Brain Stimulation 15 (2022) 1335–1336

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Repetitive TMS for refractory depression in a patient with a seizure disorder

To the Editor

We are reporting on a 35-year-old female with a history of severe treatment-resistant depression, resected brainstem glioma, and partial seizure disorder who underwent high frequency repetitive transcranial magnetic stimulation (rTMS). At the age of 14, she developed depression and headaches. Upon evaluation of her symptoms, she was found to have a brainstem glioma. She then underwent surgery to resect the tumor. Subsequently, her headaches resolved, but depression persisted. After her surgery, she also developed partial seizures. On average, she reported one to two seizures per week, each lasting approximately 1 min. Over the course of her life, the patient tried multiple antidepressants, both in augmentation and in combination, for depression. However, she only received occasional and minimal benefit. Currently, she is taking desvenlafaxine 50 mg daily, lamotrigine 400 mg daily, and aripiprazole 2 mg daily. Prior to initiation of TMS, her Montgomery Asberg Depression Rating Scale (MADRS) revealed a score of 40, and her Patient Health Questionnaire-9 (PHQ-9) was 20.

As our patient has continued to experience refractory depression, we sought alternative treatment methods. With the patient, we discussed the use of intermittent theta burst stimulation treatment (iTBS), a form of rTMS, at a high frequency. To our knowledge, this has not been done in patients with seizure disorders. After weighing the risks and benefits of rTMS, the patient agreed to proceed with intermittent theta burst stimulation treatment (iTBS). We delivered TMS in the following manner: Brainsway TMS with a H1 coil and biphasic pulse. Motor threshold was determined, and treatment was provided at 90% motor threshold except treatment 1 which at 80% for tolerability. The patient received ten bursts/train, three pulses per burst, 70 cycles and 2100 pulses per session, with a total of 35 sessions. The iTBS stimulation parameters used here were not 'standard' or evidence based. While receiving treatment, the patient reported 1–2 seizures weekly lasting about a minute, which was unchanged from her baseline seizure frequency. Her MADRS decreased from 40 to 15 and the PHQ-9 decreased from 20 to 9 after completing treatment.

rTMS is a Federal Drug Administration (FDA) approved noninvasive treatment for severe treatment-resistant depression, obsessive-compulsive disorder, and smoking cessation [1]. The treatment works by placing an electromagnetic coil on the scalp, which transmits an electromagnetic field to induce depolarization or repolarization in cortical neurons [1,2]. Dosing for rTMS is dependent on the motor threshold of the patient, which is determined by delivering a single TMS pulse and measuring what intensity is needed to induce a muscle twitch in 50% of pulses [2]. The Neuronetics trial, which resulted in FDA approval of TMS, administered dosing at 120% of the muscle twitch potential at frequency of 10 hz, and with 26 second breaks between pluses [2]. Treatment is generally done over the course of 4–6 weeks with 5 daily sessions throughout the week [2]. Theta burst stimulation is done more frequently, with three magnetic pulses 20 milliseconds apart, as well as repeated at every 200 milliseconds of 50 hz stimulation [1]. Side effects of rTMS are commonly headache and/or discomfort at the site of stimulation [3]. One of the most severe adverse are seizures, especially with increased frequency or dosing [1,2].

The rate of seizure induction in patients without a seizure disorder is relatively low, as iTBS has a 0.02% risk for seizure induction [1,4]. These seizures are generally self-limited, and do not lead to development of a new onset seizure disorder [2]. In patients with a preexisting seizure disorder, precautions are necessary. Though these patients have an increased risk for seizure induction during rTMS, it is still small. Literature shows only about a 2–3% risk for seizures in patients with epilepsy that undergo rTMS [1,5]. Most reported cases of seizures were in patients who were taking medications that lowered the seizure threshold [2]. In patients with seizure disorders, safety guidelines also recommend low frequency rTMS stimulation rather than high frequency (>1 hz) to prevent seizure induction [2]. However, more data is still needed for high frequency rTMS and iTBS for patients with a seizure disorder.

Our patient received a total of 35 iTBS treatments, with no increase in seizure frequency or duration. According to our research, this is the first case describing the use of iTBS for major depressive disorder in a patient with epilepsy. It also appears to be the most iTBS treatment that has been given to a patient with a seizure disorder. Here, the patient continued to have seizures, but was they were unchanged from her baseline prior to treatment. This case adds to the literature for the safety of TMS in patients with both severe refractory depression and epilepsy as this patient was able to receive iTBS safely and achieve a response in her depression. While current safety guidelines promote low frequency rTMS as safe for patients with epilepsy, there is some research to suggest like in this patient, higher frequencies can be used without a significant change in the seizure rate from rTMS or iTBS [5,6]. A systematic review of the safety of rTMS in patients with epilepsy found that only 1 out of 102 subjects undergoing high frequency rTMS had a seizure, or 0.98% [5]. A survey of 174 clinics and laboratories that performed rTMS from 2012 to 2016 showed that high-risk patients (including patients with risk factors other than epilepsy) had 5215

https://doi.org/10.1016/j.brs.2022.10.002

sessions of high frequency rTMS with only three sessions leading to seizure occurrence [6]. This rate of 0.58 seizures per 1000 sessions is much lower than the seizure percentages reported for patients with epilepsy [6]. There were also 183 sessions of iTBS in the same group of high-risk patients, with only one seizure occurrence, 0.55 per 1000 sessions [6].

In summary, given the findings with this patient and the above research, it is possible that high frequency rTMS and iTBS may be used safely for patients with severe refractory depression and epilepsy. The research only contains case reports and series. This case adds to the literature by documenting the largest dose of iTBS provided to a patient with treatment-resistant depression and epilepsy safely. More studies are needed to determine the safety and dosing of transcranial magnetic stimulation in patients with treatment-resistant depression and epilepsy.

CRediT author statement

Ethan Holland: Conceptualization (lead), Investigation (lead), Writing - Original Draft (lead), Writing – Review & Editing (lead), Visualization (lead). Richard Holbert: Conceptualization (supporting), Investigation (supporting), Writing – Original Draft (supporting), Writing – Review & Editing (supporting), Visualization (supporting)

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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25 August 2022
Available online 13 October 2022