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A comparison study of repetitive transcranial magnetic stimulation for tinnitus treatment in an Asian population

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ABSTRACT

Background: Tinnitus, a subjective auditory perception of sounds or noise not triggered by external auditory stimuli, carries considerable morbidity. To date, pharmacological, physical or behavioral therapy is the mainstay of management.

Methods: We compared repetitive transcranial magnetic stimulation (rTMS) of 1000 or 2000 stimulations/day at 1 Hz and 110% of the motor threshold for 5 consecutive days over the left auditory cortex.

Ratings based on the Tinnitus Handicap Inventory (THI) rating scale were completed weekly for 4 weeks. None of the patients had significant hearing impairment.

Results: All 28 patients (age range 21–72; 18 men) tolerated rTMS well and no adverse effects were observed.

Analysis of variance (ANOVA) showed significant decrease in THI scores over the entire time period ($F(1,26) = 11.33$, $p = 0.002$). At every weekly time point of evaluation, ANOVA with repeated measures demonstrated significantly lower THI score compared to baseline ($p < 0.02$ for all). RTMS treatment had resulted in tinnitus reduction in the range of 15–25% over the 4 week period.

Separately, ANOVA also demonstrated significantly reducing THI for both the 1000 pulse ($F(1,14) = 4.8$, $p = 0.04$) and 2000 pulse ($F(1,14) = 6.56$, $p = 0.02$) rTMS treatment arms.

Comparison of THI ratings between the 2 treatment arms did not result in significant difference ($F(1,26) = 1.48$, $p = 0.24$).

Conclusions: The present study has revalidated the efficacy and safety of rTMS for improving tinnitus up to 4 weeks post-treatment in Asians. However, there was no significant difference with THI evaluation between the 1000 pulse and 2000 pulse treatment arms.

1. Introduction

Tinnitus, a subjective auditory perception of sounds or noise not triggered by external auditory stimuli, may adversely affect quality of life in 1–3% of the general population [1]. To date, pharmacological, physical or behavioral therapy is the mainstay of management.

Animal data [2], and in vivo human brain imaging studies, suggest that tinnitus could be associated with maladaptive plastic brain reorganization at multiple brain levels following an initial cochlear dysfunction. Functional brain imaging changes include hyperactivity of primary auditory cortex (AC) and the secondary or associative cortex [3].

More direct evidence for the role played by the AC in the perception/ of tinnitus comes from repetitive transcranial magnetic stimulation (rTMS), a technique that transiently modulates targeted areas engaged in processing of specific cortical functions.

Most studies have employed rTMS to alleviate tinnitus at 1800–2000 pulses a day over a 1 or 2 week period [4,5]. In some cases, a single course of rTMS can result in improvement for up to 6 months [6], in tandem with SPECT imaging demonstrating reduced metabolism in the inferior left temporal lobe despite stimulation applied to the superior temporal cortex. In contrast, earlier studies utilizing only 200 pulses have also been effective in alleviating tinnitus for a very short duration [7], suggesting that shorter duration of rTMS may be investigated for this purpose. To this end, our previous experience point to a positive effect of short duration rTMS using 1000 pulses a day over 5 days using the Tinnitus Handicap Inventory (THI) evaluation [8]. Although well tolerated and convenient, this short duration rTMS protocol may prove inadequate for

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Table 1
Summary of rTMS and tinnitus data.

Patient	Pulses	Baseline THI	1 week THI	2 week THI	3 week THI	4 week THI	Intensity (dB)	Frequency (Hz)
1	1000	44	20	22	33	1	25	125
2	1000	31	24	24	25	25	55	4000
3	1000	3	3	3	1	1	NM	
4	1000	21	21	21	21	21	NM	
5	1000	24	24	24	24	24	70	8000
6	1000	2	2	2	2	2	NM	
7	1000	34	34	40	18	18	65	8000
8	1000	88	40	40	40	40	50/55	8000/1000
9	1000	44	44	44	44	44	NM	
10	1000	8	8	2	0	0	50	6000
11	1000	8	8	8	8	8	50/75	8000/8000
12	1000	68	68	68	68	68	NM	
13	1000	80	80	80	80	80	NM	
14	1000	26	26	26	26	26	NM	
15	2000	62	62	62	62	62	70/75	4000/4000
16	2000	24	24	24	24	24	70/60	8000/6000
17	2000	42	44	40	46	34	65	8000
18	2000	84	84	84	82	84	NM	
19	2000	8	4	4	4	4	NM	
20	2000	48	48	8	48	18	15/10	12,000/12,000
21	2000	42	26	32	42	42	NM	
22	2000	70	46	46	40	40	NM	
23	2000	36	34	34	34	34	NM	
24	2000	62	62	62	62	50	80/95	8000/8000
25	2000	96	28	46	48	38	NM	
26	2000	52	52	52	50	52	95	8000
27	2000	24	10	6	6	6	NM	
28	2000	12	12	12	10	10	NM	

THI: tinnitus handicap inventory; NM: not matched; The first intensity and frequency refers to the right side.

modulating maladaptive plastic changes at the cortical level, and suggest the need for delivery of more stimuli. Here, we perform a comparative trial of rTMS with 1000 or 2000 pulses a day over 5 days for tinnitus treatment.

2. Methods

With local ethics committee approval, we recruited 28 tinnitus patients in a prospective fashion, who gave written consent to participate in the study. The trial was registered with clinicaltrials.gov, with informed consent obtained from all subjects before participation.

Patients were randomized into the 1000 or 2000 pulse treatment arms, consisting of 14 patients in each arm.

Patients were randomized over a 2 year period with the main investigators (YMC, YLL) blinded to the treatment arm of each one enrolled.

A detailed history was obtained, clinical examination performed and audiogram recorded. Audiometry and otoscopy were performed at enrolment. Tinnitus and acoustic evaluations were then collected by collaborators not directly involved with rTMS application.

All patients had chronic tinnitus (>6 months duration) and no significant hearing impairment, defined as within 25 dB of the speech range.

Repetitive TMS consisted of 1000 or 2000 stimulations/day at 1 Hz and 110% of the motor threshold for 5 consecutive days over the left AC. Using the International EEG system as anatomical reference for rTMS stimulation, surface marking of the stimulation point was located over the left scalp between T3 and midpoint of line joining C3/T5, with the coil handle directed backwards. Stimulation was delivered with a Medtronic (Medtronic Corporation, New York, USA) MagPro TMS unit connected to a Medtronic C-B60 figure-of-8 shaped coil. This coil positioning was similar to that in our previous study [5,8].

Upon recruitment, patients answered a baseline tinnitus rating questionnaire prior to treatment. All patients underwent 1 week treatment consisting of 5 rTMS sessions, after which tinnitus rating was performed weekly for 4 weeks. The total study period was 5 weeks for each patient.

Ratings based on the commonly used Tinnitus Handicap Inventory (THI) rating scale consisting of a 25 point questionnaire were completed weekly [9].

3. Results

All patients included had chronic tinnitus of >6 months duration. For the 1000 pulses group, 2 of the 14 patients had bilateral tinnitus between 50 and 75 dB, and were matched to 1000 Hz. Five other patients had unilateral tinnitus between 25 and 70 dB matched to 125 and 8000 Hz. The remaining patients were unmatchable. For the 2000 pulse group, 4 of the 14 patients had bilateral tinnitus between 15 and 95 dB and matched to 4000 and 12,000 Hz. Two others had tinnitus from 65 and 95 dB, both matched to 8000 Hz. The remaining patients were unmatchable.

All 28 patients (age range 21–72; 18 men) tolerated rTMS well and no adverse effects were observed. There was no significant difference in age between the 2 treatment arms (Student's *t*-test, $p = 0.27$).

No significant differences were noted for the baseline THI of both groups (Mann–Whitney *U* test, $p = 0.18$).

Overall, analysis of variance (ANOVA) showed significant decrease in THI scores over the entire time period ($F(1, 26) = 11.33$, $p = 0.002$). At every weekly time point of evaluation, ANOVA with repeated measures demonstrated significantly lower THI score compared to baseline ($p < 0.02$ for all).

Separately, ANOVA also demonstrated significantly reducing THI for both the 1000 pulse ($F(1, 14) = 4.8$, $p = 0.04$) and 2000 pulse ($F(1, 14) = 6.56$, $p = 0.02$) rTMS treatment arms.

Comparison of THI ratings between the 2 treatment arms, however, did not reach statistical significance ($F(1, 26) = 1.48$, $p = 0.24$).

In terms of responders, the 1000 pulse arm resulted in an average of 64.3% THI reduction at 4 weeks, compared with 39.3% in the 2000 pulse arm. However, the difference was not statistically