P1 group received 10-Hz transcranial magnetic stimulation for 20 minutes, at 80% of the motor threshold, with 100 pulses/train to 20 pulses/session, and with a 50 second intertrain interval. The P2 group was the control group. Five sessions of transcranial magnetic stimulation were administered, with one session per day, by a researcher or assistant.

Main outcome measures: After five sessions or at the end of the session, the pain intensity of patients was re-examined using a numerical rating scale, and the opioid usage and the serum beta-endorphin level in the blood post-treatment was documented.

Results: The decrease in the numeric rating scale score was larger in group P1 than in group P2 ($p < 0.001$). Opioid usage was less in group P1 than P2 ($p < 0.024$). Moreover, serum beta-endorphin levels had increased in group P1 as compared to group P2 ($p < 0.001$).

Conclusions: Transcranial magnetic stimulation can decrease the pain intensity and opioid usage, and increase the serum beta-endorphin level in patients with breast cancer-related pain.

Trial registration

Clinicaltrials.gov identifier:

Keywords: beta-endorphin, cancer pain, numerical rating scale, opioid, SMT, transcranial magnetic stimulation

Introduction

Cancer is one of the main causes of morbidity and mortality in the world, with 18.1 million new cases and about 9.6 million deaths reported in 2018. More than 55% of patients undergoing cancer treatment and 66% of those in advanced or terminal cancer stages, or with metastasis, complain of pain. In advanced breast cancer stages, the pain becomes excruciating because of the involvement of internal structures, such as muscles and ribs, during respiratory movement of the chest. Chemotherapy causes afferent nerve degeneration, resulting in neuropathic pain, while radiation causes microvascular and nerve compression. Surgery may also cause discomfort if there is damage to the intercostobrachial nerve and if a neuroma forms.¹

Beta-endorphin causes analgesia by inhibiting substance P, a pain neurotransmitter, by binding to presynaptic receptors of peripheral nerves. After binding to receptors in the central nervous system, beta-endorphin produces euphoria and analgesia by inhibiting the neurotransmitter gamma-aminobutyric acid (GABA) and stimulating dopamine release.²

Transcranial magnetic stimulation (TMS) is a relatively new, non-invasive brain stimulation method for neuropsychiatric disorders, which has been shown to have utility in the management of cancer and cancer-related pain.^{3,4} TMS reduced visual analogue scale (VAS) scores and patient dysesthesia post-chemotherapy, improved cognitive dysfunction caused by chemotherapy, and increased the 1-year overall survival in cancer patients.^{5–7} In a study of patients with unilateral amputation, who had chronic phantom pain, TMS reduced VAS pain scores and Leeds Assessment of Neuropathic Symptoms and Signs, and increased serum beta-endorphin serum levels, as compared to pre-TMS, as well as compared to a non-TMS control group.⁸

We here analysed the effects of TMS on pain intensity, opioid usage, and serum beta-endorphin levels in breast cancer patients.

Methods

Ethical approval

This study was approved by the Ethical Committee of Human Biomedical Research (number 172. 1UN4.6.4.5.3U PP36/2022 and protocol UH22030114) of the Hasanuddin University Faculty of Medicine. All the patients received a verbal explanation prior to enrolment and signed a consent form to participate in the study voluntarily.

Study design

This prospective, randomized controlled trial, with a pre-test–post-test design, was conducted in the outpatient clinic at Hasanuddin University Hospital, Makassar, Indonesia, and started on April 20, 2022, until the sample number sufficed .

Population and sample

The study population comprised to admitted and outpatient breast cancer patients attending Hasanuddin

University Hospital. Forty patients who fulfilled the inclusion criteria of being 19–60 years old, used analgesics combined with opioids for pain, and agreed to enrol in the study, were included. Exclusion criteria were as

follows: current chemotherapy treatment containing alkaloids vinca, taxane, platinum-based preparations; electrodes implanted inside the head; cochlear implants; history of head trauma, seizure, or syncope; brain lesions, being on drug withdrawal; or who were pregnant during the study period. Patients were also excluded if problems arose, if a patient left the study, or when insufficient blood samples for evaluating serum beta-endorphins were obtained.

Study protocol

Patients rated their pain intensity using the numerical rating scale (NRS score). Their opioid usage was recorded, and blood samples for measuring the serum beta-endorphin level were obtained at baseline. Patients were then randomly divided into two groups. Group P1 received TMS at a frequency of 10 Hz, intensity of 80% of motor threshold (MT), with 100 pulses/train and 20 pulses/session, with an intertrain interval of 50 seconds, for 20 minutes. A figure-of-8 coil was used to deliver stimulation at M1. Five sessions of TMS were delivered, at one session per day, by a researcher or assistant. Group P2 was the control group. All patients in both groups continued analgesic treatment according to their therapeutic dose. After 5 sessions, patients were re-examined for pain intensity using the NRS, their opioid usage, and serum beta-endorphin levels.

Data analysis

Data were analysed using SPSS software (IBM Inc., Armonk, NY, USA). Numerical data are shown as mean and standard deviation or median (minimum to maximum range), while categorical data are shown as percentages. The normality of data distribution was measured by the Shapiro–Wilk test. Between-group differences were compared by independent *t*-tests if the data were normally distributed; alternatively, the Wilcoxon test was used. Pre–post differences were evaluated with the paired *t*-test if the data were normally distributed, or alternatively with the Mann–Whitney U-test. Spearman’s correlation coefficient was used to measure correlation strength among variables. $P < 0.05$ was considered statistically significant.

Results

Sample characteristics

There was no significant difference between groups P1 and P2 in terms of age ($p = 0.091$), body weight ($p = 0.756$), height ($p = 0.495$), or body mass index ($p = 0.738$), indicating homogeneity of the groups (Table 1).

Pain intensity

The NRS score was decreased in the intervention group (P1) after treatment, and was 2.00 (0 to 3) points less than that in the control group (P2) at this time-point (Table 3), which was statistically significant ($p < 0.001$).

Opioid usage

The use of opioids before and after TMS was compared by non-parametric tests (Tables 4 and 5). There was no significant difference in opioid usage between the groups at baseline. However, opioid usage was statistically significantly reduced after TMS in group P1 ($p = 0.004$), while it remained unchanged in group P2 ($p = 0.321$).

Beta-endorphin levels

Serum beta-endorphin levels pre-stimulation were higher in the TMS-treated group (52.69 [25.09 to 180.08]) than in the control group (41.69 [25.91 to 73.60]) (Table 6). Post-stimulation, group P1 showed further increased beta-endorphin serum levels (65.16 [26.05 to 265.28]), whereas the levels in group P2 had decreased as compared to pre-stimulation (37.05 [25.10 to 61.42]). The increase in serum beta-endorphin levels after intervention in group P1 was statistically significant by the Wilcoxon test ($p = 0.004$). The amount of change in serum beta-endorphin levels were significantly different between the groups ($p < 0.01$).

Correlation of pain intensity with serum beta-endorphin levels in breast cancer patients

According to the Spearman correlation test, there was a strong negative correlation between pain intensity and changes in the beta-endorphin serum level ($r = -0.630$; $p < 0.001$), with a decrease in the pain intensity (NRS score) with the increase in beta-endorphin levels.

Discussion

We here showed that five sessions of TMS led to significant reduction in the pain intensity of and opioid use by breast cancer patients, and also increased their serum beta-endorphin levels significantly.

Pain intensity comparison

Use of TMS for chronic neuropathic pain is increasingly popular due to its non-invasive nature. Single or multiple sessions of TMS with a high frequency to M1 have been shown to reduce pain intensity significantly. Multiple sessions with TMS result in longer-term pain reduction than once-off sessions.⁹

To date, the mechanism underlying the analgesic effect of TMS has remained unclear. One of the hypotheses about its analgesic mechanism is that it non-invasively induces brain plasticity, thus correcting or modulating changes related to chronic pain. According to a meta-analysis by Leung et al., TMS can significantly reduce neuropathic pain.¹⁰

Our results were similar to those of a pilot study by Goto *et al.*,¹¹ who used TMS in breast or gynaecological cancer patients suffering from chronic neuropathic pain induced by chemotherapy, and showed that it reduced pain intensity and dysesthesia. TMS has also been proven to reduce other forms of chronic pain.¹² Several studies have indicated that the underlying mechanism involves modulation of beta-endorphin.^{13,14}

Use of opioids

The use of opioids and analgesic combinations was reduced after TMS in the intervention group. Additionally, the intervention group used less opioid and analgesic combinations than the control group after completing TMS. This was similar to many previous studies that showed the efficacy of TMS in reducing pain intensity indirectly

results in reduced use of analgesics, mainly opioids.^{11,12} Moreover, TMS has even been proven to reduce the severity of addiction and opioid use disorder.¹³

In a case study by Nizard *et al.*,⁵ TMS was used as an adjuvant treatment for two cancer patients; one with rectal adenocarcinoma with liver and lung metastasis, and the second with T-cell lymphoma. They found that, after initial TMS, the first patient experienced a reduction in pain intensity and an improvement in the Medical Qualification Scale (MQS) from 126 to 56. TMS was continued for up to four sessions in total to retain these effects. In the second patient, with five sessions of TMS, there was an improvement in the MQS score from 12 to 4. The MQS score is normally used for measuring analgesic consumption and co-analgesics in patients with chronic pain, according to the drug's class and daily dose.

Taken together, TMS, besides being able to reduce pain intensity, is also able to reduce use of analgesics, including opioids. This may be due to several processes, including modulation of endogenous opioids, including beta-endorphin.

Comparison of serum beta-endorphin levels

In this study, TMS was found to increase serum beta-endorphin levels in breast cancer patients. Another study found a similar result: serum beta-endorphin levels were increased in patients who suffered from migraine and phantom pain, even in the obese population, after TMS.^{13,14}

For more than 30 years, the use of non-invasive brain stimulation for chronic pain has been studied. There are many neurotransmitters involved in chronic pain and nociception modulation, which work in the brain stem and spinal cord. One of these is beta-endorphin, an endogenous opioid that has a morphine-like effect and is also 18–33 times more potent than morphine.¹⁵

Ahmed *et al.*⁹ found that 17 of 27 patients with chronic phantom pain after amputation, who received TMS for 5 consecutive days, experienced long-lasting analgesic effects (for 2 months after the last TMS intervention). They also noted that there was a significant increase in serum beta-endorphin, while the placebo group showed no change in serum beta-endorphin levels. Thus, serum beta-endorphin can be used as an indicator that TMS is able to increase central nervous system levels of endorphins.

Misra *et al.*¹⁶ in 2013 compared patients with migraine with healthy patients. Migraine patients were given TMS intervention for 3 days (10 Hz, MT 70%, 600 pulses) at M1. Patients with migraine had lower beta-endorphin levels than did healthy patients prior to intervention. Moreover, beta-endorphin levels were lower in patients with chronic migraine than in those with episodic migraine. Patients were evaluated with VAS prior to intervention, and each week after intervention, for 4 weeks, and serum beta-endorphin levels were measured before and after the intervention. They found a clinical improvement, as shown by a decrease in the VAS score in migraine patients, along with an increase in beta-endorphin levels, which was more notable in chronic migraine patients. The pain-relieving effect of TMS delivered at M1 depends on the activation of the descending pain pathway from the brain stem (periaqueductal grey and rostral ventrolateral medulla), as proven by analgesia reversal with

naloxone. There is a high concentration of opioid receptors in this area, and they play a role in pain modulation, as examined in a neuroimaging study.¹³

Pain intensity correlation with serum beta-endorphin levels

In this study, changes in pain intensity were negatively correlated with changes in beta-endorphin levels. According to Ahmed *et al.*,⁸ serum beta-endorphin levels in patients with phantom pain were markedly higher after than before TMS intervention. The VAS score also decreased by 55% from that measured after the 5th intervention and remained low after 1–2 months after the last intervention.

Mirsa *et al.*,¹² in 2017 studied migraine patients who had experienced four migraine attacks in a month, and who were divided into three TMS groups: three TMS sessions, one TMS session, and two placebo sessions. The VAS score was measured before intervention and 1 month after intervention, while beta-endorphin was measured before and after sessions. The VAS was improved in the three-sessions group, who also showed increased beta-endorphin levels. Additionally, the elevation of serum beta-endorphin above 4 ng/ml was able to improve the headache incident rate in > 80% of these patients.

This study had some limitations. The sample size was small, and the study findings should be verified in a much larger sample. Additional factors may need to be incorporated in such a study, and the effects in other types of cancer should be investigated.

Conclusions

TMS decreased the pain intensity and the use of analgetic drugs, particularly use of opioids, and also increased serum beta-endorphin levels, in breast cancer patients.

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Table 1. Sample characteristics

Characteristics	Group				p
	P1 (Intervention Group)		P2 (control group)		
	Mean ± SD	Median [min to max]	Mean ± SD	Median [min to max]	
Age (years)	48.40 ± 8.98	49 [28 to 60]	44.55 ± 9.13	41.5 [32 to 60]	0.091
Body weight (kg)	51.15 ± 8.00	50 [32 to 65]	51.85 ± 5.98	50.5 [40 to 65]	0.756
Height (m)	1.54 ± 0.06	1.53 [1.47 to 1.70]	1.55 ± 0.04	1.55 [1.50 to 1.60]	0.495
Body mass index (m/kg²)	21.39 ± 3.04	21.87 [14.22 to 27.06]	21.56 ± 2.02	21.56 [16.65 to 25.39]	0.738

p < 0.05 was significant, by the Mann–Whitney U-test.

Table 2. Comparison of changes in pain intensity in each group

Group	Time-point	n	NRS		p
			Median [min to max]		
			Δ NRS		
P1	Pre	20	7.00 [5 to 9]	-4.50 [-3-to -7]	< 0.001 †
	Post	20	2.50 [1 to 4]		
P2	Pre	20	5.50 [4 to 7]	-2.00 [0 to -3]	< 0.001 †
	Post	20	4.00 [2 to 5]		

†significant, p < 0.05, by Wilcoxon test

NRS, numerical rating scale score

Table 3. Differences in changes in pain intensity (NRS) between groups

Group	N	Δ NRS		p
		Median [min to max]		
		Score		
P1	20	-4.50 [-3 to -7]		<0.001 [†]
P2	20	-2.00 (0 to -3]		

†significant, p < 0.05, by Mann–Whitney U-test

Table 4. Comparison of pre- and post-stimulation opioid requirements between groups

Group	Opioid use pre-stimulation		Opioid use post-stimulation	
	(milligrams morphine)		(milligrams morphine)	
	Median [min to max]	P	Median [min to max]	p
P1	15 [10 to 80]	0.398	0 [0 to 45]	0.024†
P2	20 [10 to 30]		20 [0 to 30]	

†significant, p < 0.05, by Mann–Whitney U-test

Table 5. Comparison between the use of opioids pre- and post-stimulation within each group

Group	Opioid use pre-	Opioid use post-	P
	stimulation	stimulation (milligrams	
	(milligrams morphine)	morphine)	
	Median	median	
	[min to max]	(min-max)	
P1	15 [10 to 80]	0 [0 to 45]	0.004†
P2	20 [10 to 30]	20 [0 to 30]	0.321

†significant, p < 0.05, by Wilcoxon test

Table 6. Comparison of beta-endorphin serum levels within each group

Groups	Time-point	n	Beta-endorphin level	P
			Median [min to max]	
P1	Pre	20	52.69 [25.09 to 180.08]	<0.001†
	Post	20	65.16 [26.05 to 265.28]	
P2	Pre	20	41.69 [25.91 to 73.60]	0.004†
	Post	20	37.05 [25.10 to 61.42]	

†significant, p < 0.05, by Wilcoxon test

Table 7. Comparison of change in serum beta-endorphin levels between groups

Groups	n	Change in serum beta- endorphin level	P
		Median [min to max]	
P1	30	7.52 [0.96 to 85.19]	<0.001†
P2	30	-4.28 [-6.79 to 12.36]	

†significant, p < 0.05, by Mann–Whitney U-test

Figure Legends

Figure 1 Comparison of pain intensity (numerical rating scale score [NRS]) at pre- and post-stimulation in breast cancer patients in each group

Figure 2 Comparison of serum beta-endorphin levels between pre- and post-stimulation in breast cancer patients in each group