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THE ACUTE EFFECTS OF ACCELERATED REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON SUICIDE RISK IN UNIPOLAR DEPRESSION: PRELIMINARY RESULTS

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SUMMARY

Background: *Suicide is a major health concern. Effective acute interventions are lacking. Recent studies have suggested an acute decrease of suicidal ideations following repetitive Transcranial Magnetic Stimulation (rTMS). However, placebo effects could not be excluded. We aimed to evaluate the acute effect of accelerated intermittent theta burst stimulation (TBS) on suicide risk in depression.*

Subjects and methods: *In 12 suicidal therapy-resistant depressed patients accelerated intermittent TBS was delivered on the left dorsolateral prefrontal cortex in a randomized, sham-controlled cross-over fashion. Patients received 20 sessions spread over 4 days. The change in severity of suicidal ideation was measured by the Beck Scale of Suicidal Ideation (SSI) before and after treatment.*

Results: *We found a significant decrease of SSI score over time; unrelated to active or sham stimulation. Furthermore, the attenuation of suicidal thinking was not merely related to depression severity changes caused by TBS.*

Conclusions: *Accelerated TBS treatment in depressed suicidal patients was found to be safe and well tolerated and may have the potential to acutely decrease suicidal ideations. However, the efficacy compared to sham has not yet been proven and further sham-controlled research including longer follow-up is needed to substantiate these preliminary findings.*

Key words: *accelerated theta burst stimulation - repetitive Transcranial Magnetic Stimulation - suicide ideation - Major Depressive Disorder - treatment resistance*

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INTRODUCTION

Mortality due to suicide in depression is a major health concern. Every year, more than 800.000 people die from suicide worldwide; this roughly corresponds to one death every 40 seconds. Suicide is among the three leading causes of death in some countries among those aged 15-44 years, and the second leading cause of death in the 10-24 years age group; these figures do not include suicide attempts which can be many times more frequent than suicide (10, 20, or more times according to some studies) (WHO 2012). In 1998, suicide constituted 1.8% of the total disease burden; this is estimated to rise to 2.4% by 2020 (Bertolote 2009).

With the exception of electroconvulsive therapy (ECT), currently there are few 'acute' treatments for suicide ideations and behavior (e.g. lithium, ketamine and clozapine) and these are only partially effective (Sher et al. 2010). However, due to practical limitations and side effects, the utility of ECT is limited. As far as other possible acute interventions, this is an under-studied area of research.

Recent studies have suggested an acute decrease of suicidal ideations when repetitive transcranial magnetic stimulation (rTMS) is administered over the prefrontal cortex (George et al. 2014, Hadley et al. 2011, Holtzheimer et al. 2010, Keshtkar et al. 2011). This application has well-documented positive short-term effects on depressive symptoms without major side-effects (Schutter 2009). Review of the literature also indicates a positive effect of rTMS on suicide risk factors, whether or not via improvement of associated neuropsychological dysfunctions, such as cost-benefit calculations, for example, choosing immediate reward over larger delayed rewards. (Figner et al. 2010) Of interest, it has been shown that TMS may be capable of improving preconditions for suicide, such as mood, memory, attention and executive functions (Sher et al. 2010). Moreover, TMS seems to have molecular effects similar to those seen with ECT such as increased monoamine turnover, increased BDNF, and normalization of the hypothalamic-pituitary-adrenal axis. (George 2010). Previous research has indicated a dose-response relationship of rTMS and current research shows a trend towards delivering more stimuli over a shorter period of time and at higher frequencies (Holtzheimer et al. 2010, Baeken et al. 2013, George et al. 2014). Thetaburst stimulation (TBS) uses bursts of high frequency stimulation at repeated intervals and is thought to affect brain function more profoundly when

compared to the 'classic' rTMS protocols (Di Lazarro 2008).

Consequently, for our randomized, sham-controlled cross-over pilot study, we aimed to evaluate the acute effect of accelerated intermittent TBS on suicide risk in a group of treatment-resistant depressed patients. We hypothesized that this intensified treatment protocol would result in significant decreases in suicidal ideation in the active and not in the sham condition.

SUBJECTS AND METHODS

This study was approved by the ethics committee of the University Hospital Ghent and all subjects gave written informed consent. It was part of a larger project investigating the effects of theta burst TMS on depressive symptoms and suicide risk.

From the 22 adult patients that were enrolled in this pilot study, we included only those 12 unipolar depressed patients which indicated significant suicidal ideation at baseline.

Patients were diagnosed using the structured Mini International Neuropsychiatric Interview (MINI; Sheehan et al. 1998). The 17-item Hamilton Depression Rating Scale (HDRS) was administered and patients were required to have a minimum score of 14 (Hamilton 1967). The 21-items Scale for Suicide Ideation (SSI) was used to assess the intensity of the patients' suicidal ideation and intent. The SSI is an interviewer-administered rating scale that measures the current intensity of patients' ideation, behaviors, and plans to commit suicide. Each item consists of three options graded according to suicidal intensity ranging from 0 to 2. The total score is yielded by the sum of the ratings for the first 19 items, ranging from 0 to 38. The SSI consists of five screening items. Three items assess the wish to live or the wish to die and two assess the desire to attempt suicide. If the respondent reports any active or passive desire to commit suicide, then 14 additional items are administered. These consist of suicidal risk factors such as the duration and frequency of ideation, sense of control over making an attempt, number of deterrents, and amount of actual preparation for a contemplated attempt. Two additional items record incidence and frequency of previous suicide attempts (Beck et al. 1979). We only enrolled patients who had significant suicidal ideations defined by a score of 6 or more on the Beck Scale of Suicide Ideation (SSI). This cutoff score has been used as a threshold for clinically significant suicidal ideation in several previous studies (Sokero et al. 2003). According to the Thase and Rush staging model, the patients were at least stage I therapy-resistant (Thase & Rush 1997). The mean age of our group was 44.91 years (sd=10.8) with a minimum of 22 and a maximum of 61 years old. There were 5 males and 7 females. Exclusion criteria were psychotic symptoms, current or past history of epileptic insult, alcohol dependence and contra-indications for rTMS treatment, such as, cerebral surgical interventions, having a pacemaker, metal or magnetic implants. Antidepressant and antipsychotic medication and mood stabilizers were tapered off in all patients and stopped completely two weeks before the start of the study and during the whole period of the rTMS treatment. Before and after treatment, so at baseline (T1), after the first week of stimulation (T2) and after the second week of stimulation (T3), depression severity and suicide ideation were assessed with the HDRS and the SSI respectively, both by a trained but independent rater unrelated to the study. Patients were randomised into two groups: one group received the active stimulation during the first week and the other group started with the sham condition to switch to the other condition in the second week.

Intermittent TBS stimulaton was applied using a Magstim Rapid2 Plus1 magnetic stimulator (Magstim Company Limited, Wales, UK) with a figure-of eight-shaped coil. Before the first treatment session, the resting motor threshold (MT) of each individual was determined on the right abductor pollicis brevis muscle. A stimulation intensity of 100% of the patient's MT was applied during treatment. We used the Brainsight neuronavigation system (Brainsight™, Rogue Research, Inc) to identify the site of stimulation based on structural cerebral MRI of each indivual in order to accurately target the left dorsolateral prefrontal cortex (DLPFC). TBS was delivered at five sessions per day during four days. In each session, patients received 1620 pulses per session in 54 bursts of 3 with a train duration of 2 seconds and an intertrain interval of 8 seconds. With a total of twenty sessions, this leaded to a total of 32.400 stimuli per treatment. For the sham condition, a specially designed sham coil, looking completely the same as the active coil, was placed exactly on the same target in the same position but without any active stimulation. Throughout the whole treatment (rTMS and sham), patients were blindfolded, wore earplugs and were kept unaware of the type of stimulation. Between two sessions, there was a pause of 15 minutes.

Statistical analysis

All data were analyzed using SPSS (Statistical Package for the Social Sciences; IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY). The significance level was set at $p<0.05$ for all analyses.

To examine the effect of the stimulation protocol on suicide ideation, an exploratory repeated measures ANOVA was performed with SSI scores at the three different time points as dependent variable, Time (at baseline (T1), after the first week of stimulation (T2) and after the second week of stimulation (T3)) as within-subjects variable and Order (rTMS–sham or sham–rTMS) as between-subjects factor. To further examine whether the main effect of suicidal ideation could not be attributed to a general improvement of depressive symptoms we re-analyzed the model with

Table 1. Mean SSI and HDRS scores and standard deviaton on T1, T2 and T3

	SSI					
	T1		T2		T3	
	mean	sd	mean	sd	mean	sd
Total group	14.83	5.02	7.5	9.44	2.75	6.00
TBS>sham	14.00	6.07	6.33	9.22	0.17	0.41
Sham>TBS	15.67	4.13	8.67	10.38	5.33	7.94
	HDRS					
	T1		T2		T3	
	mean	sd	mean	sd	mean	sd
Total group	21.42	5.24	16.58	7.09	14.08	6.23
TBS>sham	20.17	7.68	14.33	9.33	11.50	6.85
Sham>TBS	22.67	4.80	18.83	3.37	16.67	4.76

ANCOVA, introducing the change in HDRS score as a covariate (delta HDRS = HDRS baseline minus HDRS score after treatment).

Due to the small sample size, we also analyzed the SSI data at the different time points (T1, T2, T3) with non-parametric tests.

RESULTS

Six patients first received active rTMS and six were administered sham treatment during the first week. No serious adverse events and no suicide attempts occurred. Some patients mentioned some local discomfort at the stimulation site during treatment or headache during or after the session but these complaints disappeared spontaneously after a couple of hours or after a single intake of paracetamol. There were no dropouts. For the SSI and HDRS scores see Table 1. There was no significant difference in baseline SSI score between the two groups based on posthoc independent t-test.

The repeated measures ANOVA revealed a main effect for Time ($F(2,9)=6.76$, $p<0.01$), but not for Order ($F(2,9)=0.70$, $p=0.42$) nor for delta HDRS ($F(2,9)=0.01$, $p=0.93$). Importantly, we found no significant interaction effect between Time and Order ($F(2,9)=0.46$, $p=0.64$) and between Time and delta HDRS ($F(2,9)=0.10$, $p=0.91$) (Figure 1).

Due to the small sample size, we performed non-parametric Friedman's analysis of variance (ANOVA) for repeated measures. Overall, SSI scores over the 3 time points were significantly different ($X2(2)=14.28$, $p= 0.01$). Similar findings were observed for the group of patients who first received active TBS ($X2(2)=9.36$, $p=0.01$) or first received sham ($X2(2)=5.43$, $p=0.07$).

Wilcoxon paired t-test revealed that SSI scores significantly decreased after one week of TBS (T1 vs. T2) ($z=-2.50$, N-ties=10, $p=0.01$), and further declined after the second week of treatment ($z=-2.50$, N-ties=9, $p=0.03$). Importantly, Mann Whitney U tests (sham>active versus active> sham) showed no significant differences at T1 ($U=13.50$, $n1=6$, $n2=6$, $P=0.47$), T2 ($U=17.00$, $n1=6$, $n2=6$, $P=0.87$) or T3 ($U=10.50$, $n1=6$, $n2=6$, $P=0.24$).

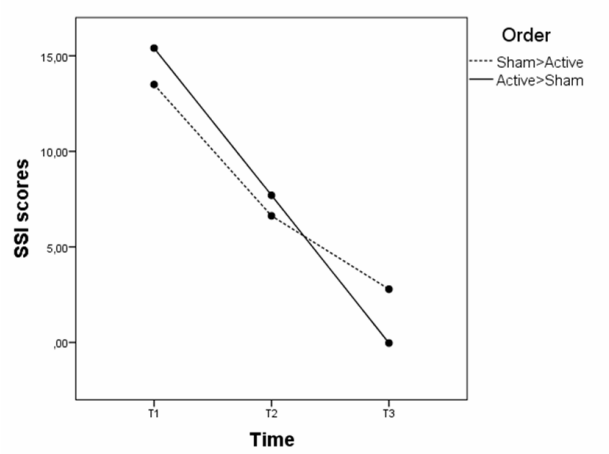

Figure 1.. Graphical presentation of the 3x2 ANOVA with Time (baseline (T1), after one week of stimulation (T2) and after finishing the treatment protocol (T3)) as within-subjects variable, Order (sham>activeTBS vs. active TBS>sham) as between-subjects factor and HDRS as covariate

Our results indicate that SSI scores significantly decreased unrelated to active or sham TBS (Order), and that this attenuation of suicidal ideation is not merely an effect of depression severity changes.

DISCUSSION

In line with other intensive rTMS treatment protocol studies, our accelerated TBS protocol was found to be safe and well tolerated. (Holtzheimer et al. 2010, Hadley et al. 2011, Baeken et al. 2013, George et al. 2014) No seizures, hypomanic or manic switches or other serious adverse events occurred. There were no dropouts indicating that the tolerance for this treatment was very high. We targeted the left DLPFC stimulation site using a neuronavigation system which has been reported to be more precise (Fitzgerald et al. 2009).

Inspite of the fact that there was an overall significant decrease in SSI scores after the whole procedure, no statistical difference in effect on suicide ideation could be observed between the active and the sham group. This seems to be in line with the observations of

George et al. (2014) who did not find a significant treatment difference between the sham and the active group after three days of TMS. Of note, it cannot be ruled out that placebo effects have interfered with our end results. However, when the effects would be merely placebo-related, it would be unlikely that general depressive symptoms (HDRS) would not decrease in 65% of our TRD patients, whereas suicidal ideation significantly decreased after TBS treatment. This would mean that the general placebo effect would only emerge on the suicidal symptoms, and not on the depression severity (HDRS). Nevertheless, Brunoni et al. (2009) confirmed that the placebo response in depressive disorder is large and is associated with treatment refractoriness. However, this concerns depressive, not suicidal symptoms. A meta-analysis of all intent-to-treat person-level longitudinal data of major depressive disorder from 16 randomized controlled trials of fluoxetine hydrochloride and 21 adult trials of venlafaxine hydrochloride, resulted in an estimated 78.9% decrease in the probability of suicidal risk for control patients after 8 weeks of study participation and a 90.5% decrease for treated patients (Gibbons et al. 2012). Importantly, Iovieno et al. (2012) described that higher placebo response rates are correlated with a lower probability to detect a statistically significant superiority of the drug versus placebo. Since our study and the beforemenioned meta-analysis by Gibbons al. (2012) also discovered a high placebo (sham) reponse rate on SSI scores, this might explain the lack of sufficient differences between the active and sham group.

As to how therapy-resistant depressed patients with active suicidal ideation would become less suicidal only due to placebo effects is not easy to explain. Hope, beliefs and expectations constitute much of the basis for the placebo response (Mommaerts & Devroey 2012), also for therapy resistent depressed individuals where a lot of attention and care is given (Baeken et al. 2013). Hadley et al. (2011) reported a significant decrease in SSI scores but they did not control with a sham condition. Our study protocol has the advantage above previous studies that examined the effects of rTMS on suicidal thoughts in being sham-controlled, neuronavigated and monotherapy theta burst TMS treatment protocol. Furthermore, we selected a diagnostically more homogeneous group of unipolar depressed patients and used an extensive suicide assessment scale (in stead of just one suicide item of a depression rating scale) (George et al. 2014, Hadley et al. 2011, Holtzheimer et al. 2010, Keshtkar et al. 2011).

One of the major limitations of our study is the relatively small sample size. Therefore our findings should be considered as preliminary. Nevertheless, research in suicidal patients is a challenge because of difficult recruitment, ethical and safety issues and patients can often be too ill to be included in a study protocol. The clinical evaluation only three days after the last stimulation might be too soon to expect the maximal effect not only on depressive symptoms but also on the effect on suicide risk. Although the SSI is a validated and commonly used instrument, scoring assumes that the total score equals to zero if the patient responds 'no' to the first five screening questions. This means it quickly turns to zero and the range of low scores is rather limited and therefore possibly limiting the interpretation.

CONCLUSIONS

Suicide is a major health concern and effective interventions are lacking. Based on this study, safety and feasability of an intensive, accelerated intermittent TBS treatment of suicidal patients can be reported. However, the efficacy compared to sham has not yet been proven. It is clear that we need to proceed in examining rTMS as a possible acute therapy for this important mental health problem. We emphasize the important effect of sham stimulation on suicide ideation in rTMS treatment protocols. Besides the use of sham-controlled rTMS paradigms, future research on suicide ideation is needed in larger patient samples including longer follow-up to evaluate these effects.

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Conflict of interest : None to declare.

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