**Randomized controlled trial of repetitive transcranial magnetic stimulation
combined with paroxetine for the treatment of patients with first-episode major
depressive disorder**

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) has been introduced as a new and

effective treatment option for major depression. This paper examined the effectiveness of rTMS on first episode depressed patients when combined with antidepressant drugs. A random sample of forty-three first-episode depressed patients received active or sham rTMS to the left dorsolateral prefrontal cortex, and concomitantly took paroxetine for 4 weeks, and paroxetine monotherapy for 4 weeks afterwards. Response was defined as a $\geq 50\%$ decrease on the total Hamilton Depression Rating Scale (HDRS) from the baseline, and remission was defined as an HDRS total residual score < 8 . The dosage of paroxetine was the average dose per day in each week. Repeated-measures ANOVA revealed a significant improvement in the HDRS with active compared with sham rTMS from the end of the 1st week to the 4th week. At the end of the 4th week, response rate was 95.5% with active and 71.4% with sham rTMS, remission rate was 68.2% with active and 38.1% with sham rTMS, while these significant differences disappeared at the endpoint of the study. These findings indicate that rTMS at 10-Hz accelerated the onset of action and augmented the response to paroxetine for first-episode depressed patients.

Keywords: Repetitive transcranial magnetic stimulation; Paroxetine; First-episode depression; Onset of action.

1. Introduction

Major depressive disorder (MDD) has a devastating effect on both the individual and the society because of high medical costs and loss of productivity (Collins et al., 2011; Murray and Lopez, 1996). A survey that was published in 2009 reported that the 1-month prevalence of MDD was 6.0% in China (Phillips et al., 2009). Core symptoms include depressed mood, anhedonia, irritability, difficulties concentrating, and abnormalities in appetite and sleep (Baxter et al., 1989). After acute-phase pharmacotherapy, psychotherapy, or both, most depressed patients either do not improve or achieve only partial symptomatic improvement (Drevets et al., 2008; Garcia-Toro et al., 2001; Hausmann et al., 2004; Rush et al., 2006a; Rush et al., 2006b). The lack of treatment efficacy may be attributable to the lack of adequate biomarkers, relatively low rates of heritability, and the heterogeneity of precipitating factors, including stress (Davidson et al., 2002; Mayberg, 2003). Moreover, only approximately 30% of treated patients with MDD could achieve satisfactory remission, despite receiving medications with different mechanisms of action and subsequently different treatment strategies (Rush et al., 2006b; Trivedi et al., 2006). Additionally, these antidepressants usually require several weeks of administration to achieve clinical efficacy.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive physical therapy that uses magnetic pulses to induce electrical currents in local brain areas. Studies of the motor cortex showed that high-frequency rTMS (≥ 5 Hz) tended to increase cortical excitability, whereas low-frequency rTMS (≤ 1 Hz) supposedly acts in

an opposite fashion (Ridding and Rothwell, 2007). High-frequency rTMS of the left dorsolateral prefrontal cortex (dlPFC) and low-frequency rTMS of the right dlPFC have been studied for the treatment of depression (Berlim et al., 2013b; Berlin et al., 2013c; Gedge et al., 2012; Keshkar et al., 2011). In 2008, the United States Food and Drug Administration (FDA) approved rTMS as a treatment modality for adults with MDD who “have not responded to a single antidepressant medication in the current episode.” The FDA-approved product label treatment parameters are of high frequency (10 Hz) rTMS, as it is applied to the left dlPFC 5 days a week for 4-6 weeks (Horvath et al., 2010). The convergence of findings suggests that rTMS exerts its therapeutic effects by altering the levels of various neurochemicals, electrophysiology, blood flow, and brain activity in a frequency-dependent manner (Rossini et al., 2005b). The alterations in brain activity that are observed after rTMS have been related to molecular processes associated with neural plasticity (Berlim et al., 2013a).

Several randomized controlled studies demonstrated that rTMS was superior to placebo in MDD (George et al., 2010; O'Reardon et al., 2007; Ray et al., 2011; Triggs et al., 2010). Meta-analyses have shown that the effect sizes of rTMS are similar to antidepressant pharmacotherapy, which is in the moderate range (Schutter, 2009; Slotema et al., 2010). Pooled responses and remission rates in randomized controlled trials for rTMS were 25% and 17% compared with 9% and 6%, respectively, for the sham condition (Lam et al., 2008). A recent systematic review (Berlim et al., 2014) of 29 randomized controlled trials (RCTs) from 1995 to July 2012 showed that 29.3% and 18.6% of the subjects who had received high-frequency (HF) rTMS were classified as

responders and remitters, respectively, compared with 10.4% and 5% of those who had received sham rTMS. Furthermore, the results revealed that HF-rTMS was equally effective as an augmentation strategy or monotherapy for major depression when treating patients with primary unipolar major depression or with mixed unipolar and bipolar major depression. Previous studies and meta-analyses also support rTMS as an add-on treatment for recurrent or treatment-resistant depression (Mogg et al., 2008; Rossini et al., 2005a; Rumi et al., 2005). Theta-burst stimulation (TBS) is a specific pattern of rTMS that was recently shown to be a promising approach for increasing the antidepressant effects of rTMS therapy (Holzer and Padberg, 2010; Huang et al., 2012; Huang et al., 2011).

Important as these findings are, few studies have directly investigated the effect of rTMS combined with antidepressants on symptomatology of first-episode depressed patients (Huang et al., 2012; Huang et al., 2011). Besides, there was no significant difference in responder rates (46% vs. 36%, $\chi^2(2) = 0.295$, $p=0.586$) or in remission rates (39% vs. 29%, $\chi^2(2) = 0.319$, $p=0.572$) between the active and sham rTMS group at 4 weeks. As such, the efficacy of selective serotonin reuptake inhibitors (SSRIs) for MDD is limited, similar to other classes of antidepressants. Some examples are of 49% response rate and of 37% remission rate in the largest “real world” study (Rush et al., 2006a). Paroxetine, a serotonin reuptake inhibitor used for combating depression and anxiety, works by enriching serotonin in the synaptic cleft (Bonnin et al., 2012) and inhibiting norepinephrine reuptake to increase norepinephrine availability (Carrasco and Sandner, 2005), two mechanisms of action that are

responsible for the relief of depressive symptoms. However, the slow onset of action after initiating treatment and serious side effects similar to other SSRIs and other classes of antidepressant often lead to discontinuation or reduction of antidepressant treatment. This could largely increase the rate of relapse and treatment failure (Henkel et al., 2009). Besides, the available empirical evidence indicates that paroxetine provides modest advantage over placebo in treatment of anxiety and depression (Sugarman et al., 2014).

To date, add-on studies have been insufficient in demonstrating whether rTMS has any additional advantage when combined with antidepressant drugs, especially in patients with first-episode depression. Therefore, the present study hypothesized that the addition of rTMS may accelerate the onset of action and reduce the dosage of the antidepressant SSRI paroxetine in first-episode depressed patients. To test this hypothesis, we recruited 48 first-episode patients with MDD in China.

2. Methods

2.1. Patients and clinical assessment

The clinical participants consisted of 48 first-episode patients with MDD. The participants were consecutively recruited from the Institute of Mental Health, Hebei Medical University, Shijiazhuang, China. Recruitment occurred between January 2010 and January 2011. The participants' ages ranged from 18 to 45 years (mean $\pm$ SD: 29.42 $\pm$ 8.88 years). All 48 participants and their legal caregivers provided written informed consent to participate in this study, of them forty-three completed the entire study. Five participants did not complete the study.

The 43 patients who completed the study reported no history of any other psychiatric disorders and no history of taking any antidepressants. They all met the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, 4th edition) (American Psychiatric Association, 2004) criteria for major depression disorder. The diagnosis was further established by using the Structured Clinical Interview for DSM-IV (SCID), which was performed by two experienced psychiatrists. A minimum score of 20 points on the 24-item Hamilton Depression Rating Scale for depression (HDRS) (Hamilton, 1967) was required for this study. Duration of the present depressive episode was in the range of 1 to 8 months. Education of the participants should be more than 6 years.

The exclusion criteria included (i) age < 18 years or > 45 years, (ii) comorbid DSM-IV diagnosis, including alcohol or illicit drug abuse, and other Axis I psychiatric disorders, (iii) current or past serious physical illness (e.g., active tuberculosis, acute hepatitis, cirrhosis, renal illness, cardiovascular illness, or unstable diabetes), (iv) diastolic blood pressure < 60 mm Hg or heart rate < 60 beats per minute, (v) HDRS suicidal ideation score ≥ 3 , (vi) risk factors for the rTMS procedure (e.g., epilepsy, severe and repetitive headache episodes, previous neurosurgery, implants of metal or clips, and pregnancy), and (vii) those female participants who were pregnant or were planning to become pregnant.

The results of the participants' physical examination, electrocardiogram, hepatorenal function, and routine urinalysis were within normal limits. All procedures in the present study were conducted in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the First Hospital of Hebei Medical

University, China. They were performed with the patients' adequate understanding and written consent. Each patient took paroxetine (GlaxoSmithKline, Tianjing, China) for 8 weeks. The paroxetine dosage began with 10 or 20 mg daily (taken after breakfast) for the first week and then was titrated to 20 or 30 mg daily from day 8 onward. Some of the patients required 40 mg daily beginning on day 29 if the reduction of the HDRS score was < 50% at the end of the 4th weekend.

2.2. Design and rTMS protocol

This 8-week double-blind trial consisted of two phases: Phase 1 (rTMS combined with paroxetine treatment) and Phase 2 (paroxetine treatment alone). In Phase 1, the participants were randomly assigned in a 1:1 ratio to either active rTMS ($n = 22$) or sham rTMS ($n = 21$) five times per week combined with paroxetine for 4 consecutive weeks. From the first day of the 5th week, the participants were offered paroxetine treatment alone for an additional 4 weeks in Phase 2. Patient randomization numbers were concealed in sealed envelopes that were opened only by the rTMS operators immediately before the first session of stimulation. The participants, care providers, assessors, and all personnel other than the rTMS operators remained blind to group allocation until unmasking occurred on the 8th weekend after treatment.

rTMS was administered using a MAGSTIM Rapid 2 magnetic stimulator (Magstim Company, Whitland, U.K.) with a vacuum-cooled 70-mm figure-8 coil. The participants were seated upright in a comfortable chair during the procedure. Before the first treatment, we determined the motor threshold at rest for the right abductor pollicis

muscle as in previous studies (Padberg et al., 2002; Pascual-Leone et al., 1996). Stimulation occurred in the left dlPFC, which was defined as 5 cm in front of the site of the right abductor pollicis muscle in the parasagittal plane (the thumb) as described previously (George et al., 2000). The stimulation parameters in the rTMS group were the following: 10 Hz, 80% of motor threshold over the left dlPFC, and 40 trains of 20 pulses (2 s each, with a 28-s intertrain interval). A total of 800 pulses were administered per day, with 20 sessions (five sessions per week) for 4 weeks. Sham rTMS was administered using the Magstim Sham coil which contains a mu-metal shield that diverts the majority of the magnetic flux such that a minimal (less than 3%) magnetic field is delivered to the cortex (Rossi et al., 2007). This coil looks and sounds like an active coil, however it does not feel exactly like active rTMS, which generates a stronger tapping sensation on the scalp. The sham procedures were identical to active rTMS. None of the participants had received rTMS prior to this study and were not familiar with the differences between sham and active rTMS with regard to its acoustic and tactile artifacts.

2.3. Outcome measures and response criteria

The participants were evaluated for the severity of depressive symptoms using the HDRS-24 at baseline and on the 7th, 14th, 21th, 28th, and 56th day of treatment. The rater was blind to treatment assignment. The side effects of rTMS were assessed daily by the participants who maintained a written diary. The primary efficacy measure was the HDRS-24. Participants with at least a 50% reduction in the absolute HDRS-24

score at the end of the 4th and 8th week of treatment from baseline were classified as responders and were considered remitted with a HDRS-24 residual score < 8 (Frank et al., 1991). The dosage of paroxetine was the average dose per day in each week. The safety and tolerability of rTMS were reported by the participants on the second day after each session of treatment. The following question was asked: “Do you have any uncomfortable feelings after the rTMS session yesterday?” If they answered “yes,” then the researcher asked the following questions: “What is it?” “How long did it last?” “Can you endure it?”

2.4. Statistical analysis

The statistical analyses were performed using SPSS 20.0 software (SPSS, Chicago, IL, USA). The χ^2 test and Student's *t*-test were applied to comparing demographic and clinical data between the active and sham groups. The χ^2 test was also used to comparing response and remission rates between the two groups. Fisher's Exact test was used when expected counts in a cell were < 5. Repeated-measures analysis of variance (ANOVA), with adjustments for non-sphericity, were applied to evaluate the group and time-dependent effects of rTMS on the HDRS score and paroxetine dosage over 4 weeks and subsequent 4 weeks. Student's *t*-test was applied to analyze differences in the HDRS score and paroxetine dosages between the two groups at baseline and the end of the 1st, 2nd, 3rd, 4th, and 8th week. All tests were conducted with two-sided significance levels ($p < 0.05$) without corrections for multiple comparisons because of the small sample size and exploratory nature of

the study.

3. Results

3.1. Demographics and baseline clinical characteristics of the study population

As shown in Table 1, the active and sham groups did not differ significantly in demographics or baseline clinical ratings. Five of the 48 patients dropped out of the study. Three of these five patients were randomized to active rTMS, two of whom were actively suicidal, and one left in the middle of the study because of family reasons. The other two patients who dropped out withdrew their consent because they found the procedure intimidating (these two patients were subsequently assigned to sham rTMS). The data from these dropouts were not included in the analysis.

3.2. Changes in depression symptomatology

As shown in Fig. 1 and Table1, the HDRS score in the rTMS group was lower than that in the sham group (repeated-measures ANOVA, $F_{1,41} = 4.18$, $p = 0.047$) without a significant Group by Time Point interaction ($F_{5,205} = 1.92$, $p = 0.093$). At the end of the 1st week, the HDRS score was significantly lower in the rTMS group than that in the sham group, and this effect continued to the end of the 4th week (independent-sample t -test, $p < 0.05$). At the end of the 8th week, however, this significant difference disappeared.

..... Fig. 1 about here.....

3.3. Response and remission rates in both groups

As also shown in Table 1, at the end of the 4th week, the overall response rate (HDRS score reductive ratio $\geq 50\%$) was higher in the rTMS group than that in the sham group (95.5% vs. 71.4%, respectively; $\chi^2 = 4.55$, $p = 0.041$). The remission rate (HDRS-24 score < 8) was also higher in the rTMS group than that in the sham group (68.2% vs. 38.1%, respectively; $\chi^2 = 6.776$, $p = 0.009$). At the end of the 8th week, these significant differences were not found in either response rates or in remission rates (90.9% vs. 85.7%, respectively, $\chi^2 = 3.91$, $p = 0.189$ for response rate; 86.4% vs. 76.2%, respectively, $\chi^2 = 4.02$, $p = 0.069$ for remission rate).

3.4. Paroxetine dosage in both groups

As shown in Fig. 2, the paroxetine in the sham group was higher than that in the rTMS group (repeated-measures ANOVA, $F_{1,41} = 9.18$, $p = 0.004$). At the end of the 1st week, no significant difference in paroxetine dosage was found between groups. From the 2nd week to the 8th week, the paroxetine dosage in the sham group was higher than that in the rTMS group (independent-sample t -test, $p < 0.05$).

..... Fig. 2 about here.....

3.5. Safety and tolerability

None of the participants reported significant side effects. The rTMS sessions were well tolerated, with no seizures, hearing impairment, or subjective complaints about memory or concentration. The common side effects of rTMS were not different

between the active and sham groups. Twelve participants reported headache or scalp pain (five in the rTMS group and seven in the sham group; 22.7% and 33.3%, respectively) at the end of the 4th week. The incidence of side effects significantly decreased after stopping rTMS treatment. Three participants reported headache or scalp pain (two in the rTMS group and one in the sham group; 9.1% and 4.8%, respectively) at the end of the 8th week. All uncomfortable feelings were mild, and the participants could endure them.

4. Discussion

In the present study, we found that active rTMS accelerated the ameliorating effects of paroxetine on depressive symptoms in first-episode depressed participants and decreased the paroxetine dosage during the entire 8 weeks of treatment.

The response to active rTMS combined with paroxetine was fast and consistent with studies of first-episode depressed participants who had received citalopram treatment (20 mg per day) in combination with a 2-week period of either rTMS or sham rTMS of the dlPFC (10 Hz, 90% motor threshold) (Huang et al., 2012; Huang et al., 2011). This showed that the HDRS score reduction was more rapid with active rTMS than with sham. In fact, a recent meta-analysis reported that HF-rTMS was a promising strategy for accelerating the clinical response to antidepressants in major depression (Berlim et al., 2013a). rTMS (5 Hz, 120% motor threshold) of the dlPFC for 4 weeks also accelerated the onset of action and augmented the response to amitriptyline in nonpsychotic MDD (Rumi et al., 2005). In the present study, the response and

remission rates were significantly higher in the active rTMS group after the stimulation period but not at the endpoint of the study. This is consistent with a previous study (Rossini et al., 2005b), in which the effect of rTMS appeared to be unaffected by the specific concomitantly administered drug in non-drug-resistant MDD patients who had received venlafaxine, sertraline, or escitalopram combined with a 2-week period of sham or active 15-Hz rTMS of the dlPFC.

Additionally, adjunctive rTMS of the dlPFC showed significant improvements in both depression and anxiety in the treatment of anxious depression (Diefenbach et al., 2013). However, the present findings are inconsistent with other previous studies. The study by Poulet et al. (Poulet et al., 2004) involved 18 patients aged 18-65 years who received 400 pulses per day combined with paroxetine for a duration of 2 weeks. No difference in efficacy was found between the rTMS combination therapy and paroxetine monotherapy. The contrasting results may be related to the sample size and the age of participants. Similarly, other randomized controlled trials showed that adjunctive HF-rTMS of the dlPFC was not more effective than sham rTMS in the treatment of depression (Garcia-Toro et al., 2001; Hausmann et al., 2004; Mogg et al., 2008). The common characteristics of these studies are that the patients were older (mean age, > 43 years), and most of them had previous depressive episodes (> 3), even as many as seven previous episodes in one of such studies (Garcia-Toro et al., 2001). These factors likely contributed to the lack of efficacy of adjunctive rTMS treatment for depression.

In this study, a very low dose of stimulation was used with regard to the intensity.

Some scholars believed that higher intensity was associated with greater clinical effects, but with very little evidence for significant effect seen at 80% of the resting motor threshold. Lefaucheur and his colleagues (Lefaucheur et al., 2014) discovered that the rate of responders significantly increased when the number of sessions was greater than 10, the total number of pulses delivered per session greater than 1000, and the stimulation intensity greater than 100% RMT. There are just 5 researches used 80% of the resting motor threshold in the 38 evidences of definite antidepressant effect of HF rTMS of the left dlPFC from 1996 to 2014. In our clinical practice, we found that most of patients would be unable to continue treatment for severe headache, if the RMT was more than 100%. Such obvious difference in RMT with HF rTMS treatment might result from the certain physical differences between Chinese and Westerners (Bretlau et al., 2008), and of course, inter-individual variation was also involved in it. No matter what, our results added the evidence for the very low stimulation intensity as the same as higher intensity has the similar effects on the depression.

Previous study (George et al., 2000) reported that effects of rTMS could be improved significantly over the placebo group after the cessation of rTMS stimulation for 12- week follow-up. However, in our study, the significant difference in response rate and remission rate between two groups disappeared at the 8th weekend. This phenomenon might be resulted from the dosage of paroxetine gradually increased at the 5th week after the cessation of rTMS stimulation according to the reduction rate of the score of HDRS. In other words, it is not that the effectiveness of rTMS that disappeared, it is that the effectiveness of paroxetine that increased for the incremental

dosage.

rTMS is a non-invasive physical therapy shown to be with minimal side effects. It may be used to accelerate the ameliorating effects of antidepressants on depressive symptoms with short-term application during early treatment. rTMS was approved by the U.S. FDA in 2008 as a treatment for adults with MDD who do not respond to a single antidepressant medication in the current depressive episode. Short-term rTMS during early treatment in first-episode depressed patients appears to shorten the onset of action of antidepressants, thus reducing the dosage of antidepressants. One goal is to increase response and remission rates at the end of 4 weeks of antidepressant treatment. A previous study (Henkel et al., 2009) suggested that early improvement during the first 2 weeks might predict, with high sensitivity, later responses and remission even to hospitalized patients who had suffered more severe depression. This rapid onset of antidepressant efficacy may also be helpful for reducing the risk of suicide and relapse and help patients spend less time in the hospital and return to society sooner. This effectiveness of rTMS needs to be further tested in the future. Alternatively, there is more friendly procedure of TMS protocol, such as low frequency on the right hemisphere (Pallanti et al., 2010), that has been shown as equally effective. This low frequency TMS protocol also needs to be further tested in the future.

5. Limitations

In our present study, we did not use the neuronavigation system with which the coil could be accurately placed over the desired brain area, and just used the “standard

procedure". A recent review (Lefaucheur et al., 2014) argued that such "standard procedure" could greatly biased to experiences of investigators in determining the "motor hotspot" as well as to the inter-individual variability of cortical anatomy. They also noted that such as "standard procedure" of targeting the dlPFC (the "5 cm rule") was anatomically incorrect as the resulting targeted area reached was in the majority of the cases the premotor cortex and the frontal eye field rather than prefrontal cortex (Brodman's areas 46 and 9). However, our active rTMS treatment showed up a superior antidepressant efficacy compared to sham treatment. This may result from good connection between dlPFC and the subgenual cingulate gyrus (Fox et al., 2012) or first episode patients with depression or some other reasons. In future studies, neuronavigation and functional imaging could be combined to explore the rTMS mechanism of action in depression. Secondly, this study was conducted to explore whether rTMS could enhance the antidepressant efficacy of the SSRI paroxetine in first - episode depressed patients. We think rTMS combine with paroxetine as a whole of treatment method and regard the participants in one group as a whole. The dose of stimulation of rTMS must be fixed during the study. The effectiveness included both paroxetine and rTMS. If the effectiveness is obvious with rTMS, the dosage of paroxetine will be smaller during the study than that with paroxetine monotherapy. Otherwise, the dosage of paroxetine will be no different. If the dosage of paroxetine was less in active rTMS group than that in the control group, it can imply the rTMS is benefit to depression. Thirdly, the sample size is comparatively small, and the follow-up is short. We will perform another research with a big sample size and as far as possible

for a long time of follow-up to clarify the long-term therapeutic effects of rTMS for depression in the future.

6. Conclusion

This randomized controlled trial provided evidence that 10 Hz rTMS at 80% MT effectively accelerates and augments the therapeutic response to paroxetine and is safe and well tolerated in Chinese patients with first-episode depression.

Figures Legends

Fig. 1. Changes in HDRS score in both groups. HDRS ratings were performed each week after five sessions of rTMS and at the end of the 8th week. The data are expressed as mean and standard error. * $p < 0.05$, different from sham group. rTMS, repetitive transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale.

Fig. 2. Paroxetine dosage in both groups. * $p < 0.05$, different from sham group. The data are expressed as mean and standard error. rTMS, repetitive transcranial magnetic stimulation.

Table 1. Demographic and clinical characteristics of the two groups.

Characteristic		Active rTMS group	Sham rTMS group	<i>p</i>
Gender				0.441 ^a
Male, n (%)		12 (54.5%)	11 (47.6%)	
Female, n (%)		10 (45.5%)	10 (52.4%)	
Age (years)		28.82 ± 8.46	30.05 ± 9.47	0.655 ^b
Education (years)		12.95 ± 4.91	11.62 ± 4.65	0.366 ^b
Mean duration of current episode (months)		4.32 ± 2.25	4.31 ± 1.83	0.989 ^b
HRSD score	Baseline	43.50 ± 9.89	42.81 ± 9.29	0.815 ^b
	Week1	32.36 ± 6.28	37.24 ± 8.03	0.00 ^b
	Week2	25.00 ± 4.74	28.52 ± 5.67	0.02 ^b
	Week3	17.95 ± 3.82	21.95 ± 4.98	0.00 ^b
	Week4	8.41 ± 4.02	11.29 ± 4.60	0.00 ^b
	Week8	7.32 ± 3.24	8.14 ± 4.50	0.48 ^b
Response	Week4	95.5%	71.4%	0.041 ^a
	Week8	90.9%	85.7%	0.189 ^a
Remission	Week4	68.2%	38.1%	0.009 ^a
	Week8	86.4%	76.2%	0.069 ^a

^a χ^2 test. ^b Student's *t*-test. HRSD, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation.

Authors' contributions

Su-Xia Li, Xue-Yi Wang designed the trial and was responsible for obtaining approval by the Ethics Committee of the First Hospital of Hebei Medical University, China;

Yu-Mei Wang, Ning Li contributed to recruit participants, data analysis and manuscript preparation;

Mei Song contribute to the treatment of patients and also do data collection;

Lin Lu was responsible for directing and monitoring all details of the study.

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Figure. 1

Figure. 2