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Adjunctive neuronavigated accelerated continuous theta-burst stimulation in obsessive-compulsive disorder: a randomized sham-controlled study

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Abstract

Background. Approximately 40% of patients treated for obsessive-compulsive disorder (OCD) do not respond to standard and second-line augmentation treatments leading to the exploration of alternate biological treatments. Continuous theta burst stimulation (cTBS) is a form of repetitive transcranial magnetic stimulation inducing more rapid and longer-lasting effects on synaptic plasticity than the latter. To the best of our knowledge, only one recent study and a case report investigated the effect of cTBS at the supplementary motor area (SMA) in OCD.

Objective. This study aimed to examine the effect of accelerated robotized neuronavigated cTBS over SMA in patients with OCD.

Methods. A total of 32 patients with OCD were enrolled and randomized into active and sham cTBS groups. For active cTBS stimulation, an accelerated protocol was used. Bursts of three stimuli at 50 Hz, at 80% of MT, repeated at 5 Hz were used. Daily 2 sessions of 900 pulses each, for a total of 30 sessions over 3 wk (weekly 10 sessions), were given. Yale–Brown Obsessive-Compulsive Rating Scale (YBOCS), Clinical Global Impressions scale (CGI), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A) were administered at baseline and at end of weeks 3 and 8.

Results. A total of 26 patients completed the study. Active cTBS group showed significant group × time effect in YBOCS obsession ($P < .001$, $\eta^2 = 0.288$), compulsion ($P = .004$, $\eta^2 = 0.207$), YBOCS total ($P < .001$, $\eta^2 = 0.288$), CGI-S ($P = .010$, $\eta^2 = 0.248$), CGI-C ($P = .010$, $\eta^2 = 0.248$), HAM-D ($P = .014$, $\eta^2 = 0.224$) than sham cTBS group.

Conclusions. Findings from our study suggest that adjunctive accelerated cTBS significantly improves psychopathology, severity of illness, and depression among patients with OCD. Future studies with larger sample sizes will add to our knowledge.

Introduction

Obsessive-compulsive disorder (OCD) is a common and chronic disorder. This disabling disorder is characterized by several obsessions and/or compulsions. Although few psychological interventions are effective as an augmentation to selective serotonin reuptake inhibitors (SSRIs) in treating OCD,[1] many patients cannot engage or do not respond to such treatments. Some patients with OCD who are on SSRIs experience adverse reactions. This led researchers to investigate alternate biological treatments for OCD. Repetitive transcranial magnetic stimulation (rTMS), being one such brain modulatory approach, has shown to have a positive effect on mood disorders with stimulation of the prefrontal cortex.[2] Greenberg et al[3] were the first to hypothesize that inhibition of the prefrontal activity might be useful for obsessive-compulsive symptoms. Cortico–striato–thalamo–cortical (CSTC) circuitry malfunction has been hypothesized to be pathogenic in OCD. A recent network meta-analysis has found three different sites to be included for modulation of rTMS in OCD. These are the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), and pre-supplementary motor area (SMA).[4] But the authors found that rTMS was efficacious compared with sham across three different rTMS protocols (high-frequency [HF] bilateral dlPFC, low-frequency [LF] pre-SMA, and LF right dlPFC) for the treatment of OCD but failed to recommend one protocol over another. Poor inhibition of irrelevant information and response control is found to be due to higher-than-normal levels of cortical excitability in patients with OCD.[5,6] This is supplemented by a neuroimaging study as well, where the SMA was found to be related to deficit inhibitory behavior control.[7] While only a recent open-label study[8] had examined neuronavigated accelerated cTBS in OCD on the right frontal cortex, only one randomized sham-controlled study had looked into the effect of conventional cTBS over SMA in OCD.[9] To date, very few randomized sham-controlled studies

have examined low-frequency stimulation of supplementary motor cortex (SMA) in OCD.[9-14] In such study with 21 medication-resistant patients with OCD, rTMS to the SMA bilaterally, consisting of 1200 pulses/day, at 1 Hz and 100% of motor threshold (MT), showed a response in 67% of completers compared with 22% in the sham group at 4 wk. Active group showed a 25% reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores compared with a 12% reduction in the sham group.[11] In another randomized double-blind trial with 22 treatment-resistant patients with OCD, active rTMS group (1-Hz, 20-min trains (1200 pulses/day) at 100% of resting MT, once per day, 5 d per week, for 2 wk) to bilateral SMA showed 41% response rate compared with 10% with sham treatment and an average of 35% reduction on the Y-BOCS compared with baseline.[10] Another randomized double-blind study tested the efficacy of 1-Hz rTMS over pre-SMA among 40 patients with OCD randomized into active or sham groups. The study did not find any significant differences in Y-BOCS scores between groups.[13] Low-frequency rTMS over 6 wk, applied over the SMA in 21 patients with OCD showed a clinically significant decrease in Y-BOCS scores in the active group compared with both the baseline and the sham group.[12] On the contrary, another double-blind randomized sham-controlled trial of low-frequency bilateral rTMS over pre-SMA did not find such improvement.[14] A recent randomized sham-controlled trial that used continuous theta burst stimulation (cTBS) over SMA did not find a significant reduction in OCD symptoms.[9] Another randomized trial attempted to examine the effect of the same on the OFC in OCD.[15] Over the last 10 y, TBS, characterized by lower stimulation intensity and a shorter time of stimulation compared with conventional TMS protocols, has been increasingly used as an experimental and therapeutic tool. Research claims that it could induce more rapid and longer-lasting effects on synaptic plasticity than conventional TMS protocols.[16]

Despite several systematic reviews and meta-analyses,[17,18] no consensus has been established on the most efficacious protocol for OCD treatment.[4] To the best of our knowledge, only one recent study and a case report investigated the effect of TBS at SMA in OCD.[9,19] To add to this, recent research suggests that compared with traditional TMS protocol, an accelerated protocol compresses an entire course of traditional TMS treatment (usually 6 wk) down to a much shorter duration. A recent pilot study attempted accelerated TBS in OCD over a 5-d protocol.[8] This study applied cTBS over five consecutive days among seven treatment-refractory patients with OCD. The authors reported a response rate at ≥1 time point of 71% with minimal side effects. Accelerated protocols are capable to promote metaplasticity.[20] Thus, this study aimed to examine the effect of accelerated robotized neuronavigated cTBS over the SMA among patients with OCD on the severity of obsession and compulsions.

Methods

The study was a prospective hospital-based, randomized, sham-controlled study, conducted at the Neuromodulation Centre of a tertiary Psychiatric hospital located in Eastern India. The study was approved by the Institute Ethics Committee and was registered with the Clinical Trial Registry of India [CTRI/2019/07/020366]. The data were collected between August 2019 and June 2020. The inclusion criteria for consenting patients were (1) diagnosis of OCD using Diagnostic Criteria for Research (DCR) of International Classification of Disease-10th edition (ICD-10) by World Health Organization,[21] (2) patients who were between 18 and 60 years old of either sex, (3) patients with OCD on SSRI medications for more than 12 wk, (4) patients with OCD on a stable dose of SSRI for preceding 8 wk before checking for eligibility for the study, and (5) right-handed. Patients with (1) severe depression (Hamilton Rating Scale for Depression[22] > 23), (2) comorbid neurological or other psychiatric disorder(s), (3) comorbid substance dependence, except nicotine and caffeine, (4) having any metallic implants/parts in the body were excluded from the study, (5) history of receiving any brain stimulation intervention (eg ECT, rTMS, and tDCS), (6) history of non-pharmacological therapy (eg exposure therapy, cognitive-behavior therapy) were excluded from the study. Informed consent was obtained from each eligible patient before enrolling in the study. Enrolled patients were sequentially randomly assigned to groups with a single random-number sequence (no stratification). The numbers were written in a series of sealed envelopes. The envelope for each patient was opened immediately before the commencement of the first treatment session by the clinician administering the cTBS after the administration of the baseline assessment. The patients and rater were blinded to treatment, but the clinician administering the cTBS was aware of the treatment group. Figure 1 shows the CONSORT flow chart for study progression.

Sample size

Sample size calculation was performed by using software G*POWER with a priori calculation of moderate effect size with a level of significance at 0.05 and at 80% power between 2 groups over three times points. The sample calculated was 28. Considering the 10% dropout rate, the desired sample size was 32 (16 patients with OCD in the Active group and 16 in the Sham group).

Tools

The following tools were used: (1) Socio-demographic and Clinical Data Sheet—a semi-structured proforma for recording demographic details like age, sex, marital status, religion, education, occupation, socio-economic status, habitat, and family type as well as clinical data; (2) Handedness Preference Schedule[23]—Hindi version was used to determine right-handedness of the patients before enrolling for the study, (3) *Y-BOCS*[24]—to rate the severity of OCD; (4) CGI Severity and Improvement[25]—the severity of illness (CGI-S) and global improvement or change (CGI-C) parts were used (5) Hamilton Depression Rating Scale (HAM-D)[22]—to sate severity of depression; (6) Hamilton Rating Scale for Anxiety (HAM-A)[26]—to rate severity for anxiety were used, (7) rTMS Standard Screening Questionnaire[27]—this questionnaire was proposed by the International Federation of Clinical Neurophysiology. It is a screening standard questionnaire for cTBS candidates comprising fifteen questions to screen patients for inclusion for cTBS. Each question was to be answered in a yes/no format. (8) rTMS Side Effect Checklist[28] (Adapted from Slotema et al[28]) was used to assess the side effects of cTBS after each session. (9) Magstim Rapid Square plus for MEP and delivery of cTBS sessions—The Rapid works by inducing electrical currents in tissues using a non-invasive stimulating coil at frequencies of up to 100 Hz. The stimulating coil is placed near the intended site of stimulation. Magstim Rapid magnetic stimulators combine stimulation frequencies from 1 Hz to 100 Hz with a touch screen interface that controls every aspect of the stimulator's control and operation. For an active stimulation figure of eight coils and for sham stimulation sham coils were used. (10) Visor Neuronavigation device and robotic arm for coil positioning—A neuro navigation system

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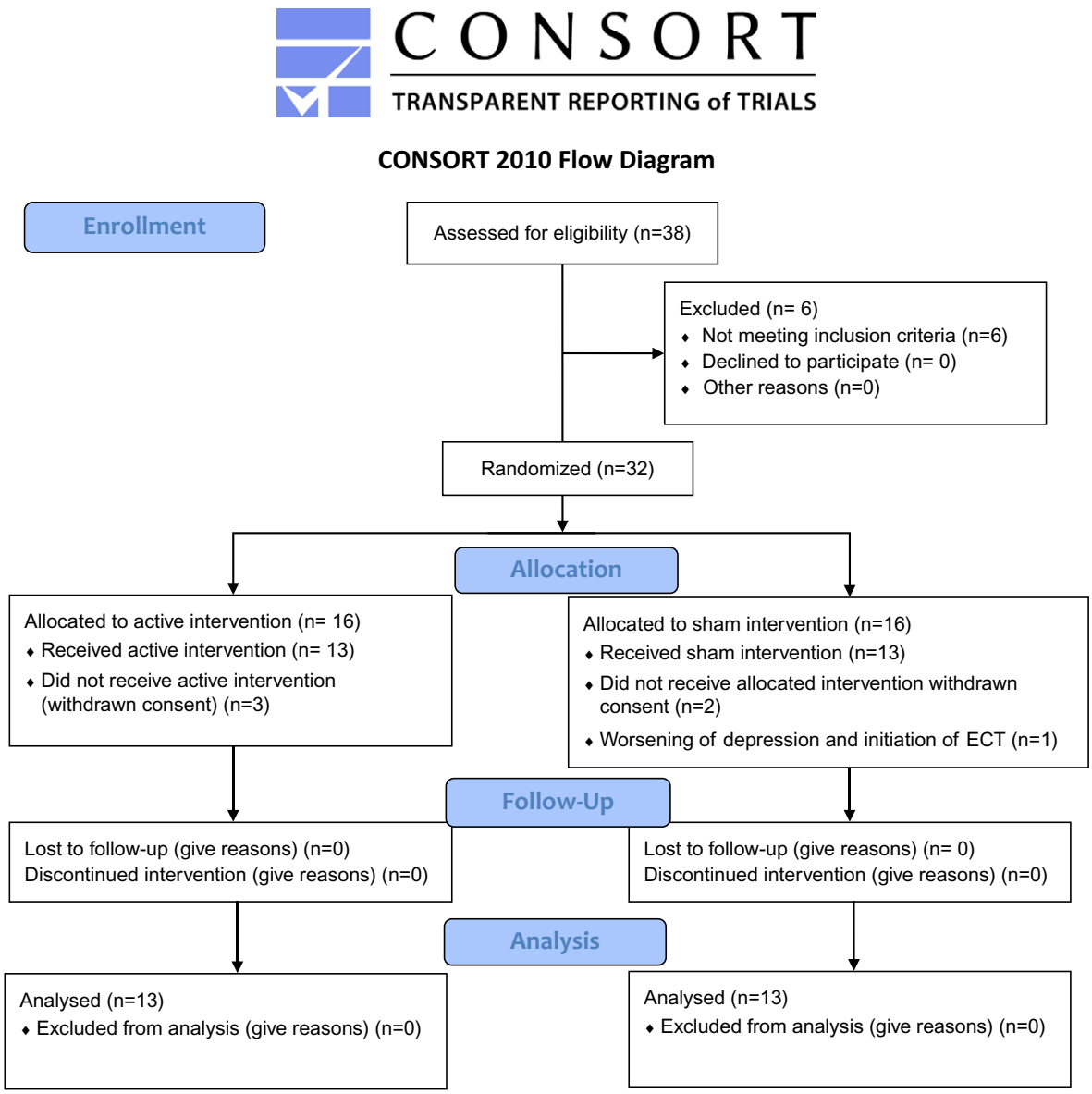

Figure 1. CONSORT flow diagram of the study.

(Visor neuro navigation System) was adapted to navigate the coil according to the standardized anatomy[29] as visualized by high-resolution structural T1-weighted magnetic resonance imaging (MRI). The Visual Neuronavigation System (VNS) allowed the visualization of the coil location in relation to the brain in real-time on a computer screen.

Procedure for data collection

The patients with OCD fulfilling inclusion and exclusion criteria were admitted as inpatients. Informed consent was taken from patients after explaining the procedure in detail. A screening standard questionnaire for cTBS was applied. Handedness Preference Schedule was applied to recruit right-handed patients only. A detailed physical examination was done to rule out any neurological disease. Socio-demographic data was collected.

Estimation of motor threshold

The MT for the left abductor pollicis brevis (APB) was determined using a figure-of-eight shaped coil at 1-Hz frequency according to the Rossini–Rothwell algorithm.[30] To find the hand area of the motor cortex, the center of the figure-of-eight TMS coil was positioned 5 cm lateral to the vertex on the interauricular line and the handle was angled 45° away from the sagittal plane.[29] Therefore, our point of stimulation began in approximately this region. The stimulations were given at 1 Hz, and the coil was methodically moved across the right frontoparietal region of the cranium centered at the above-indicated point until the motor cortex for the APB was located. Up to 10 single pulses were given at each level of intensity. Beginning at 50% intensity, it was increased or decreased by 2% and the procedure was repeated until APB MT was achieved, which was defined as the stimulus intensity that reliably produces visibly observable left APB muscle contractions and/or produced 5 MEP responses of at least 50 μV in 10 trials.[31] This was measured once at baseline before cTBS sessions started.

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Robotised neuronavigated cTBS

Patients were randomly assigned to real (active) or sham treatment. A high-resolution T1-weighted magnetic resonance (MR) anatomical image using a 3-T MR scanner of the patient was taken for use in the neuronavigational system. Nasion–Ear coordinate markers were set. Segmentation was used to divide the MRI into the scalp and brain compartments. Then SMA for the cTBS stimulation site was determined by "Visor Neuronavigational System" using Montreal Neurological Institute (MNI) coordinates. Patients were comfortably seated on a neuronavigation chair, which can be adjusted for height and angle. The MT was determined before starting the first session, for left APB. The cTBS was given over SMA using Magstim Rapid[2] plus device at 80% of MT, a burst of three stimuli at 50 Hz, repeated at 5 Hz frequency using a figure of 8 coils. Daily 2 sessions of 900 pulses each (total 1800 daily stimulations) spaced apart by minimum 5 h, for a total of 30 sessions over 3 wk (weekly 10 sessions; 18,000 stimulations) were given. Thus an "accelerated" protocol with more than 1000 pulses per day for more than 2 wk was used in our study.

Magstim Rapid Square Plus machine was used to deliver magnetic stimulation using a figure of 8 coils. The figure of 8 coils was calibrated on the "Visor Neuronavigation System." A robotized arm coupled with a neuronavigation system (Visor Neuronavigational system) was used for the coil to assist in maintaining its position over the target area. Thus, a standardized selection of the target was made with real-time compensation for the head and body motions of the patients. Once the area was defined, it was kept constant for the cTBS session and, as an advantage over classical cTBS, approximately 100% of the magnetic load was delivered over the target. Sham stimulation was provided with the figure of 8 sham coils in an identical manner to the active stimulation. cTBS side effect checklist was applied after each session.

During the study period, all patients remained admitted to the hospital for 3 wk of cTBS sessions. Rescue medications were administered if any emergency arose. For this purpose, parenteral/oral lorazepam was used. Patients were continued with SSRI and the dosage was kept stable throughout the study period till 8 wk of follow-up. Y-BOCS, HAM-D, HAM-A, and CGI scores were obtained at baseline before delivering cTBS on the first day. All measures were repeated once at the end of cTBS sessions in week 3 and a second time at end of week 8 after the last cTBS sessions.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences version 25.0 for Windows. After checking for normality with skewness statistics, group differences for demographic and clinical characteristics of two groups at baseline were examined with an independent *t*-test, Mann–Whitney *U* test, and χ^2 test, wherever applicable. The overall effect of treatment over time between active TBS and sham TBS groups was analyzed with a multivariate repeated-measures analysis of variance (ANOVA). Treatment and time were used as between-group and within-subject factors. Greenhouse–Geisser correction for sphericity was applied if sphericity was violated. Bonferroni adjustment was applied for multiple pairwise comparisons. A level of significance of $P < .05$ (2-tailed) was taken to consider a result statistically significant.

Results

A total of 32 patients with OCD fulfilling the inclusion and exclusion criteria were recruited for the study. Coronavirus disease-2019 (COVID-19) pandemic and related lockdown prevented us to continue patient recruitment. Among 32 randomized patients, six patients dropped out. One patient dropped out because of worsening depression and the initiation of electroconvulsive therapy. Five patients dropped out due to being unwilling to continue cTBS sessions. For the final analysis, 26 patients were taken for study; of which 13 received active extended cTBS stimulation and 13 received sham stimulation. Supplementary Table S1 describes baseline comparisons between active and sham groups. Both groups were comparable in their demographic and clinical characteristics. Clinical response was considered as a 35% reduction in YBOCS scores or CGI-C scores less than or equal to 2 at 8 wk after the last session of cTBS. While three patients in the active group and none from the sham group showed YBOCS clinical response, this was not statistically significant (Yate's correction = 1.50, df = 1, $P = .22$). Also, four patients from the active group and one from the sham group showed a response in CGI-C score at 8 wk this was comparable (Yate's correction = 0.99, df = 1, $P = .32$).

Supplementary Table S2 shows the group × time interaction effects between 2 groups. Active cTBS group showed significant improvement in YBOCS obsession, YBOCS compulsion, YBOCS total, CGI-S, CGI-C, and HAM-D scores) than the sham group with a high effect size ($\eta_p^2 > 0.14$). Pairwise comparisons showed that YBOCS obsession, compulsion, and total scores significantly improved both at week 3 ($P < .001$) and week 8 ($P < .001$) compared with baseline. A similar pattern of improvements was observed in CGI-S, CGI-C, HAM-D, and HAM-A as well ($P < .001$). Figures 2–8 show estimated marginal means of, YBOCS obsession, YBOCS compulsion, YBOCS total, CGI-S, CGI-C, HAM-D and HAM-A respectively. Overall, while a significant improvement from baseline was observed both at weeks 3 and 8, improvement between weeks 3 and 8 remained comparable.

There were no major side effects like an attack or seizure as reported with high frequency rTMS stimulation. Four patients (three in the active and one in the sham group) complained of headache localized to the stimulation site, mild to moderate in intensity soon after the cTBS session that subsided spontaneously without the need for analgesics.

Discussion

Study design

Our study tested the effect of adjunctive accelerated neuronavigated cTBS over SMA among patients with OCD. We chose SMA based on recent findings that implicate the hyperactivity of the SMA and pre-SMA (the rostral part of SMA) in the pathogenesis of OCD.[32,33] Over conventional ones (over 4–6 wk), we used an accelerated protocol, which has earlier been found to prolong the stimulation after-effects on cortical excitability multiple times.[34,35] Researchers have speculated that longer-lasting after-effects of an accelerated protocol might be due to physiological mechanisms observed in earlier animal models where the repeated application of stimulation increased the lifetime of synaptic plasticity.[36-38] The Neuronavigation system enabled us to precisely locate the site of stimulation, which was an advantage over other studies and has been used in very few studies only.[13] Thus, compared with earlier studies, our study had twofold advantages in the cTBS protocol.

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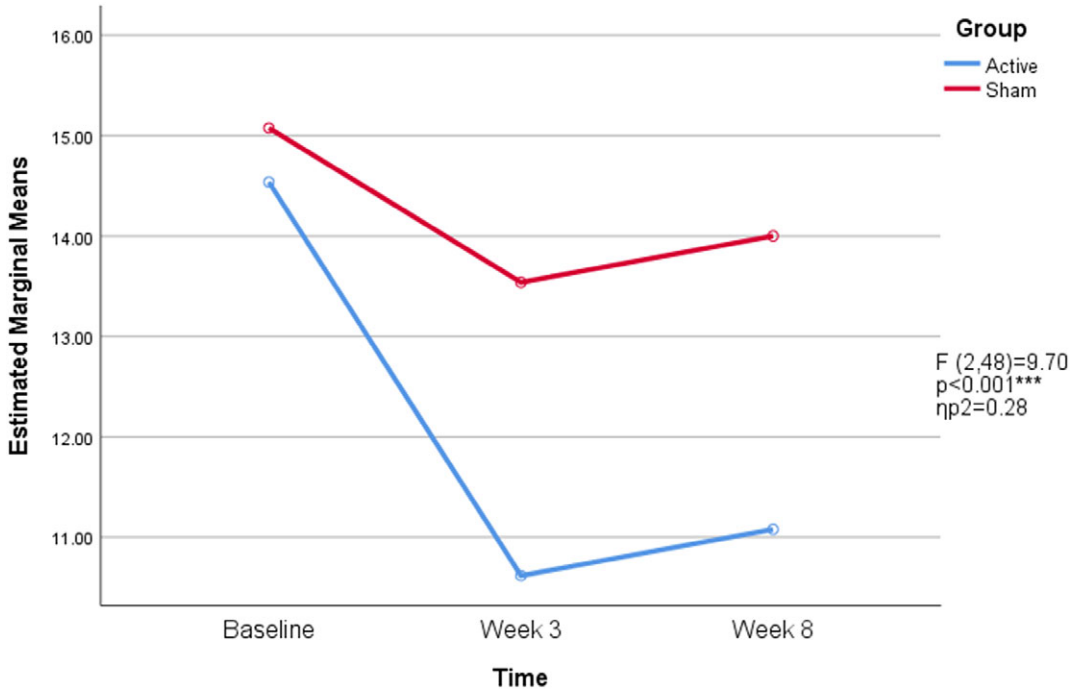

Figure 2. Estimated marginal means of YBOCS obsession.

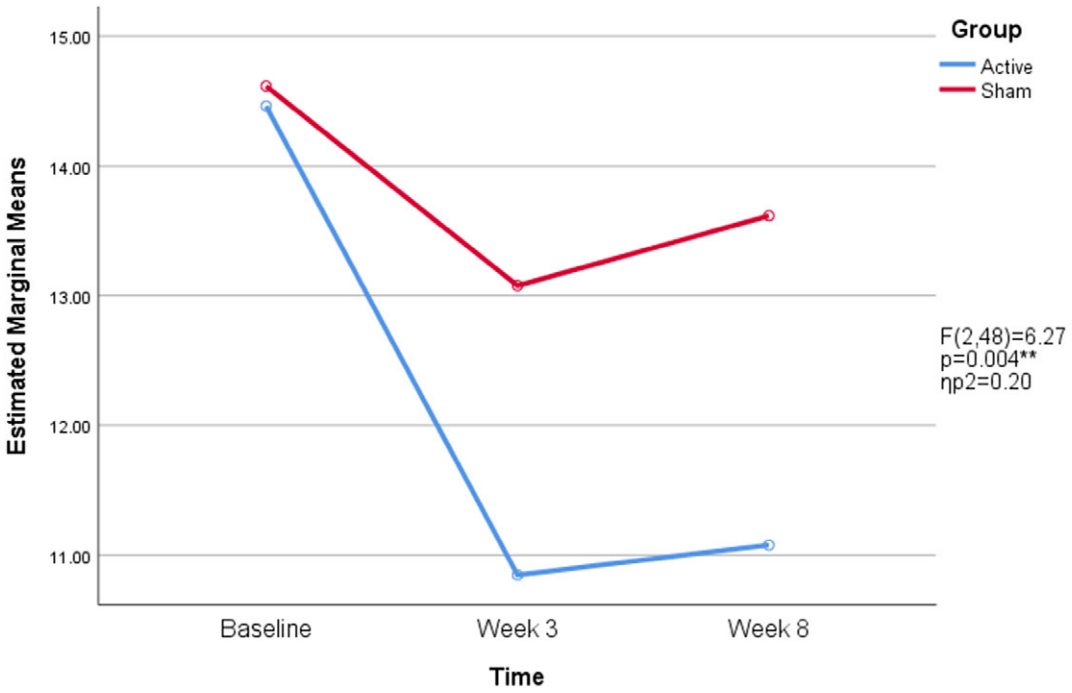

Figure 3. Estimated marginal means of YBOCS compulsion.

Sample characteristics

The active and sham groups were comparable in terms of age, sex, education, marital status, occupation, religion, and habitat. Males and females were equally represented in our study. Such an equal distribution of both sexes was ensured only in one previous study.[3] In most other studies, the male population was overrepresented,[39,40] while females predominated in a few studies.[13,41] At baseline patients included in our study had moderate-to-severe OCD (mean YBOCS > 24) which was like most of the earlier studies.[4] Our study did not include only treatment-resistant OCD, unlike most of the earlier studies which might be one of their potential limitations.[4,10,11,39,40] As mentioned above both depression (means HAM-D < 17) and anxiety (mean HAM-A < 17) symptoms among our sample were mild or mild to moderate severity. To minimize the

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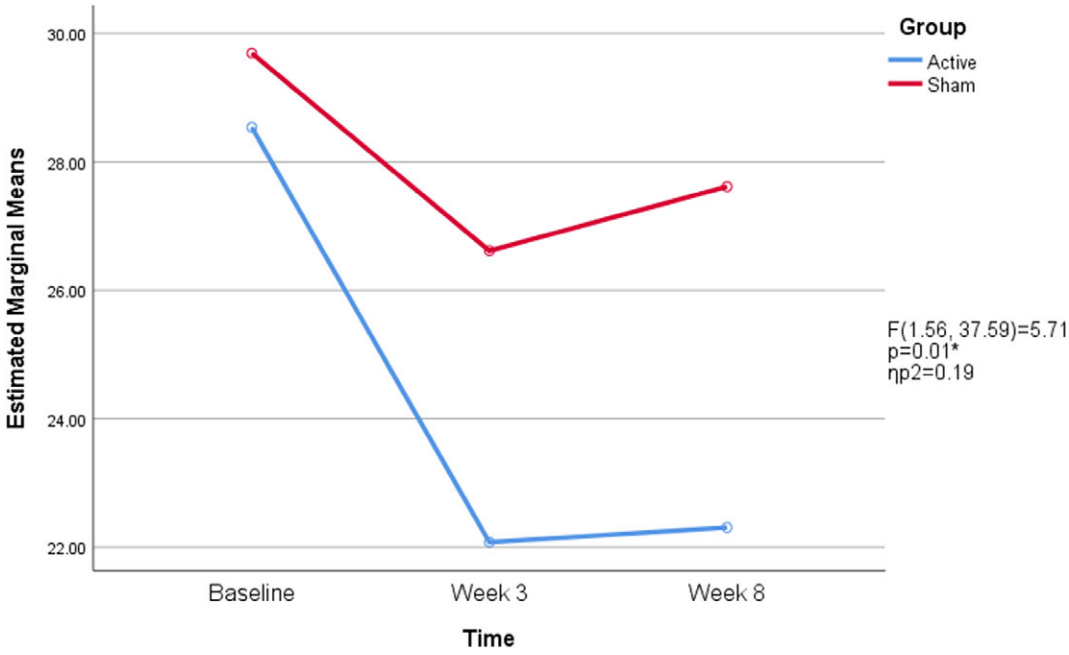

Figure 4. Estimated marginal means of YBOCS total.

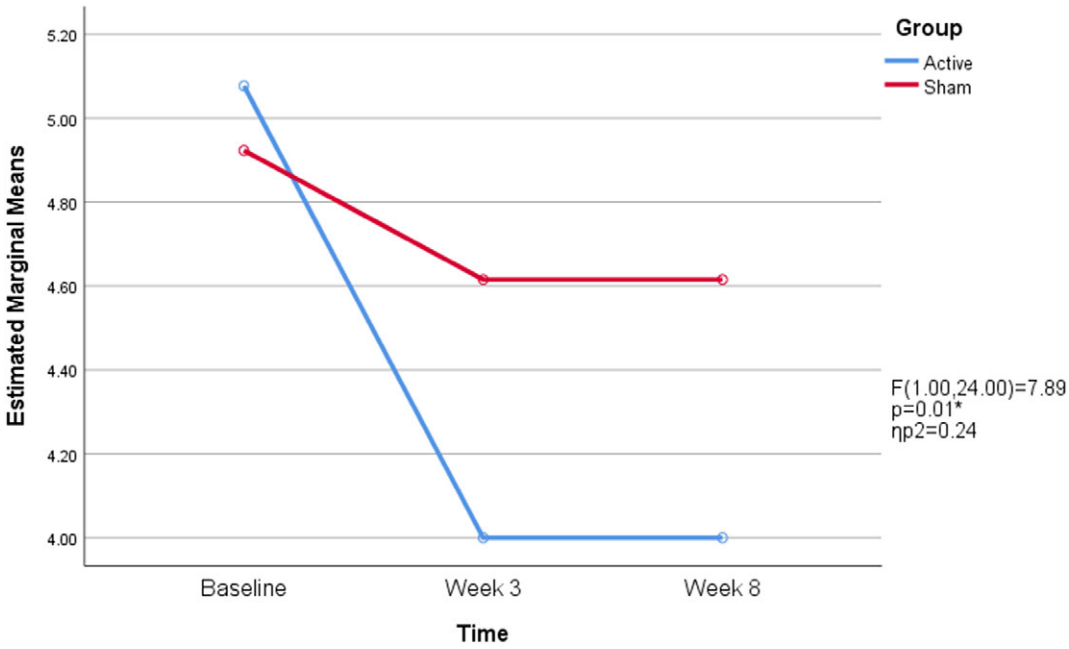

Figure 5. Estimated marginal means of CGI-S.

confounding effect of depression in the sample, our study samples excluded severe depression like earlier studies[41,42] but not in few other studies.[3,39,43] Unlike an earlier study[39] which included comorbid tic disorder, our study did not include psychiatric comorbidities except mild to moderate depression.

Outcome measures

Our study found a significant reduction in YBOCS total score, obsession, and compulsion sub scores in the active TBS group compared with the sham group. Hawken et al[12] found a similar reduction at the end of 6 wk following rTMS at SMA though they did not examine obsession and compulsion sub-scores. An earlier study with sequential rTMS at right PFC followed by at SMA did not find such a difference.[40] As possible reasons for this, the authors speculated about OCD-related regions such as left orbitofrontal and bilateral prefrontal characteristic hypermetabolism and/or partial real stimulation effect in the sham group. Mantovani et al[11] found that low-frequency rTMS delivered to SMA resulted in more clinical responders among 4-week active treatment

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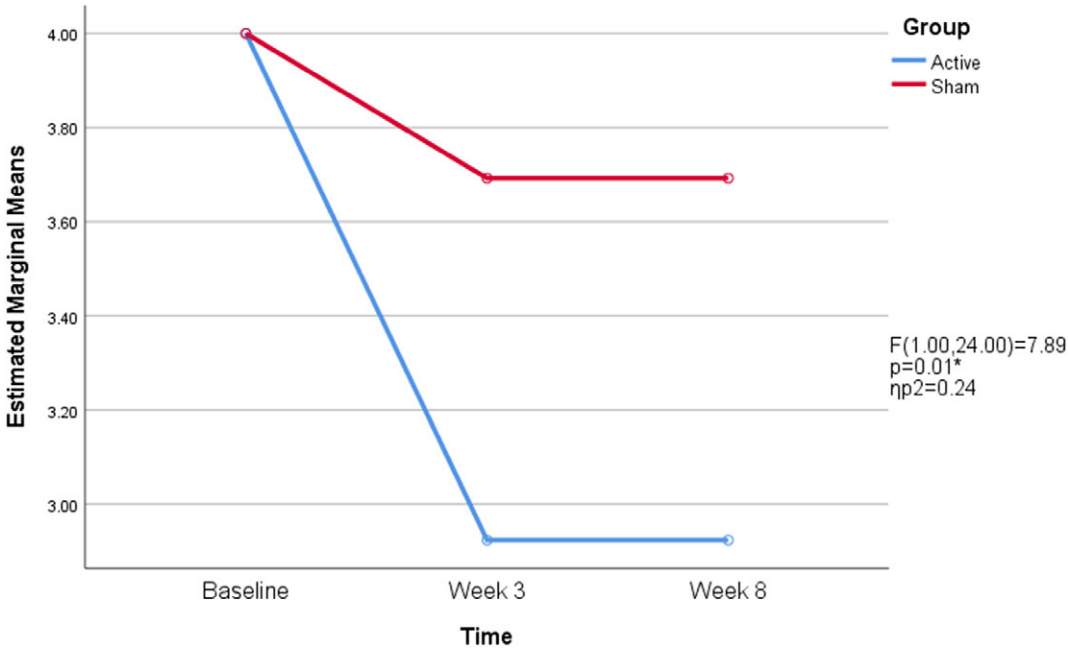

Figure 6. Estimated marginal means of CGI-C.

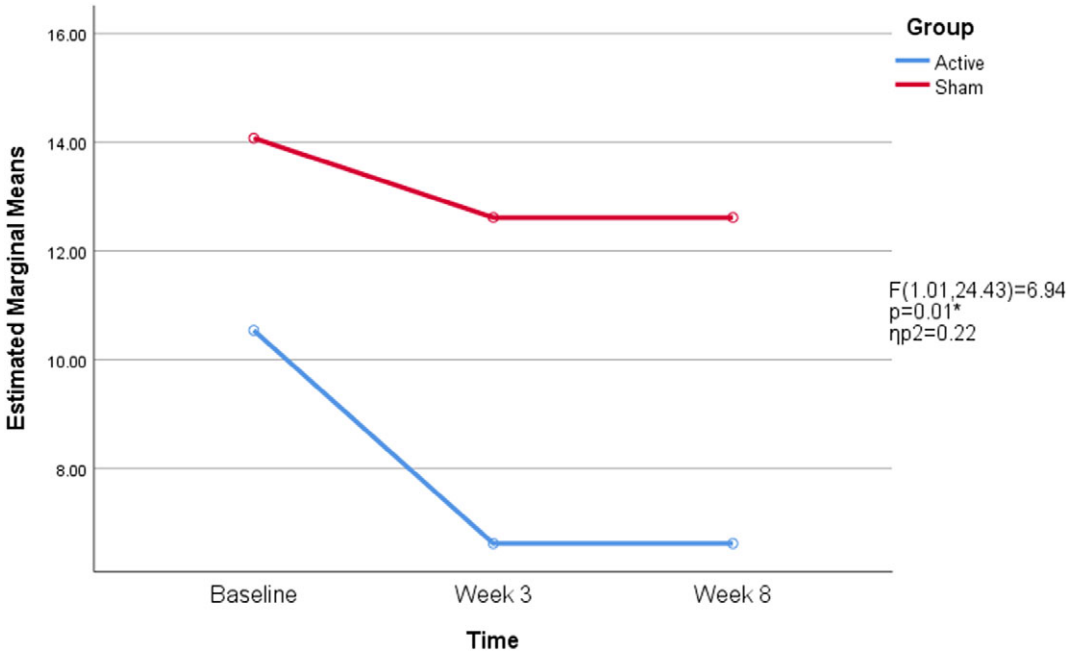

Figure 7. Estimated marginal means of HAM-D.

compared with the sham group though the difference was non-significant. Note that this included only treatment-resistant OCD only which might have a bearing on its results. Another study that included treatment-resistant OCD only as well applied rTMS at pre-SMA found similar improvement in the active group compared with the sham group though their study suffered from not fulfilling placebo system for their sham stimulation[44] mentioned limitation of sham stimulation quality in their study.[10] A recent study that examined the effect of TBS at SMA in OCD did not find any difference.[9] One of the reasons for their failure to find a difference between the groups they mentioned was the lack of optimal stimulation characteristics and the inclusion of resistant OCD. None of the earlier studies had considered YBOCS obsession and compulsion sub-scores whereas improvement in both subscales in our study can be well reasoned for improvement in YBOCS total score. This can well initiate generating evidence for the effectiveness of TBS in OCD variants like predominant obsession and predominant compulsion types.

As a secondary outcome measure, our study looked into changes in CGI score which were significant in the active cTBS

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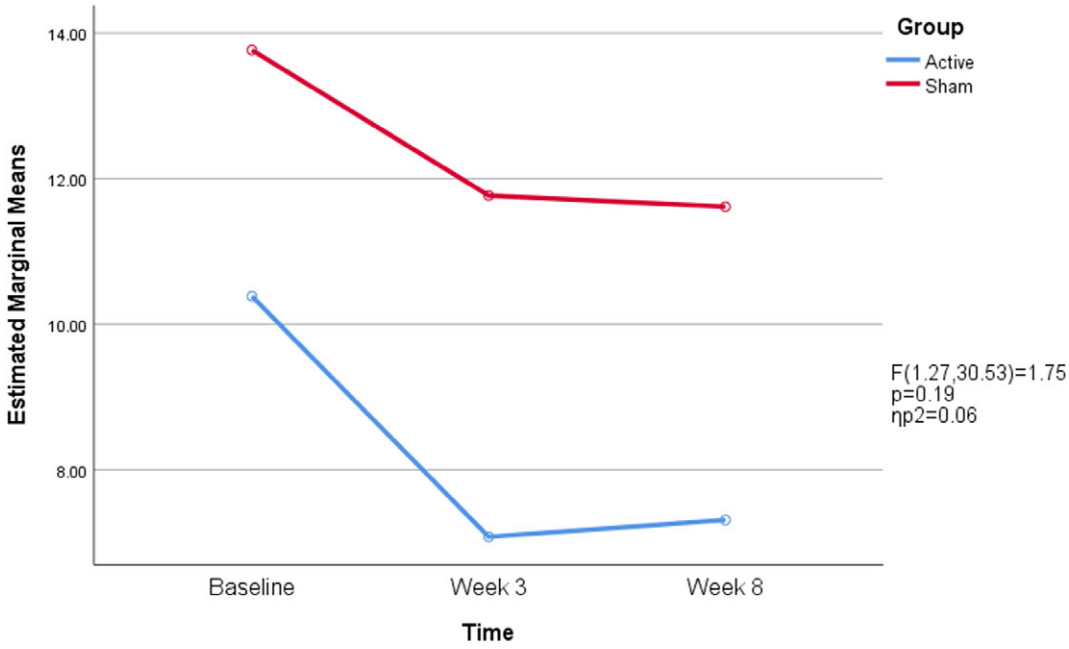

Figure 8. Estimated marginal means of HAM-A.

group compared with the sham cTBS group. Harika-Germaneau et al[9], in their recent study, did not find any such difference in CGI between groups which might be due to their treatment-resistant nature of illness and lack of optimal stimulation characteristics as discussed above. Both groups in our study showed improvement in HAM-D and HAM-A. This might be due to ongoing SSRI medications. Also, placebo effects are well recognized and are thought to be due to the expectancy of improvement by patients which influences outcomes of any placebo drug or sham intervention.[45-47] This additionally might explain the improvement in anxiety and depression in the sham group as well. However, our study found significant changes in HAM-D but not in HAM-A over time in the active group compared with the sham group. Except for Hawken et al[12], all earlier studies had measured depression and anxiety as a secondary outcome.[9-11,40] None of these studies found significant improvement in either depression or anxiety except Mantovani et al[11] who found a significant difference in anxiety as the main effect of time. The significant improvement in depression in the active group compared with the sham group in our study might be dependent on the improvement of OCD symptoms or because of TBS on depression.[48] Though a recent study has attempted to examine the effect of iTBS in post-traumatic stress disorder (PTSD)[49] research so far for TBS in anxiety is very limited. Our study suffered from few limitations.

Our study had a few limitations. No blinding questionnaire was used to check blinding throughout the trial. Owing to COVID-19 restrictions and attrition, we could recruit only 26 instead of desired 28 which reduced the power of the study. The follow-up was restricted to 8 wk only.

Conclusions

To the best of our knowledge, this was the first randomized sham-controlled study that examined the effect of neuronavigated accelerated cTBS protocol over SMA in clinical symptoms of OCD. Though the clinical response was comparable between groups, results of our randomized sham-controlled study showed adjunctive neuronavigated accelerated cTBS significantly improved clinical symptoms of OCD than sham cTBS. Future studies with larger sample sizes should focus on replicating and modifying this accelerated neuronavigated cTBS protocol by testing a different number of stimulations per session and number of sessions per day and the number of days of treatment, and so forth to maximize clinical improvement of disabling symptoms of patients with OCD.

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Supplementary Materials. To view supplementary material for this article, please visit http://doi.org/10.1017/S1092852922000980.

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