

Transcranial magnetic stimulation: review of accidental seizures

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Abstract

Transcranial magnetic stimulation (TMS) is a new technique that has been used for the treatment of neuropsychiatric disorders, specially depression. It uses a magnetic stimulator that generates a magnetic field that is applied over the patient's skull with a coil. Possible seizures may be induced accidentally by TMS. TMS is usually used with sub threshold stimuli and seizures may occur by chance, especially when over the safety parameters. This article reviews the eight cases of undesirable seizures occurred with rTMS. The possible mechanisms of seizure induction and the patients profile with a higher risk of convulsion are also described.

Keywords: Convulsions. Therapy. Depression.

Introduction

Transcranial magnetic stimulation (TMS) is a new technique that has been used for the treatment of psychiatric disorders, mainly depression. It is a treatment which does not use medications, in which a stimulating device creates a high-intensity alternate magnetic field which is applied on the skull with a stimulating coil.¹

Currently, TMS has not been approved yet for therapeutic use in the US by the Food and Drug Administration, but it is under intense study as a treatment for depression and other psychiatric and neurological disorders.^{2,3} In our service, several projects using TMS are under development (e.g., comparison with electroconvulsive therapy, augmentation of antidepressants, efficacy on depression in Parkinson disease and schizophrenia).

There are two types of TMS: single pulse or repetitive pulses. Simple pulse stimulation is generally used in neurology and neurophysiology, especially in the study of motor functions.

The use of repetitive TMS or rTMS in psychiatry is more relevant when pulses are repeatedly administered at variable frequencies. rTMS is typically administered in subthreshold stimuli for seizure induction.⁴ As this is a painless process, the patient remains awake during the procedure, not being necessary an anesthetic induction. The treatment consists of repeated administration of series of stimuli at each session, which

can last up to 30 minutes, being the treatment performed five times a week with mean duration from two to four weeks.

The use of TMS aiming to induce seizures (magnetic convulsive therapy), as a possible replacement for electrically-induced seizures (electroconvulsive therapy - ECT), has been studied, but there are still technical issues to be solved (mainly the need of a very high intensity to achieve the convulsive threshold in most of the patients). For example, to compensate the anti-convulsant effects of anesthesia, a modified device with an increased maximal threshold should be used (60 Hz, 100% of the maximal capacity, 6.6 seconds of duration).⁴ The therapeutical use of purposely-induced convulsions is beyond the scope of this review.

Despite the increasing number of publications, the efficacy of TMS has still not been completely established. Up to the moment, the main meta-analyses and systematic reviews have not concluded for a strong evidence of the treatment benefits.^{5,6,7} The variations in sample sizes and in the duration of treatment and the use of different stimulating parameters in the studies may explain the great heterogeneity of results. Fitzgerald et al.⁸ have recently published a controlled study confirming the efficacy of TMS for resistant depression.

Among the possible side-effects shown by patients, besides mild headache, which improves with ordinary analgesics, seizures are deemed the main risk to which are exposed

patients submitted to subthreshold stimulation.

Since the beginning of modern use of TMS, there were 8 cases of accidentally-induced convulsions.¹

In this article we performed a detailed review of cases in which convulsions with TMS have occurred as well as of the possible consequences for its safe utilization.

Seizure-induction mechanism

Seizures may be induced by chemical (e.g., cardiazol), electrical (ECT) or magnetic brain stimulation, with enough intensity to reach the convulsive threshold of a patient. The discharge that achieves such a threshold tends to propagate generating a generalized tonic-clonic convulsive crisis, identical to that observed among patients with grand mal epilepsy.

In cases of brain stimulation with subthreshold loads (below the convulsive threshold of a patient), there are three known mechanisms, through which the cortical excitability can be raised, up to a point to induce a convulsion. The first one is the kindling effect which consists in triggering an action potential after several sequential subthreshold stimuli. The most effective frequency for the kindling is near to 60 Hz, well above the capability of the most commonly available stimulators. Pascual-Leone et al.,⁹ in a classical study in which rTMS was used in normal voluntary subjects, observed the propagation of the stimulus by means of EEG in some patients. Only one had generalized convulsion. No kind of further electroencephalographic complication or alterations had occurred. However, it is unknown if that was due to the kindling.

The second mechanism is known as secondary epileptogenesis, in which an epileptogenic activity which is occurring in a certain place seems to induce the appearance of a mirror focus in the opposed hemisphere. Theoretically, rTMS could be an inducing factor of epileptogenesis in distant sites (Pascual-Leone et al., 2002).

Lastly, the third mechanism is the long-term potentiation, in which the repetitive stimulation of the brain in high frequencies results in a long-term physiological potentiation and ultra-structural alterations in central synapses. However, this mechanism seems to be more related to the therapeutic effects of rTMS than to its epileptogenic potential.¹

Accidental induction of seizures with single-pulse TMS

In some patients with extensive brain stroke or other structural lesions, seizures were induced with single-pulse TMS. The anatomic extension of these lesions was not reported in all cases. However, apparently there are no reports of seizures in patients with exclusively subcortical lesions. At least one of these patients has developed subsequent epilepsy, presumably as a result of an underlying lesion.¹⁰

Epileptic patients without frank lesions may also be at a small risk under single-pulse TMS. Many studies have assessed single-pulse TMS as a procedure that may provoke seizures in epileptic patients. The results were, nonetheless, dissimilar. Other studies^{11,12} performed a series of trials, in varied patients, reporting that TMS may occasionally induce convulsions or activate electroencephalographic epileptic foci. However, Tassinari et al.¹³ have not succeeded in provoking con-

vulsions in 58 medicated patients. Only one case was reported, in which single-pulse TMS could produce repeated convulsions in only one subject.¹⁴

Accidental induction of seizures with repetitive TMS

Most of the current studies on repetitive TMS (rTMS) use sub-convulsive stimulation and aim at the therapeutical efficacy without the need of inducing a convulsion. Since safety limits for the stimulation parameters have been established, there was no description of cases of accidentally-induced convulsions.¹⁵ In the first studies, however, when this fact was still not well known, there were eight cases of accidental seizures with rTMS which we will detail below.

Several formal studies with patients known as epileptic have failed to induce convulsions, both clinical and electroencephalographic. This has been observed even when subdural electrodes were used to monitor the convulsive activity in patients with untreatable epilepsy.¹⁶

The induction of convulsions by rTMS has occurred in six normal voluntary subjects and one depressed patient.¹⁰ There was also an eight patient who had temporal lobe epilepsy, with secondary generalization; in this case it was erroneously supposed that the focus would be contra-laterally placed regarding the stimulated hemisphere.¹⁷

The number of described cases in which there was a convulsion is proportionally insignificant (eight cases, including six normal voluntary subjects) for thousands of applications all over the world.^{9,18,19,20,21} Most of them occurred with stimulation of the primary motor cortex but three of them occurred with pre-frontal stimulation.²¹ An important part of them occurred with normal voluntary subjects.

Cases reports of accidental seizures with rTMS

The first case occurred during one study on rTMS's safety,^{9,18} before the creation of a guide on safety parameters. They had stimulated patients well above the current safety limits.

Two of the subsequent convulsions occurred in studies using rTMS series whose intensity was within the safety limits, but were applied in intervals lower than 1 second.¹⁹ The short interval between the series seems to have allowed a cumulative increase in the cortex excitability.²²

The fourth case of convulsion occurred when the researchers chose a combination of parameters which was at the top safety limit.¹⁹

The fifth and the sixth cases were simple partial crises (one of them occurred with stimulation within the safety parameters).¹⁰

The last case occurred with a psychotically depressed woman who was participating in a trial with rTMS.²³ Although the stimulation was within the safety parameters, the patient had started to use, without the researchers' awareness, amitriptyline and haloperidol (medications which are known to reduce the convulsive threshold).

There was no kind of complication in these cases. It was observed that in most cases the convulsions occurred under a combination of parameters beyond safe levels.

Dhuna et al.,¹⁷ using stimuli series of 8-25 Hz, have not succee-

Table 1 – Current safety guide of TMS: maximum duration for simples series of rTMS, based on the experience of the National Institute of Neurological Disorders and Stroke²¹

Frequency (Hz)	INTENSITY (% OF MEP – MOTOR EVOKED POTENTIAL – THRESHOLD)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	.8	.9	.8	.5	.6	.4	.3	.3
20	2.05	1.6	1.0	.55	.35	.25	.25	.15	.2	.25	.2	.1	.1
25	1.28	.84	.4	.24	.2	.24	.2	.12	.08	.12	.12	.08	.08

NOTE: numbers preceded by > are the most long durations tested. In these combinations of stimuli frequency and intensity it was not observed posterior discharge of propagation of excitation with simples series of rTMS.

Table 2 – Current safety guide of TMS: safe intervals between series

Frequency	INTENSITY OF RTMS	
	≤ 110% of the motor threshold	>110% of the motor threshold
≤ 20 Hz	5 s (Maybe less; definitely > 1 s)	60 s (Probably less)
> 20 Hz	60 s (Probably less)	60 s (Probably less)

SOURCE: Adapted from CHEN et al.²²

ded to induce focal epileptiform discharges or convulsions in 8 patients known as epileptics. It is recognized that frequencies between 5 and 20 Hz increase the motor cortex excitability²⁴ and that lower frequencies (up to 1 Hz) seem to diminish the corticospinal excitability.²⁵

In one case, the concomitant use of medications which decrease the convulsive threshold (tricyclic antidepressants and antipsychotics) could have influenced in triggering the convulsion.²⁶

The interval between series seems to have also an important role in triggering any convulsive focus. Intervals below 1 second between stimuli seem to increase significantly the risk of producing a convulsion, whereas intervals above 20 seconds seem extremely safe.¹⁹

Patients at risk of accidental seizures

George and Belmaker²⁶ suggest six groups of patients for whom the exclusion from studies with rTMS should be considered due to the higher risk of inducing accidental seizures:

- 1) Patients with focal or generalized encephalopathy (i.e., tumor, stroke, meningitis, encephalitis) or severe head trauma, as these conditions favor the formation of an epileptogenic focus.
- 2) Subjects with non-treated epilepsy.
- 3) Subjects who have first-degree relatives with idiopathic epilepsy.
- 4) Patients who have recently started the use of medications which reduce the convulsive threshold (e.g., tricyclic antidepressants and antipsychotic medications).
- 5) Subjects with heavy alcohol consumption are under higher risk, in case the consumption be suddenly interrupted. The same applies to those currently using epileptogenic drugs (e.g., cocaine).

6) Subjects with a severe heart cardiac disease or with an increase in the intracranial pressure are under higher risk of severe sequelae after a possible convulsion.

It is currently recommended that rTMS be performed in a room equipped with oxygen and emergency devices. Safety parameters internationally accepted are synthesized in Tables 1 and 2.²¹

Up to now, in our service 111 patients have already received applications without any complication.

Conclusion

Currently, TMS is one of the most interesting instruments with therapeutical potential in psychiatry. Its utilization (mainly with subconvulsive stimuli) for the treatment of depression and possibly of other psychiatric disorders has significantly increased, despite the fact that many issues are not yet completely understood (which are the best parameters, how many days of treatment, etc).

With subliminal stimulation, there is the risk of inducing accidental convulsions. When aiming at a treatment with subconvulsive stimulation (rTMS), the safety parameters should be observed, and patients with higher risk of having an accidental convulsion should be excluded.

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