Clinical Neurophysiology 127 (2016) 1895–1900

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Safety and tolerability of navigated TMS for preoperative mapping in neurosurgical patients

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ARTICLE INFO

Article history:
Accepted 26 November 2015
Available online 11 December 2015

Keywords:
Transcranial magnetic stimulation, TMS
Navigated transcranial magnetic stimulation, nTMS
Eloquent brain tumor
Pre-operative mapping
Motor mapping
Language mapping

HIGHLIGHTS

- This large, multicenter series describes the safety of pre-operative navigated TMS mapping in 733 neurosurgical patients.
- Navigated TMS was well-tolerated overall; the median VAS score was 0 with monopulse TMS and 5 with repetitive TMS.
- The safety profile of navigated TMS in neurosurgical patients was excellent, with no persistent headaches reported and no provoked seizures in the series.

ABSTRACT

Objective: Navigated transcranial magnetic stimulation (nTMS) is a non-invasive technique for presurgical motor and language mapping in patients with brain lesions. This study examines the safety and tolerability of nTMS in a large, multi-center cohort of neurosurgical patients.
Methods: Functional mapping with monopulse and repetitive nTMS was performed in 733 patients. In this cohort, 57% of patients had left-sided tumors, 50% had frontal tumors, and 50% had seizures secondary to the lesion. Side effects and pain intensity related to the procedure were documented.
Results: Patients undergoing monopulse stimulation underwent an average of 490 pulses while those undergoing repetitive stimulation received an average of 2268 pulses. During monopulse stimulation, 5.1% reported discomfort (VAS 1–3), and 0.4% reported pain (VAS > 3). During repetitive stimulation, 23.4% reported discomfort and 69.5% reported pain. No seizures or other adverse events were observed.
Conclusions: nTMS is safe and well-tolerated in neurosurgical patients. Clinicians should consider expanding nTMS to patients with frequent seizures, but more evaluation is necessary to evaluate this risk fully.
Significance: nTMS is safe and well-tolerated, even in neurosurgical patients with persistent occasional seizure secondary to a lesion. It should be considered in any patient with a lesion in a presumed peri-eloquent or eloquent brain region.

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http://dx.doi.org/10.1016/j.clinph.2015.11.042
1388-2457/

1. Introduction

Navigated TMS (nTMS) is a non-invasive modality for pre-surgical motor and language mapping in patients with brain lesions in presumed eloquent and peri-eloquent regions. Its incorporation into the standard pre-operative workflow for these patients is becoming more widespread. nTMS has been shown in multiple studies to correlate well with intraoperative direct cortical stimulation (DCS) and is likely superior in accuracy to fMRI and MEG (Krings et al., 2001; Picht et al., 2009; Krieg et al., 2012; Tarapore et al., 2012). Additionally, there is increasing evidence that pre-surgical nTMS improves patient outcomes: patients who have undergone pre-surgical nTMS mapping receive greater extent of resection (Frey et al., 2014; Krieg et al., 2014a) and have fewer long-term neurological deficits (Krieg et al., 2014a, 2015; Sollmann et al., 2015) than patients who have not. This modality therefore confers significant benefits in management of patients with peri-eloquent lesions, and its usage will likely increase as evidence mounts supporting its benefits. Given these expanding applications for nTMS, it is of paramount importance that the procedure itself is safe and well-tolerated in the neurosurgical population. Our goal with this analysis is to characterize the safety and tolerability profile of nTMS in neurosurgical patients undergoing pre-surgical motor and speech mapping.

1.1. Theoretical basis and protocols

TMS relies on the principle of electromagnetic induction. A powerful electrical current is rapidly discharged through a figure-of-8 TMS coil, generating a brief, cone-shaped magnetic field. This magnetic field can penetrate the skin, skull, and meninges without encountering significant distortion and, according to Faraday's law, induces an electrical field in the underlying brain (Tarkiainen et al., 2003). The magnitude of this electrical stimulation is proportional to the time rate of change of the magnetic field. The higher-order effect of this stimulation depends on the TMS protocol being employed. Single pulses result mostly in simple action potentials, and are useful for activation-based mapping protocols, such as motor mapping. Trains of pulses, so-called repetitive TMS (rTMS), are considered to have an inhibitory effect at low frequency (<10 Hz) and a facilitatory effect when high frequency (>10 Hz) (Rossini et al., 1994; Rossi et al., 2009). The language protocols evaluated in this study all relied on low frequency rTMS for lesion-based mapping.

1.2. Reported complications

When the parameters of stimulation are maintained within established ranges (Wassermann, 1998; Rossi et al., 2009), the rates of complications associated with TMS protocols are low. Minor adverse effects include headache (28–40%) (Machii et al., 2006; Loo et al., 2008), temporary high-frequency hearing loss (9%) (Pascual-Leone et al., 1991; Loo et al., 2001), and pain (39–40%) (Machii et al., 2006; Loo et al., 2008). The most severe acute adverse effect is seizure. High frequency rTMS protocols have the highest risk of provoking seizure; low-frequency trains have also been reported to cause seizure, but at rates of <1% (Homberg and Netz, 1989; Kandler, 1990; Dhuna et al., 1991; Schrader et al., 2004). When employed for pre-surgical mapping, the FDA-approved nTMS protocol (which is a low-frequency protocol) requires exclusion of patients with 'uncontrolled' or 'poorly controlled' seizures, which are defined as a seizure frequency greater than 1 per week. These measures are intended to minimize the probability of provoking a seizure during nTMS mapping.

The most recent consensus guidelines for ethical application of TMS in clinical and research settings were established in 2009, at the TMS consensus conference, which took place in Siena, Italy (Rossi et al., 2009). Although this publication contains the most thorough review of the TMS safety literature to date, it does not specifically discuss the risks associated with performing TMS in neurosurgical patients with brain lesions due to lack of published data on this technique in the neurosurgical population. nTMS has only recently become widely utilized in these patients and, as more of them undergo nTMS-based mapping procedures, it is important that the risk and tolerability of the modality be described and reported in greater detail. Given that neurosurgical patients are often at greater risk of neurological complication (including seizure), the application of any neuro-stimulatory technique must be undertaken with a careful understanding of the risks involved to the patient.

Here, our aim was to conduct a systematic evaluation of the risks associated with nTMS-based pre-surgical mapping in neurosurgical patients. Our secondary aim was to identify ways to optimize the procedure for maximizing patient comfort while still obtaining the best possible mapping results. This series is the largest published to date, and reflects over 6 years of cooperation in establishing and refining nTMS-based pre-surgical mapping at 3 institutions: Charité-Universitätsmedizin, Berlin (CHB), Technische Universität, Munich (TUM), and University of California, San Francisco (UCSF).

2. Materials and methods

In this study, data from three institutions was pooled: Charité-Universitätsmedizin, Berlin (CHB), Technische Universität, Munich (TUM), and University of California, San Francisco (UCSF). At each of these institutions, patients with tumors in eloquent or peri-eloquent regions were identified by their neurosurgeons and referred for nTMS-based mapping for pre-surgical planning. Demographic and clinical data was gathered prospectively and stored in a local database housed at the relevant institution (CHB, TUM, or UCSF). Additionally, parameters specific to each mapping session were stored: stimulator intensity (as a % of maximal stimulator output), e-field strength, number of stimuli, duration of mapping, and frequency of stimuli trains (for rTMS protocols). Patients were visually monitored by a third person during the whole session and any signs of discomfort were noted. The study protocol stated that in case of hints for imminent clinical seizure (e.g. aura reported by patient, muscle twitching or increasing EMG activity) the examination had to be stopped. Following each mapping session, patients were asked to rate from 1 to 10, according to the visual analog scale for pain (VAS), the maximum level of discomfort they experienced during the mapping session. Patients were also asked to report levels of transient hearing changes or tinnitus, cognitive changes, and any other biological effects that were experienced. Any complications during the procedure, specifically seizure, were recorded as well.

Due to the evolving protocols for rTMS-based mapping during the period of this study, frequencies of 5, 7, and 10 Hz were employed in various patients at various times. All patients also underwent single-pulse motor mapping, either to document the map itself or to establish a motor threshold for subsequent language mapping. A subset of patients underwent only single-pulse motor mapping; the remainder underwent both single-pulse motor mapping and rTMS-based speech mapping.

2.1. Mapping protocols

Details of the motor-mapping (Picht et al., 2009; Tarapore et al., 2012) and speech mapping (Picht et al., 2013; Tarapore et al., 2013; Krieg et al., 2014b) protocols have been published elsewhere.