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Review Article

Transcranial Magnetic Stimulation and Epilepsy

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Abstract: Transcranial magnetic stimulation (TMS) is a form of focal electrical brain stimulation where electrical currents are induced in the brain using a powerful magnetic field. TMS has been approved for the treatment of major depression using a specific high frequency repetitive TMS (rTMS) protocol. Recently, low frequency rTMS (0.3-1 Hz), resulted in lasting reduction in cortical excitability suggesting a potential therapeutic value for patients with intractable epilepsy. The risks of rTMS are minimal but include a small possibility of triggering seizures. In this paper we present a comprehensive updated review on the use of TMS for the treatment of epilepsy. We conclude that TMS has a potentially important therapeutic role and should continue to be evaluated in properly designed clinical trials.

Keywords: (Transcranial / Magnetic / Stimulation / epilepsy / seizure)

INTRODUCTION

Epilepsy is defined as recurrent unprovoked seizures resulting from abnormal excessive electrical cortical discharges (1). Despite the development and availability of many antiepileptic drugs (AEDs), 25-35% of patients remain intractable (2). Non-pharmacological treatments are considered for drug resistant patients and include epilepsy surgery, noninvasive brain stimulation, and modulation techniques. One of these modalities is transcranial magnetic stimulation (TMS), a safe and well-tolerated method for focal electrical brain stimulation where small intracranial electric currents are induced by strong and fluctuating extracranial magnetic fields (3,4). Repetitive TMS (rTMS) is a variation of TMS where stimulation is provided in sessions at various frequencies and durations to induce longer-term cortical excitation or inhibition depending on the stimulation rates (5). The electromagnetic impulse painlessly and safely passes through the skin and skull. A motor response is elicited at a certain threshold when TMS is applied on the motor area (motor threshold). Then, a number of parameters are determined to reach different treatment goals including the number of stimulations, stimulation intensity, stimulation frequency, length of intervals between stimulations, and targeted areas of the brain (6,7). In this paper we present an updated review on the use of TMS for the treatment of epilepsy.

HISTORIC PERSPECTIVES

TMS causes electromagnetic induction, a process in which electrical energy is converted into magnetic energy. Faraday initially established this concept in 1831 and argued that the relation between electrical energy and magnetic field was reciprocal (8). Human experiments revealed that the use of magnetic coils applied over the scalp could stimulate the neurons of patients and potentially treat depression, epilepsy and other psychiatric disorders (9). The main challenge of early studies was to consistently elicit such effects by stimulating clearly identified areas on the head. In addition, the initially produced TMS machines (capacitors) were not capable of generating high enough intensity or frequency stimulations. The current clinical use of TMS started back in 1985 when Barker and others produced the initial modern prototype machine in Sheffield, UK (10). Further technical advances allowed for higher rates of repetitive stimulation (11). The Food and Drug administration (FDA) of the United States approved TMS in 2008 for treating selected patients with depression (12). TMS remain under investigation for other psychiatric and neurologic conditions, including epilepsy (13).

TECHNICAL ASPECTS

Different components of the TMS mechanism from the pulse inside the coil to the intensity of the stimulation follow the

fundamental laws of physics. The equipment is generally simple and consists of a transformer for charging a large capacitor, which rapidly discharges to create a magnetic field pulse in the stimulation coil (Fig 1,2). There are circuits to control the intensity and repetition of the pulses. The maximum voltage is around 2000 volts generating currents of around 10000 Amps. It is necessary to have a high-voltage electrical input for effective stimulation (14). Once the device is charged with electrical current, magnetic fields develops around the coils (Fig 3). If there are two coils beside each other (butterfly design shown in figure 2), the electrical energy is concentrated in the central joint area for targeted area stimulation (15). The current rTMS equipment is capable of producing magnetic induction as deep as two centimeters into the brain (Fig 3). This technology can easily excite cortical regions as deep as the gray-white matter junction causing electrical changes in the range of 70 millivolts (15). Therefore, deeper structures are not accessible for direct TMS.

PATHOPHYSIOLOGY

In epilepsy, the mechanism by which TMS may suppress seizures is not completely understood, but likely relates to the physiologic phenomena of synaptic plasticity where repetitive electrical brain stimulation leads to lasting changes in neuronal signaling. In epilepsy, low frequency electrical cortical stimulation at 0.3-1 Hz reliably *reduces* regional cortical excitability (16). Thus, if it is assumed that excess cortical excitability is a critical abnormality in epilepsy then suppression of regional cortical excitability could reduce seizure frequency. Numerous open label trials and a few placebo-controlled experiments support an eventual therapeutic role for TMS when applied over the epileptogenic region (17-21). These effects occur even when TMS is applied on a neutral scalp location, such as the vertex. Interestingly, the favorable response of some patients with focal epilepsy to TMS outside of the epileptogenic zone and in one series a favorable response of patients with primary generalized seizures to TMS raises the possibility of a widespread therapeutic benefit elicited by focal cortical stimulation (22,23). From a scientific perspective, this suggests that the TMS antiepileptic mechanism may not be as simple as local suppression of intra-cortical excitability, but rather a network resetting effect.

TMS Epilepsy Protocols

TMS protocols may be divided into single-pulse TMS (spTMS), paired-pulse TMS (ppTMS), and repetitive TMS (rTMS). In epilepsy, spTMS and ppTMS can be useful for presurgical mapping of cortical function and for detecting abnormalities in the cortical excitation inhibition ratios (24). Repetitive TMS (particularly low-frequency rTMS) has been tested as a means to induce lasting reductions in cortical excitability and thus reduce seizure frequency. The ppTMS as a means to assess cortical inhibition or facilitation is emerging as a potentially practical measure of the excitation-inhibition ratio in patients with epilepsy. It is more experimental than clinical, but may have a role in patient management in the near future. In most ppTMS protocols two closely spaced TMS pulses are delivered to the motor cortex to elicit contractions of a hand muscle that is measured as a motor evoked potential (MEP) by electrodes connected to the skin of the hand. The first of the pair of pulses activates an inhibitory cortical response such that when a second TMS pulse is delivered to the same region, the motor response is reduced. The ratio between motor responses to the initial (conditioning) and second (test) pulse reflects the efficiency of inhibitory signaling. Thus in epilepsy syndromes characterized by deficient cortical inhibition, ppTMS may help to track disease severity. Similarly, ppTMS may also aid in measuring the effectiveness of treatments aimed to improve cortical inhibition in epilepsy.

There is still no agreement on optimized stimulation parameters of rTMS for epilepsy (25). The patterns of rTMS application to achieve the maximum efficiency are still not clear. TMS effects are highly variable across individuals and depend on parameters such as frequency (Hz), number of stimuli within a train, stimulation intensity, type of coil, coil position, duration of stimulation, and inter-train interval (26). However, in general, low frequency (≤1 Hz) rTMS reduces cortical excitability, while higher frequencies (conventionally standardized as ≥1 Hz) enhance cortical excitability (27). These effects are analogous to those of long-term depression (LTD) and long-term potentiation (LTP) phenomena, and it is the LTD-like depression induced by low-frequency rTMS that has interested the epilepsy community as a potential therapeutic tool for seizure suppression. Such stimulation is provided at 80-90% of motor threshold (28). Although patients with refractory epilepsy showed a significant decrease in the number of seizures in a randomized sham-controlled clinical trial of low-frequency rTMS, well-designed multi-parametric rTMS studies, with strict inclusion criteria, are needed to increase data consistency and to ascertain reproducibility of such effects. Such studies should take into consideration different underlying epileptogenic mechanisms and etiologies.

TMS and KINDLING

Kindling is a process in which repetitive cortical stimulation results in enhanced epileptic tendency (29). The cerebral cortex is generally more resistant to kindling than the limbic system. Investigators have examined possible kindling effects with rTMS frequencies of 0.1, 0.5, 1, and 2 Hz (29). The kindling process and subsequent seizures were unlikely to develop unless >10Hz stimulation was used. This is therefore should not be encountered in standard low frequency rTMS protocols. In fact, such stimulation rates have preventive effects in addition to reducing neuronal excitability (30,31).

RISK OF SEIZURE EXACERBATION

TMS is generally safe with some potential side effects including transient headache, pain at the site of stimulation, discomfort due to muscular contraction, and transient tinnitus occurring in up to 15% of patients (32). Although very rare, induced seizures are the most worrisome adverse effect of rTMS, and therefore, it is especially important given the seizure-prone profile of patients with epilepsy. Reports have

been published about epileptic foci activation by rTMS in patients with medically intractable complex partial seizures, as well as seizure induction in patients with epilepsy and in healthy volunteers (33). It seems that rTMS is more likely to induce seizure, compared with single or paired pulse TMS. A detailed analysis of 30 studies of TMS in epilepsy patients estimated a crude per subject seizure risk of 1.4% (16). A more recent study found a crude risk of seizures per subject during rTMS of 2.9% (34). Such association is not necessarily causal as most patients had ongoing frequent seizures and therefore seizures in patients with severe epilepsy may be coincidental. While this finding supports the safety of rTMS, it should be interpreted with caution considering the heterogeneity of rTMS application duration among different patients (35). Baseline seizure frequency seems to be an important potential confounder, given that low-frequency rTMS is most probably administered to patients with severe epilepsy. Future studies controlling for baseline seizure frequency are therefore required to obtain more data on risk factors for seizures associated with rTMS application.

It is also relevant to assess whether other factors can increase the risk of seizures associated with rTMS. One potential risk factor is the use of antidepressant drugs. In one study, 6 out of the 8 seizures among individuals without epilepsy occurred in patients that were taking antidepressant drugs (32). However, a meta-analysis of randomized, double blind, and sham controlled studies of rTMS combined with antidepressants for treatment-resistant depression did not report any seizures (36). It is important to note that rTMS protocols for depression generally use high-frequency stimulation, which warrants a need for assessing its safety when applied to patients with concurrent epilepsy. Considering that it is common for patients with epilepsy to have psychiatric comorbidities, further studies comparing risks of seizures are required (37). This could provide greater understanding of both the protective effects of antiepileptic drugs and the pro-convulsive effects of antidepressants on seizure induction during rTMS.

FUTURE DIRECTIONS

Further studies are needed to better understand the responsiveness of different epileptic to rTMS. Several other questions need to be addressed including the long-term antiepileptic effects, role of co-administration of AEDs, and role of TMS in the acute seizure management (38). Safety concerns and risk-benefit ratios needs further assessment given the varying operating parameters and used devices. Structured and consistent training instructions and guidelines for rTMS are needed. Such guidelines should take in consideration the growing and evolving evidence produced by ongoing studies. Finally, some cortical regions may require different types of rTMS treatment protocols (39). Investigating different parameters, including the intensity, quantity of pluses in each session, and quantity of sessions for a given cortical region are needed, particularly in regards to therapeutic outcomes (39).

CONCLUSIONS

TMS is an important and promising technology in treating selected patients with epilepsy. Research advances are coinciding with industry interests and developments making it more readily available at reasonable cost. This would translate into greater accessibility to TMS for both clinical and research work relating to patients with intractable epilepsy, particularly those who are not surgical candidates. Specifically, TMS has a potentially important therapeutic role in selected patients with partially originating seizures. Although there are some minor or transient side effects, rTMS is considered very safe with a potential for achieving a greater role in the field of epilepsy in the future.

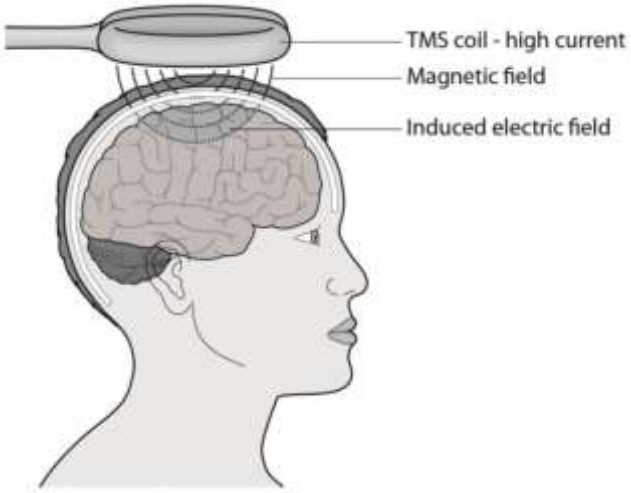
Fig 1: Examples of TMS consoles from different manufacturers.
Source: http://www.medicalexpo.com

Fig 2: Stimulation coils with a preferred butterfly design. **A:** Lighter coil suitable for focused stimulations equipped with power control and trigger button (in red). **B:** Heavier cooled coil designed for demanding stimulation protocols requiring a high number of stimuli and connected to an external Cooler Unit (**C**).
Source: http://www.magventure.com
A:

B:

C:

Fig 3: Using the butterfly coil, the stimulation is maximal at the center of the coil where the two circulating currents join reaching a cortical depth of stimulation of around 2 cm.
Source: http://nuffieldbioethics.org



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