Randomized Trial

Repetitive Transcranial Magnetic Stimulation at Different Frequencies for Postherpetic Neuralgia: A Double-Blind, Sham-Controlled, Randomized Trial

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Background: Repetitive transcranial magnetic stimulation (rTMS) at 5 Hz and 10 Hz is effective in improving pain, sleep quality, and anxiety among patients with postherpetic neuralgia (PHN). But it has not been reported which frequency is more effective and which frequency is safer.

Objectives: This study aimed to observe the efficacy and safety of rTMS at different high frequencies (5 Hz, 10 Hz) for PHN.

Study Design: The design of the study was a prospective randomized, controlled clinical trial.

Setting: The research was conducted within a department of pain management at a university hospital in China.

Methods: Sixty patients with PHN who were treated at the Department of Pain Management at Xuanwu Hospital of Capital Medical University were recruited. Using a computer-created number list, the cases were equally divided into 3 groups (n = 20), namely, the sham rTMS group, 5-Hz rTMS group, and 10-Hz rTMS group. The sham rTMS group received sham stimulation, and the other 2 groups received high-frequency (5-Hz and 10-Hz) rTMS, respectively. The primary motor cortex (M1) on the healthy side was stimulated with an intensity of 80% transcranial magnetic stimulation (RMT). For the 5-Hz rTMS group, each stimulation session consisted of a series of 300 one-second pulses with a frequency of 5 Hz and an interval of 2.5 seconds between each train, giving a total of 1500 pulses per session. For the 10-Hz rTMS group, each stimulation session consisted of a series of 300 0.5-second pulses with a frequency of 10 Hz and an interval of 3 seconds between each train, giving a total of 1500 pulses per session; the total time of stimulations was 17.5 minutes. rTMS was performed once daily for 10 days. The 3 groups received conventional medication therapy. Baseline data (gender, age, course of disease, affected side) were recorded in the 3 groups. At different time points (before treatment, T0; during treatment, T1-T10; 1 month after treatment, T11; and 3 months after treatment, T12), the patients were evaluated on the following scales: Visual Analog Scale (VAS), short-form McGill Pain Questionnaire (SF-MPQ), Quality of Life (QOL) scale, sleep quality (SQ) scale, Self-Rating Depression Scale (SDS), Patient Global Impression of Change (PGIC), and incidence of adverse events.

Results: Compared with the sham rTMS group, there was a significant reduction in VAS scores in the 5-Hz rTMS group and 10-Hz rTMS group at T2-T12 ($P < .05$). VAS scores in the 10-Hz rTMS group at T7-T12 were significantly lower compared with the 5-Hz rTMS group ($P < .05$). The average VAS reduction was significantly different between the 5-Hz and 10-Hz rTMS groups; 28.3% (95% confidence interval [CI],19.48%-49.35%), compared to 39.89% (95% CI, 22.47%-58.64%), with ($F = 5.289$, $P = .022$). The 3 groups did not differ significantly in general SF-MPQ, QOL, SQ, SDS, and PGIC scores. However, the QQL, SQ, and PGIC scores of the 5-Hz rTMS group and the 10-HZ rTMS group at T12 were significantly higher than that of the sham rTMS group.

Limitations: The study's follow-up period was limited to 3 months.

Conclusions: rTMS at either frequency, 5 Hz or 10 Hz, relieved PHN and improved the patients'

quality of life. rTMS at 10 Hz was superior to rTMS at 5 Hz in terms of pain relief, quality of life, and improvement in sleep quality, though the latter had higher safety. rTMS at either 5 Hz or 10 Hz can be used as an adjuvant therapy for PHN.

Key words: Repetitive transcranial magnetic stimulation, postherpetic neuralgia, pain evaluation

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Postherpetic neuralgia (PHN) is a chronic neuropathic pain syndrome persisting for over 3 months in the affected area following herpes zoster. PHN is usually accompanied by anxiety, depression, and disappointment, which severely affects quality of life (1). However, the pathogenesis of PHN is not fully clarified, and no effective therapy is yet available (2). Medication and nerve ablation are the most common therapies in clinical practice. Although these therapies can partially relieve the pain, they may cause considerable side effects and bring about high risks and complications (3). Therefore, therapies that can relieve neuropathic pain noninvasively without causing severe side effects are favored. Transcranial magnetic stimulation (TMS) is a painless and noninvasive therapy in which magnetic signals stimulate the cranial nerves after passing freely through the skull without attenuation (4). Clinical practice has demonstrated that TMS applies not only to cranial stimulation, but also to the simulation of peripheral nerves and muscles. Along with these technical developments, repetitive TMS (rTMS) has emerged and has been widely applied to clinical psychiatry, neurologic disorders, and rehabilitation (5-7). The existing studies have proven that rTMS at 5 Hz and 10 Hz is effective in improving pain, sleep quality, and anxiety of patients with PHN (8-9). But it has not been reported which frequency is more effective and which frequency is safer. At present, there are no standard parameters of rTMS for PHN. In this study, 3 treatment schemes, namely, sham stimulation, rTMS at 5 Hz, and rTMS at 10 Hz, were employed for patients with PHN. The efficacy and safety of these treatments were compared so as to provide reference for rTMS treatment.

Methods

Experimental Design

A RCT (randomized clinical trial) design was adopted. The present study was a prospective single-center RCT undertaken by the Department of Pain Management at Xuanwu Hospital of Capital Medical University.

Patients

Patients with PHN who were receiving treatment at the Department of Pain Management, Xuanwu Hospital of Capital Medical University, were recruited. The inclusion criteria were as follows: aged above 50 years old, conforming to the diagnostic criteria of PHN, PHN lasting for over one month, Visual Analog Scale (VAS) scores above 4, and having clear consciousness. Those with a personal or family history of epilepsy; history of craniocerebral surgery; intracranial implants; cardiac pacemakers; heart, liver, or kidney insufficiency; and coagulation disorders were excluded. The patients will be quit at any time once they were no longer fit for further treatment due to severe complications, special physiological changes, or nontreatment factors; or upon the request of the patients or their guardians; no longer fit for further treatment due to severe complications, special physiological changes, or nontreatment factors; or upon the request of the patients or their guardians.

This study was approved by the ethical committee of the faculty of medicine. Before the formal experiment, patients were fully informed of the treatment procedures and signed the informed consent. Patients were randomly allocated to 3 groups by using a computer-created number list, which was concealed in sealed envelopes without blocking, and they were opened by the researcher before application of the procedure.

Treatment Schemes

The patients were randomly divided into 3 groups: the sham rTMS group, 5-Hz rTMS group, and 10-Hz rTMS group. All 3 groups first received a nerve block or medication therapy. For the nerve block, the segment to be blocked was first determined according to the position of pain. Those with headache and facial pain received a nerve trunk block; those with pain in

the chest, back, and lumbar regions received a paravertebral block. After locating the segment to be blocked, a 20-mL mixture of 10 mg triamcinolone acetonide and 2.5 mL of 2% lidocaine was given. The nerve block was performed once weekly. Oral drugs prescribed included gabapentin, tramadol, and mecobalamin. Other analgesics, such as tylox and bulleyaconitine, were also administered twice daily if necessary.

In addition to nerve block or medication, all 3 groups also received rTMS at the same time of the day. rTMS was performed using a transcranial magnetic stimulator (Yiruide CCY-III, Wuhan, Hubei, China). The treatment parameters were as follows:

Sham rTMS group: Stimulation was performed using a fake magnetic stimulation coil, which produced the same sound as the real stimulation coil, but no magnetic field, and hence no stimulation effect.

5-Hz rTMS group: The stimulation frequency was -5 Hz, and the stimulation intensity was -80% motor threshold (MT), with the total number of pulses at 1500. The primary motor cortex (M1) on the healthy side was stimulated. The total duration of stimulations was 17.5 minutes. The duration of each stimulation was 1 second and the interval between 2 stimulations was 2.5 seconds. The number of stimulations was 300. rTMS was performed for 15 days consecutively, once daily. The medication scheme remained constant during rTMS.

10-Hz rTMS group: The stimulation frequency was -10 Hz, and the stimulation intensity was -80% MT, with the total number of pulses at 1500. M1 on the healthy side was stimulated. The total duration of stimulations was 17.5 minutes. The duration of each stimulation was 0.5 seconds and the interval between 2 stimulations was 3 seconds. The number of stimulations was 300. rTMS was performed for 15 days consecutively, once daily. The medication scheme remained constant during rTMS.

The procedure was done by a senior staff pain clinician. Patients in the 3 groups were followed up at 1 month and 3 months after rTMS, respectively. The follow-up (regarding pain assessment and treatment protocol) was accomplished by a pain clinician blinded to the study intervention.

Evaluation Indicators

The baseline data, including gender, age, course of disease, and affected side, were compared between the 3 groups.

VAS scores were recorded for the 3 groups before rTMS (T0), during rTMS (T1-T10), at 1 month after rTMS (T11), and at 2 months after rTMS (T12), respectively. Pain severity was evaluated based on VAS scores that ranged from 0 to 10. The higher the VAS scores, the higher the severity.

The short-form McGill Pain Questionnaire (SF-MPQ) was used to assess pain from 2 aspects, namely, affective and sensory aspects (10). The questionnaire consisted of 15 words. The first to the eleventh words were used to describe the sensory aspect of pain, and the twelfth to the fifteenth words were used to describe the affective aspect. Four severity levels, namely, no pain, mild pain, moderate pain, and severe pain, were represented by 0, 1, 2, and 3, respectively. The present pain intensity (PPI) was measured on a scale of 0 to 5, representing no pain, mild pain, uncomfortable pain, distressing pain, terrible pain, and unbearable pain, respectively. Efficiency of pain reduction was assessed as follows: VAS reduction percentage (%) = (VAST0-VASTx)/VAST0*100%.

Quality of life (QOL) was expressed by scores on the SF-MPQ at T0, T5, T10, T11, and T12. Sleep quality (SQ) was taken as an independent indicator of QOL, measured on a scale of 0 to 10.

The self-rating depression scale (SDS) was used to evaluate the depressive mode of the 3 groups of patients at T0, T5, T10, T11, and T12, respectively (11).

Patients' Global Impression of Change (PGIC) scale (12) was administered after rTMS intervention by asking the patients about disease improvement. A scale of 0 to 7 was used as the grading system, ranging from "very much worse" to "very much improved."

Medication regulation (MR) scores were measured on a 3-point scale: drug discontinuance was given 0, reduced dosage 1, the same dosage 2, and increased dosage 3. Efficacy of rTMS for patients with PHN was evaluated based on PGIC and MR scores at T5, T10, T11, and T12.

During rTMS treatment from T1 to T10, the patients in the 3 groups were asked whether they had headache, neck pain, dry mouth, dizziness, or other discomfort to evaluate the incidence of adverse events during rTMS.

Data Analysis

Intent-to-treat analysis (ITT) was adopted. Measurements including baseline data, descriptive statistics of treatment, and scores on the VAS, SF-MPQ, QOL, SQ, SDS, PGIC, and MR scales were expressed as mean ± standard deviation. Multiple comparisons were performed by using one-way analysis of variance (ANOVA). If there was any significant difference, the

least significant difference (LSD) test was further employed for multiple comparisons. All statistical analyses were undertaken using SPSS Version 16.0 (SPSS Inc., Chicago, IL). $P < .05$ indicated a significant difference.

Results

Grouping and Clinical Data of Patients with PHN

The clinical information of patients with PHN receiving rTMS is shown in Fig. 1. Eighty-four patients with PHN were preliminarily recruited into the clinical trial on rTMS following PHN. Among them, 9 patients were considered ineligible (including 3 patients with contraindications for TMS, 2 patients with cardiac pacemakers, and 1 patient with a cranial implant; after the treatment began, 2 patients refused to receive further treatment; 1 patient refused to take medicine regularly). These patients were excluded. The remaining patients were equally divided into 3 groups using a computer-created number list: the sham TMS group (n = 25), 5-Hz rTMS group (n = 25), and 10-Hz rTMS group (n = 25). Sixty-seven patients with PHN finished the prospective clinical trial within about one year; 22 patients came from the sham TMS group, accounting for 88% of initially recruited patients (2 patients dropped out during rTMS due to fever and asthma, respectively; another patient did not finish rTMS due to knee pain during treatment); 23 patients came from the 5-Hz rTMS group, accounting for 92% of initially recruited patients (1 patient dropped out during rTMS due to asthma; 1 patient received treatment at another hospital and the contact with this patient was lost); 22 patients came from the 10-Hz rTMS group, accounting for 88% of initially recruited patients (2 patients dropped out due to fever and trigeminal neuralgia, respectively; another patient received treatment at another hospital and the contact with this patient was lost). Seven patients were lost to follow-up: 2 from the sham TMS group, 3 from the 5-Hz rTMS group, and 2 from the 10-Hz rTMS group. The drop-out rates were compared between the groups using Fisher's test. $P > .05$ indicated a significant difference. Therefore, the final number of recruited patients was 20 in each group.

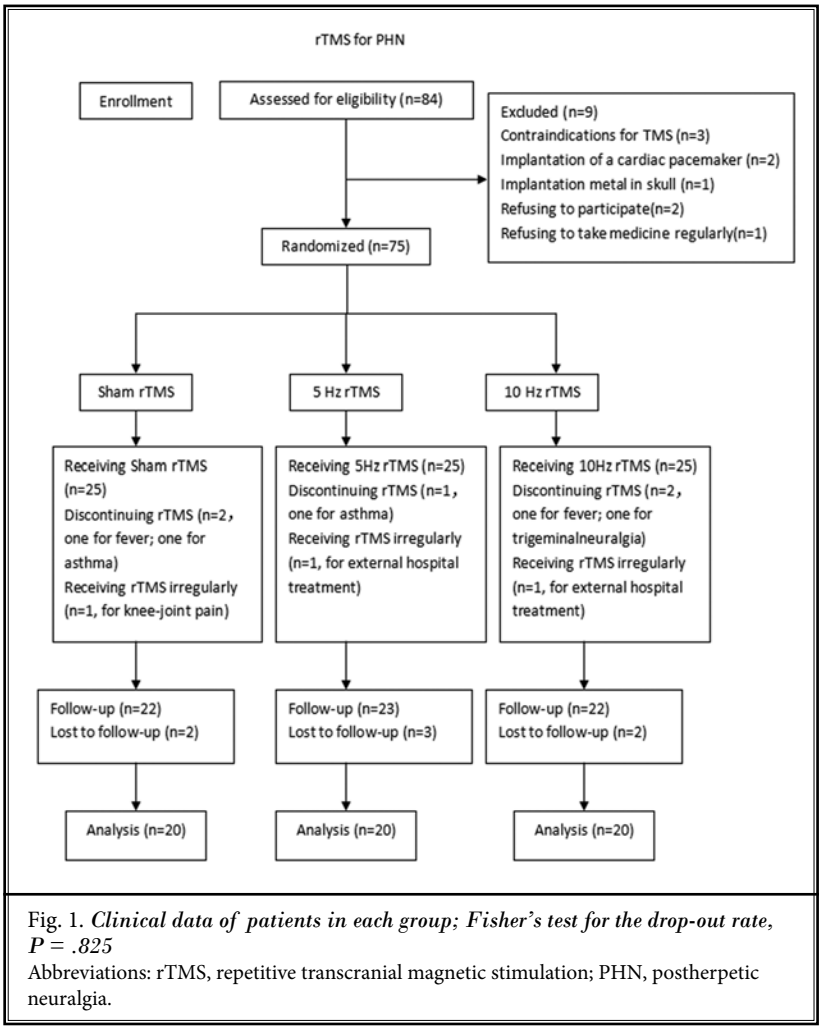

Fig. 1. *Clinical data of patients in each group; Fisher's test for the drop-out rate,* $P = .825$
Abbreviations: rTMS, repetitive transcranial magnetic stimulation; PHN, postherpetic neuralgia.

The baseline information and clinical data for the 3 groups are shown in Table 1. The 3 groups showed no significant differences in gender, age, and pain intensity, and the baseline information for the 3 groups satisfied the balance principle of clinical trials ($P > .05$). The 3 groups also had no significant differences in the scores of VAS, SF-MPQ, QOL, SDS, and SQ before treatment ($P > .05$), which satisfied the requirement.

Table 1. *Baseline information and clinical characteristics of the 3 groups.*

Clinical Features	Sham (n = 20)	rTMS	5-Hz (n = 20)	rTMS	10-Hz (n = 20)	rTMS	*P* Value
Gender (female)	9	45%	10	50%	11	55%	.455
Age (yrs, mean ± SD)	67.3 ± 11.9		65.9 ± 12.3		65.4 ± 10.5		.747
Course of Disease (mos, mean ± SD)	15.7 ± 23.2		16.5 ± 20.4		17.3 ± 24.1		.478
Treated Painful Region (upper body, n%)	9	45%	9	45%	9	45%	.925
VAS (baseline 0~10 cm, mean ± SD)	6.8 ± 1.6		6.9 ± 1.1		6.3 ± 1.7		.395
SF-MPQ (baseline 0~60, mean ± SD)	16.8 ± 10.4		16.2 ± 8.9		15.7 ± 6.2		.735
QOL (baseline 0~70, mean ± SD)	21.1 ± 9.5		20.9 ± 8.3		20.7 ± 7.4		.927
SDS (baseline 20~80, mean ± SD)	30.7 ± 8.5		29.9 ± 8.3		28.9 ± 7.6		.657
SQ (baseline 0~10, mean ± SD)	5.2 ± 2.2		4.5 ± 2.3		4.7 ± 2.3		.445
Affected Side (right, n%)	7	35%	7	35%	7	35%	
Underlying Disease (n%)							
Hypertension	4	20%	3	15%	3	15%	
Diabetes	6	30%	4	20%	3	15%	
Cardiopulmonary Disease	4	20%	3	15%	4	20%	
Cerebral Infarction	4	20%	5	25%	4	20%	
Previous Treatment (n%)							
Medication Regime	20	100%	20	100%	20	100%	
Nerve Block	13	65%	12	60%	10	50%	
Current Medication Regime (n%)							
Gabapentin	18	90%	18	90%	16	80%	
Tramadol	8	40%	7	35%	5	25%	
Mecobalamin	7	35%	5	25%	6	30%	
Acetaminophen	3	15%	3	15%	2	10%	
Oxycodone	3	15%	2	10%	2	10%	

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; VAS, Visual Analog Scale; SF-MPQ, short-form McGill Pain Questionnaire; QOL, quality of life; SDS, self-rating depression scale; SQ, sleep quality.

Moreover, the 3 groups were equivalent in terms of affected sites, underlying diseases, previous treatment, and current medication regimes.

Short-Term VAS Reduction in Patients with PHN

Before rTMS treatment, the 3 groups had similar VAS scores, which were 6.8 ± 1.6, 6.9 ± 1.1, and 6.3 ± 1.7, respectively, indicating no significant difference (*P* = .395). Short-term efficacy of rTMS was calculated by [T0-T10]/T10×100%. rTMS was considered effective in the short term if the value was ≥ 25%. The values for each group are shown in Table 2. The mean VAS percent reduction was significantly different between the 5-Hz and 10-Hz rTMS groups; 28.38% (95% confidence interval [CI], 19.48%-49.35%), compared to 39.89% (95% CI, 22.47%-58.64%) in the 10-Hz rTMS group, with significant difference (F = 5.289, *P* = .022). However, after being corrected for age, gender, course of disease, affected site, affected side (left or right), and initial VAS scores and SQ scores, the short-term efficacy of rTMS in the 5-Hz rTMS group and that of the 10-Hz rTMS group did not differ significantly (*P* > .05).

VAS Reduction at Different Time Points After rTMS in the 3 Groups

VAS reduction at different time points after rTMS was determined in the 3 groups (T0-T12). VAS scores decreased gradually in both the 5-Hz rTMS and 10-Hz rTMS groups, as shown in Fig. 2. Except T0 and T1, VAS scores of the 5-Hz rTMS group were significantly lower

Table 2. *VAS reduction in the short term after rTMS treatment in 3 groups.*

	Subgroup of 5-Hz rTMS group				Subgroup of 10-Hz rTMS group			
	Case Number	Efficacy Rate, %	95% CI	*P* Value	Case Number	Efficacy Rate, %	95% CI	*P* Value
Age (yrs)								
< 70	11	34.11	(13.47-51.24)	.317	12	39.59	(19.34-59.84)	.106
≥ 70	9	37.28	(20.83-48.28)		8	40.94	(28.23-53.65)	
Gender, n%								
Female	10	43.78	(25.58-53.13)	.342	9	49.57	(27.64-71.50)	.630
Male	10	35.57	(15.44-43.72)		11	32.40	(17.64-47.17)	
Course of the Disease (mo)								
< 6 mos	9	45.22	(28.49-69.33)	.249	8	51.92	(30.72-73.12)	.106
≥ 6 mos	11	33.19	(17.65-49.62)		12	32.27	(16.89-47.64)	
Affected Site								
Upper Body	9	38.82	(21.25-62.73)	.472	9	43.73	(22.45-65.00)	.630
Lower Body	11	32.45	(18.38-49.57)		11	37.18	(20.11-54.25)	
Affected Side								
Left	13	42.35	(25.88-62.92)		13	41.87	(23.24-60.49)	.526
Right	7	35.58	(20.05-49.50)		7	36.90	(23.36-50.44)	
VAS (baseline)								
≥ 7	10	47.62	(30.13-63.33)		9	51.95	(32.57-71.34)	.058
< 7	10	31.57	(17.46-50.14)		11	30.45	(14.81-46.10)	
SQ (baseline)								
≥ 5	12	43.58	(28.49-60.34)	.489	11	49.33	(31.91-66.75)	.370
< 5	8	31.34	(15.48-49.28)		9	28.89	(11.69-46.09)	

The 95% confidence interval was calculated using the Clopper-Pearson method.
Abbreviations: VAS, Visual Analog Scale; rTMS, repetitive transcranial magnetic stimulation; SQ,sleep quality.

compared with the sham rTMS group at all other time points (*P* = .438, .111, .047, .022, .019, .013, .008, .005, .003, .001, .001, .001). In addition, the VAS scores of the 10-Hz rTMS group were significantly lower compared with the sham rTMS group (*P* = .399, .091, .040, .018, .014, .011, .006, .003, .001, .001, .001, .001). But starting from T7, the VAS scores of the 10-Hz rTMS group were significantly lower compared with the 5-Hz rTMS group (*P* = .928, .847, .505, .232, .119, .093, .037, .025, .013, .007).

Changes in the Scores of QOL, SQ, PGIC, and MR in the 3 Groups

For both the 5-Hz rTMS and 10-Hz rTMS groups, VAS scores decreased from T2 to T12, while those of the sham rTMS group did not change significantly. The 3 groups showed no significant differences in SF-MPQ scores (F = 0.935, *P* = .338). Neither were there significant differences in SDS scores among the 3 groups (F = 1.121, *P* = .296). No significant differences were observed in QOL scores among the 3 groups (F = 0.826, *P* = .351) (Fig. 3). But at T12, the QOL scores of both the 5-Hz rTMS and 10-Hz rTMS groups were significantly lower compared with the sham rTMS group (F = 7.449, *P* = .016; F = 7.492, *P* = .008). Moreover, the QOL scores of the 10-Hz rTMS group were significantly lower compared with the 5-Hz rTMS group (F = 3.175, *P* = .0317). Neither were there significant differences in SQ scores among the 3 groups (Fig. 4). At T12, the SQ scores of the 5-Hz rTMS and 10-Hz rTMS groups were significantly lower compared with the sham rTMS group (F = 6.352, P = .024; F = 8.264, *P* = .011). The SQ scores of the 10-Hz rTMS group were much lower compared with the 5-Hz rTMS group (F = 2.228, *P* = .0427). But at T10 (F = 2.348, *P* = .008; F = 4.284, *P* = .006), T11 (F = 5.205, *P* = .006; F = 5.927, *P* = .005), and T12 (F = 5.925,

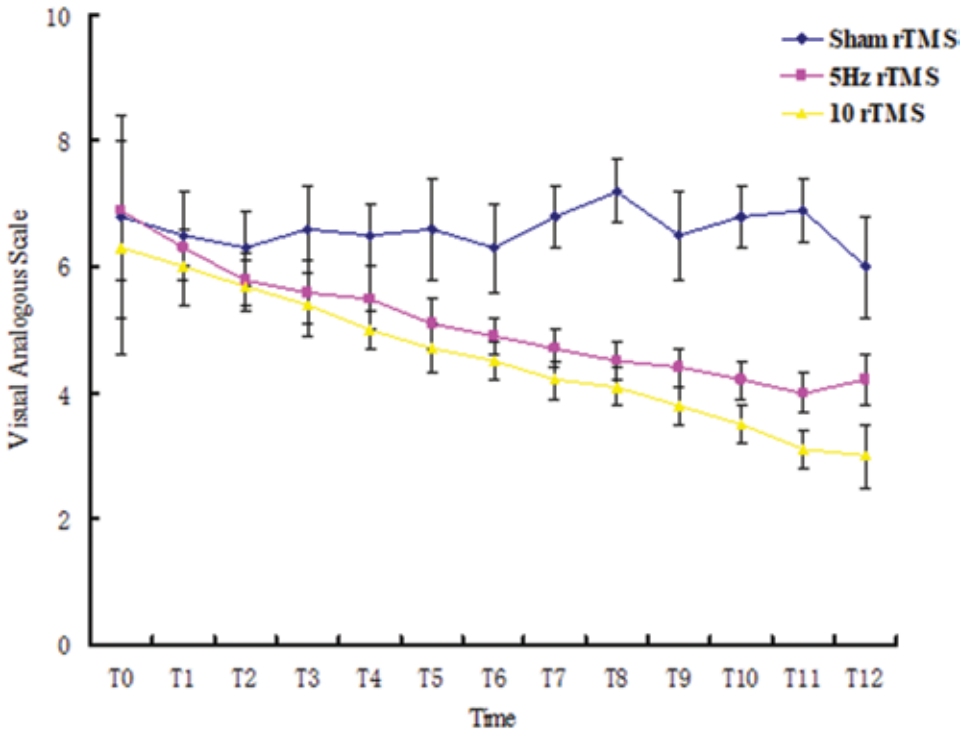

Fig. 2. *VAS reduction at different time points in the 3 groups*

Abbreviations: VAS, Visual Analog Scale; rTMS, repetitive transcranial magnetic stimulation.

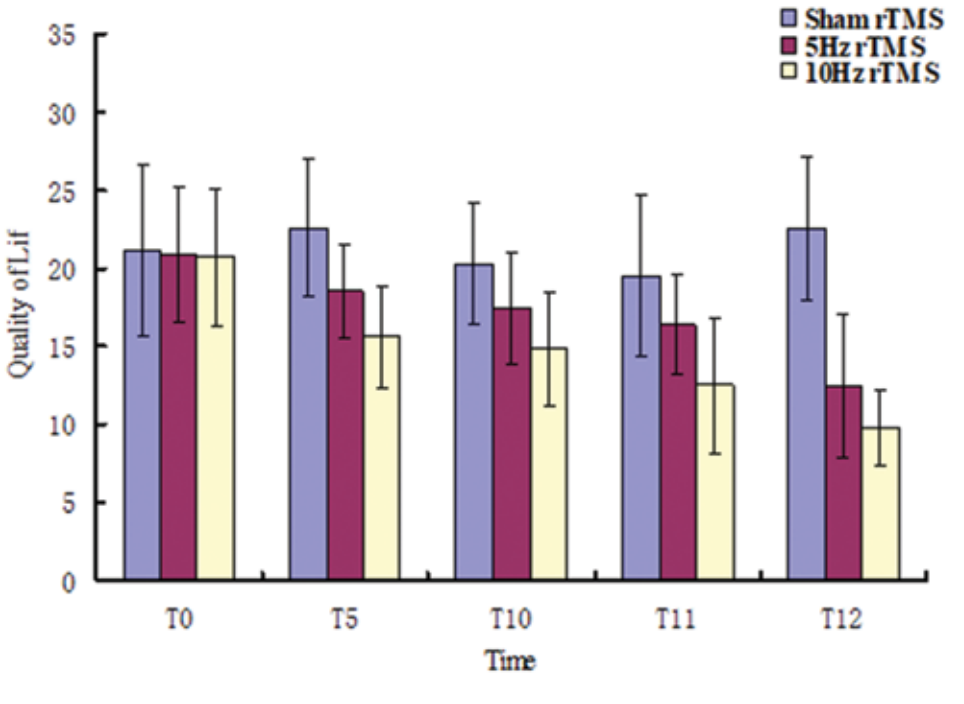

Fig. 3. *Changes in QOL scores in the 3 groups*

Abbreviations: QOL, Quality of Life; rTMS, repetitive transcranial magnetic stimulation.

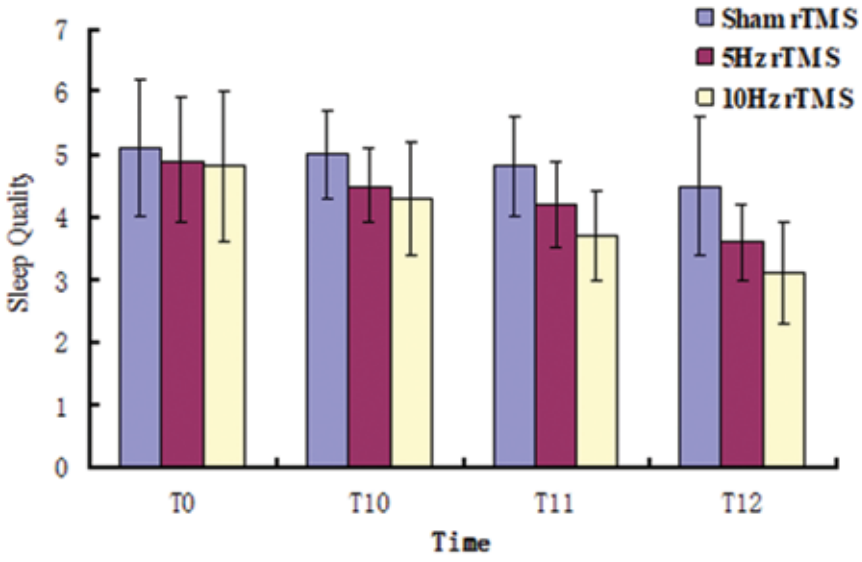

Fig. 4. Changes in SQ scores in the 3 groups .

Abbreviations: SQ, sleep quality; rTMS, repetitive transcranial magnetic stimulation.

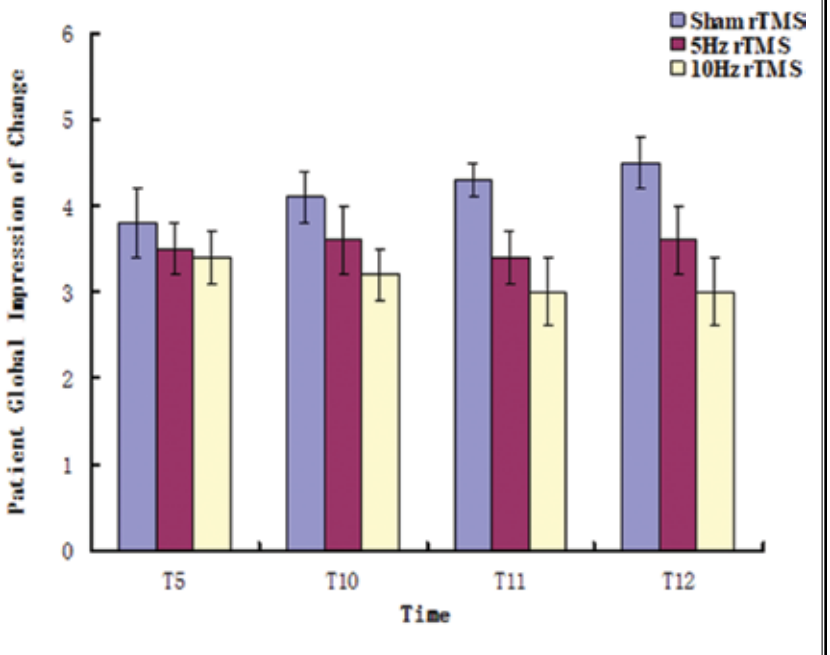

Fig. 5. Changes in PGIC scores in the 3 groups
Abbreviations: PGIC, Patient Global Impression of Change; rTMS, repetitive transcranial magnetic stimulation.

P = .011; F = 4.233, *P* = .009), PGIC scores for the 5-Hz rTMS and 10-Hz rTMS groups were significantly lower compared with the sham rTMS group (Fig. 5). There was a reduction in medication dosage in the 5-Hz rTMS and 10-Hz rTMS groups, but no significant difference was observed in MR scores (F = 0.458, *P* = .241; F = 0.528, *P* = .114) (Fig. 6).

Incidence of Adverse Events Following rTMS in the 3 Groups

Incidence of adverse events following rTMS in the 3 groups is shown in Table 3. One patient in the sham rTMS group had headache, 3 patients had neck pain, and 1 patient suffered dizziness. In the 5-Hz rTMS group, 1 patient had headache and 1 patient suffered neck pain. For the 10-Hz rTMS group, 1 patient had dry mouth, 2 patients suffered headache, 2 patients had neck pain, and 1 patient suffered dizziness.

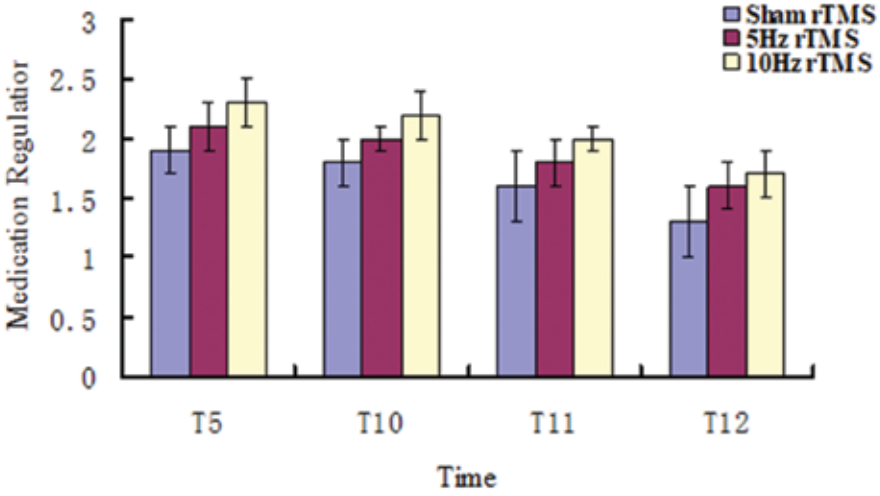

Fig. 6. Changes in MR scores in the 3 groups. Abbreviations: rTMS, repetitive transcranial magnetic stimulation; MR, medication regulation.

Table 3. *Incidence of adverse events related to rTMS in the 3 groups.*

	Sham rTMS		5-Hz rTMS		10-Hz rTMS		Total	
Adverse Events	n (20)	%	n (20)	%	n (20)	%	n (60)	%
Dry Mouth	0	0	0	0	1	5	1	1.67
Headache	1	5	1	5	2	10	4	6.67
Neck Pain	3	15	1	5	2	10	6	10
Dizziness	1	5	0	0	1	5	2	3.33

Abbreviations: rTMS,

There were no significant differences in the incidence of adverse events among the 3 groups (F = 1.047, *P* = .572).

Discussion

PHN is the most common and most severe sequela of herpes zoster, which is also one of the refractory pain symptoms affecting many middle-aged and elderly people (6). Little is known about the pathogenesis of PHN. Some believe that reduced immunity at peripheral branches of the sensory ganglia spreads to the central branch, which causes further damage to the peripheral and central nerves (13). No effective treatment is available for PHN, and medication is considered as the most common treatment. However, pregabalin and gabapentin, the 2 most widely used drugs in clinics, can hardly eradicate PHN. Besides, long-term use of these drugs may lead to tolerance and side effects (14). rTMS exerts an analgesic effect via a similar mechanism as an epidural stimulation implant. rTMS may have different efficacy by using different frequencies. High frequency (> 1 Hz) of rTMS is mainly used for excitation, and low frequency (≤ 1 Hz) is used for inhibition (15). Because of its painless and noninvasive features, rTMS is known as one of the most important brain technologies of the 21st century (16).

In the latest research, Ma Shu Min et al found that 10-Hz rTMS was applied to patients with PHN as a safe and effective treatment (5). Considering the interindividual variability in tolerance to the rTMS frequency, we administered rTMS of different frequencies (i.e., 5 Hz, 10 Hz) to patients with PHN. We found that VAS reduction was significant from T2 to T12 in the 5-Hz rTMS and 10-Hz rTMS groups. The short-term efficacy measured by VAS reduction was 28.38% [95% CI, 19.48%-49.35%] in the 5-Hz rTMS group. This indicated that rTMS of either 5 Hz or 10 Hz was effective in providing pain relief for patients with PHN.

Pain is a subjective feeling. The most effective indicator of pain is pain intensity, which can be self-rated using different types of sensory scales. The VAS can be used to measure pain intensity and variation

of pain intensity before and after treatment (17-18). In addition, other scales such as the SF-MPQ, QOL, SQ, SDS, PGIC, and MR are all primary indicators. They can reflect pain intensity, psychological status, sleep quality, efficacy, and safety of patients with PHN before and after treatment (19-20). In our study, there were no significant differences in QOL and SQ scores in the 5-Hz rTMS and 10-Hz rTMS groups compared with the sham rTMS group. But at T12, 3 months after rTMS, the QOL and SQ scores in the 5-Hz rTMS and 10-Hz rTMS groups were significantly higher compared with the sham rTMS group. This indicated that, although the efficacy was limited during rTMS treatment, rTMS did have long-term benefits, such as improvement in quality of life and sleep quality. Moreover, at T10, T11, and T12, PGIC scores in the 5-Hz rTMS and 10-Hz rTMS groups were significantly lower compared with the sham rTMS group; this also demonstrated the efficacy of rTMS in PHN. VAS reduction in the 5-Hz rTMS group was also lower compared with the 10-Hz rTMS group. Comparison of QOL and SQ scores at T12 indicated that QOL and SQ scores in the 5-Hz rTMS group were significantly lower compared with the 10-Hz rTMS group. As to PGIC scores, a similar trend was observed in the 2 groups at T10, T11, and T12. This indicated that the 5-Hz rTMS treatment was inferior to the 10-Hz rTMS treatment in terms of pain relief and improvement of quality of life and sleep quality.

Despite the superiority of 10-Hz rTMS over 5-Hz rTMS in some aspects, the efficacy of 5-Hz rTMS for PHN was non-negligible. We compared the incidence of adverse events between the 3 groups after rTMS, and there were no significant differences. This indicated that both frequencies were safe, though the incidence of adverse events was lower with 5 Hz than 10 Hz. Thus, 5-Hz rTMS was safer than 10-Hz rTMS and more easily accepted by patients. Considering interindividual variability in initial acceptance of rTMS, we recommend that rTMS is started from 5 Hz for PHN.

Limitations and Future Works

The main limitation of this work was that the patients were only followed for 3 months. In future work, we will follow patients for 6 months or even longer to observe the efficacy and safety of rTMS at different high frequencies for PHN. What is more, the current study had a small sample size due to time limitations, and we could have refined the screening for rTMS evaluation indicators. In the future, we will enlarge the sample size and confirm the current findings on the efficacy of rTMS for PHN.

Conclusion

In conclusion, we have demonstrated that both 5-Hz rTMS and 10-Hz rTMS are safe and effective for PHN, as they can relieve pain and improve patients' quality of life. rTMS can be used as an adjuvant therapy for PHN.

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Declaration of Conflicts of Interest

None of the authors have any conflict of interests to report for this work. The final version was approved by all the authors.

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