

Effectiveness and safety of repetitive transcranial magnetic stimulation for the treatment of morphine dependence

A retrospective study

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Abstract

Morphine dependence (MD) is a very common complication because of the chronic morphine consumption. Studies suggest that repetitive transcranial magnetic stimulation (rTMS) can be used for the treatment of MD. However, there is still lacking evidence to support rTMS for MD. Thus, this retrospective study aimed to investigate the effectiveness and safety of rTMS for patients with MD.

In this retrospective study, a total of 100 patients with MD were included, and they were divided into a rTMS group (n=50), and a control group (n=50). All patients in both groups received occupational therapy. In addition, patients in the rTMS group received rTMS. All patients in both groups received a total of 8 weeks treatment. The outcomes comprised of morphine craving intensity, depression, anxiety, and sleep quality, which were appraised by Visual Analogue Scale (VAS), Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), and Pittsburgh Sleep Quality Index (PSQI), respectively. In addition, treatment-related adverse events were also considered for assessment.

After 8 weeks treatment, patients in the rTMS group exerted better benefits in improving VAS ($P < .01$), SDS ($P < .01$), SAS ($P < .01$), and PSQI ($P < .01$), than patients in the control group. In addition, this study did not identify treatment-related adverse events in both groups.

The findings of this study showed that rTMS treatment showed promising effectiveness on patients with MD. However, future studies should focus on warranting the present findings.

Abbreviations: MD = morphine dependence, PSQI = Pittsburgh Sleep Quality Index, rTMS = repetitive transcranial magnetic stimulation, SAS = Self-Rating Anxiety Scale, SDS = Self-Rating Depression Scale, VAS = Visual Analogue Scale.

Keywords: morphine dependence, repetitive transcranial magnetic stimulation, effectiveness, safety

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1. Introduction

Opioid analgesics are one of the most frequently prescriptions globally.^[1,2] It is also the most powerful analgesics for pain management.^[3–5] However, its long-term usage accompanies a lot of serious comorbidities, including hyperalgesia, and addiction.^[6,7] In addition, it is also associated with dependence, tolerance, immunosuppression, and gastrointestinal disorders.^[8–10]

Morphine is an opioid medication.^[11,12] It acts directly on the central nervous system to relieve both acute and chronic severe pain.^[13,14] It can be taken by mouth, injection to the muscle, skin, and intravenous injection.^[15–19] It is a highly addictive substance, and people who administrated morphine are more likely to develop morphine dependence (MD).^[20–22] If such condition can not be managed effectively, it may cause very severe and poor quality of life in patients with MD.

Repetitive transcranial magnetic stimulation (rTMS) is a form of noninvasive brain stimulation, based on the induction of neuromodulation and electromagnetic phenomena.^[23–25] It is reported that rTMS implicates a series of short magnetic pulses that directly implements brain nerve cells. Studies suggested that rTMS can be utilized for the treatment of MD. However, there is still insufficient supporting evidence. Thus, this retrospective study aimed to investigate the effectiveness and safety of rTMS for the treatment of MD.

2. Methods

2.1. Study design

This retrospective study was conducted at the First Affiliated Hospital of Jiamusi University between January 2018 and May 2020. We included a total of 100 patients with MD. Those patient cases were divided into a rTMS group and a control group according to the different treatments they received, each group 50 patients. They all received occupational therapy in both groups. In addition, 50 patients also underwent rTMS. Written informed consent was obtained from all eligible patients.

2.2. Ethical approval

This study was approved by the Medical Ethics Review Board of the First Affiliated Hospital of Jiamusi University, and it only analyzed data from completed patient records.

2.3. Patients

All included patients who were diagnosed as MD were included in this retrospective study, based on the diagnostic criteria of DSM-IV opioid dependence. All eligible patients aged between 18 and 65 years old. All of them received long-term use of morphine, or long-term use of heroine that is metabolized into morphine (diacetylmorphine). In addition, all included patients completed the study treatment.

Patients were excluded if they met the following criteria:

1. acute opioid withdrawal period;
2. severe nervous system or mental diseases caused by other diseases than chronic opioid dependence;
3. history of brain trauma or brain injury;
4. have history of neurological diseases;
5. family history of mental diseases; and
6. taking any psychotropic drugs or dependent on drugs or other substances.

2.4. Treatment schedule

All participants in both groups received occupational therapy, once daily, 5 days weekly for a total of 8 weeks. In addition, the participants in the rTMS group received rTMS treatment, 1 session daily, 5 sessions weekly for a total of 8 weeks. Each session was applied for 20 minutes at 20 Hz and 100% intensity, with stimulation period of 5 seconds, and stimulation interval of 15 seconds. In the control group, all subjects did not receive rTMS.

2.5. Outcome measurements

The outcomes include morphine craving intensity, depression, anxiety, and sleep quality. The morphine craving intensity was assessed by Visual Analogue Scale (VAS). It ranges from 0 (no craving need) to 10 (strongest craving intensity).^[26] The depression was measured by Self-Rating Depression Scale (SDS).^[27] It varies between 20 and 80, with higher score indicating more severity of depression. The anxiety was evaluated by Self-Rating Anxiety Scale (SAS),^[28] and the sleep quality was appraised by Pittsburgh Sleep Quality Index (PSQI).^[29] SAS ranks from 20 to 80, with higher score meaning poorer anxiety. PSQI ranges from 0 to 21, with the higher score suggesting poorer sleep quality. All outcomes were assessed after 8-week treatment.

2.6. Statistical analysis

This study utilized SAS package (Version 9.1; SAS Institute Inc., Cary, North Carolina) for data analysis. All continuous data were analyzed using *t* test or Wilcoxon test, while all categorical data were analyzed using the Pearson Chi-Squared test or Fisher exact test. Statistical significance was defined as the value of $P < .05$ (2-side).

3. Results

In this retrospective study, we included 100 eligible patients with MD. Of those, 50 patients who received rTMS were assigned to the rTMS group, while the other 50 subjects who did not undergo rTMS were allocated to the control group. We have summarized the baseline demographics and clinical characteristics of both groups in a Table 1. No significant differences were detected in those baseline demographics and clinical characteristics between 2 groups.

Before treatment, there were not significant differences in VAS ($P = .91$, Table 2), SDS ($P = .22$, Table 3), SAS ($P = .91$, Table 4), and PSQI ($P = .70$, Table 5) between 2 groups.

After 8-week treatment, the patients in the rTMS group exerted better outcomes in VAS ($P < .01$, Table 2), SDS ($P < .01$, Table 3), SAS ($P < .01$, Table 4), and PSQI ($P < .01$, Table 5), than those of patients in the control group. As for safety, no treatment-related adverse events were reported in both groups in this study.

4. Discussion

Opioid analgesics are very common prescriptions for pain management in the clinical practice.^[1–5] It can not only help relieve a variety of acute and chronic pain conditions, but also accompanies various serious adverse events, such as addiction and dependence.^[6,7] Of those, MD is a very tricky disorder,^[20–22] which results from chronic morphine consumption. Thus, it is very important to explore alternative therapy with fewer additional adverse events for MD treatment.

Table 1

Comparison of patient characteristics between 2 groups.

Characteristics	rTMS group (n=50)	Control group (n=50)	P
Mean age (year)	33.8 (7.5)	36.2 (8.0)	.12
Gender			
Male	36 (72.0)	39 (78.0)	.49
Female	14 (28.0)	11 (22.0)	-
Ethnicity	50 (100.0)	50 (100.0)	-
Education background			
Elementary school or below	21 (42.0)	24 (48.0)	.55
Secondary school	16 (32.0)	20 (40.0)	.41
High school	7 (14.0)	4 (8.0)	.34
College or university	6 (12.0)	2 (4.0)	.16
Employment	35 (70.0)	32 (64.0)	.52
Unemployment	15 (30.0)	18 (36.0)	-
Marriage status			
Single	11 (22.0)	15 (30.0)	.36
Married	27 (54.0)	22 (44.0)	.32
Divorced	12 (24.0)	13 (26.0)	.82
Drug abuse			
Duration (year)	6.8 (3.6)	7.1 (3.3)	.66
Initial age (year)	26.4 (6.7)	28.1 (7.0)	.21
Frequency (times/weekly)	2.7 (1.1)	2.9 (0.8)	.30

Data are present as mean ± standard deviation or number (%).

rTMS = repetitive transcranial magnetic stimulation.

Table 2**Comparison of morphine craving intensity between 2 groups.**

VAS	rTMS group (n=50)	Control group (n=50)	P
Before treatment	7.95 (3.12)	8.02 (3.04)	.91
After treatment	1.79 (1.53)	5.10 (2.08)	
Change from prior treatment	6.15 (4.49, 7.95)	2.94 (2.01, 4.06)	
Difference		3.21 (2.43, 4.15)	<.01

Data are present as mean ± standard deviation (range).

rTMS = repetitive transcranial magnetic stimulation, VAS = Visual Analogue Scale.

Table 3**Comparison of depression between 2 groups.**

SDS	rTMS group (n=50)	Control group (n=50)	P
Before treatment	69.47 (7.39)	71.40 (8.42)	.22
After treatment	39.73 (8.92)	54.56 (9.26)	
Change from prior treatment	29.74 (22.16, 36.44)	16.84 (13.43, 21.25)	
Difference		12.90 (9.25, 15.30)	<.01

Data are present as mean ± standard deviation (range).

rTMS = repetitive transcranial magnetic stimulation, SDS = Self-Rating Depression Scale.

Studies reported that rTMS can benefit patients with MD. However, currently, there is still insufficient evidence of rTMS for the management of MD. This retrospective study included 100 eligible patients with MD, and they were equally allocated into a rTMS group and a control group. We evaluated its effectiveness through the enhancement of morphine craving intensity, depression, anxiety, and sleep quality. The result of this retrospective study found that patients in the rTMS group showed more effectiveness in VAS, SDS, SAS, and PSQI, than those of patients in the control group. It indicates that rTMS may benefit for the management of MD.

There are several shortcomings in this retrospective study. Firstly, this retrospective study only appraised its effectiveness and safety within 8-week treatment period. No longer term follow-up data was recorded after the present treatment. Second,

this retrospective study did not utilize randomization and blinding approach to both patients and researchers, which may increase risk of patient selection. Third, this retrospective study had its intrinsic limitation, which may affect its findings. Finally, this retrospective study documented limited outcome measurements to assess its effectiveness and safety. Future studies should focus on more comprehensive outcome indicators.

5. Conclusion

This study found that rTMS may benefit patients with MD. Future clinical trials with high quality are still needed to warrant the present findings.

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Table 4**Comparison of anxiety between 2 groups.**

SAS	rTMS group (n=50)	Control group (n=50)	P
Before treatment	24.01 (5.18)	23.89 (5.25)	.91
After treatment	12.37 (4.20)	16.52 (5.30)	
Change from prior treatment	11.64 (9.55, 13.81)	7.37 (5.24, 9.37)	
Difference		4.28 (3.15, 5.44)	<.01

Data are present as mean ± standard deviation (range).

rTMS = repetitive transcranial magnetic stimulation, SAS = Self-Rating Anxiety Scale.

Table 5**Comparison of sleep quality between 2 groups.**

PSQI	rTMS group (n=50)	Control group (n=50)	P
Before treatment	12.47 (1.75)	12.60 (1.62)	.70
After treatment	7.18 (1.93)	9.66 (2.01)	
Change from prior treatment	5.29 (4.31, 6.40)	2.94 (2.10, 3.88)	
Difference		2.35 (1.89, 2.73)	<.01

Data are present as mean ± standard deviation (range).

rTMS = repetitive transcranial magnetic stimulation, PSQI = Pittsburgh Sleep Quality Index.

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