

TRANSCRANIAL MAGNETIC STIMULATION: TERMINOLOGY AND SAFETY ASPECTS CONCERNING THERAPEUTIC PROTOCOL AND DEVICE RELIABILITY

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Abstract: An evaluation of Transcranial Magnetic Stimulation (TMS) safety parameters issues concerning the current situation of therapeutic protocol and device reliability is presented. Harmonization in terminology was analyzed, as well as possible misunderstandings that might arise from the lack of it. A notable example studied is the recommendation of safety parameters by the 2012 resolution of the Brazilian Federal Council of Medicine, when compared to international consensus and guidelines. The TMS device reliability is discussed considering technical standards and the International Commission on Non-Ionizing Radiation Protection reference limits for magnetic field exposure, applicable to both patients and therapeutic staff. The critical issues are pointed out, providing suggestions toward terminology harmonization and evaluation of metrological reliability of TMS systems.

Keywords: Transcranial Magnetic Stimulation, Metrological Reliability, Safety, Terminology, Stimulation Protocol.

Introduction

Transcranial Magnetic Stimulation (TMS) is a technique in which a rapidly changing current is passed through a small coil which is placed on the scalp [1]. The magnetic field generated by the coil allows getting electric energy across the scalp and skull without the pain of direct percutaneous electrical stimulation.

The TMS pulses can depolarize neurons and, when repeated pulses are applied, they can modulate cortical excitability, depending on the parameters of stimulation. This has behavioral consequences and therapeutic potential [2].

In the early stages of TMS, efforts were employed in the analysis of this technique as a tool for neural imaging, but as researches developed, new modalities and applications were described. This resulted in a growing lexicon regarding this field of study [1]. Notably, repetitive Transcranial Magnetic Stimulation (rTMS), consisting in performing TMS with particular time varying patterns, was shown to be an invaluable asset in the treatment of medication resistant depression, among other neurologic and psychiatric disorders.

Besides the clinical efficacy of TMS and all its modalities, another relevant research subject that has been approached by several studies concerns the safety

parameters of stimulation protocols [1, 2]. There were two major international workshops on safety of TMS and ethical aspects. These were held in 1996 and 2008, and the relevant generated information was compiled into tables of recommended values [1, 2].

Another important safety aspect that has to be taken into account concerning patients and therapeutic staff is the magnetic field exposure limits according to reference levels recommended by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [3, 4, 5].

Regarding the device reliability [6], TMS is currently approved by Health Surveillance Agencies of Israel, Canada, New Zealand, Brazil, Australia, United States, European Union, among others [2, 7, 8]. In Brazil, although already approved for use by the Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária - ANVISA*) since 2007, TMS was recognized as a scientifically valid clinical procedure for utilization in health care on medical practice with the resolution 1.986/2012, published by the Federal Council of Medicine (*Conselho Federal de Medicina - CFM*) [8]. This acknowledgement regarded applications of surface TMS for the treatment of uni and bipolar depressions, hearing hallucinations on schizophrenias and neurosurgery planning. Notably, treatment parameters were recommended for each of those health disorders. In the mentioned CFM resolution, surface TMS for other indications, as well as deep TMS, remained being considered as experimental procedures.

Considering that full and reliable reports of the parameters that characterize TMS stimulation protocols are especially relevant for the advancement of research as well as their clinical effectiveness, it is fundamental to harmonize the employed terminology. The uniformity of dose description contributes to reproducibility, comparability, accurate interpretation, accomplishment of the desired clinical outcome, and prevention of adverse events.

Besides the complete and proper stimulus description, aspects regarding device reliability, including safety and performance checks should be satisfactorily considered [6]. To be registered by health agencies, TMS devices must demonstrate compliance with several technical standards. However, up to the present, no specific standard for TMS devices was

published.

The present work envisioned bringing forth some of the details and possible issues that arise from the safety concerns encompassing terminology of stimulation protocols and TMS device reliability. For this purpose, among other studies concerning TMS safety, publications reporting consensus for safe treatment parameters, relevant safety guidelines published by regional and international institutions and any applicable technical standards pertaining to this issue were evaluated.

Harmonization of TMS stimulation dose parameters report

In Brazil, the treatment parameters for TMS currently recommended by the CFM consist on the frequency and intensity of the stimulus, the duration of trains, the number of trains, the total number of pulses, the interval between trains, the number of days of treatment and the location to apply the stimulus [8].

Notably, the total number of pulses is presented on the CFM document with a dot separating the first two digits from the three last ones. This notation does not follow the International System of Units (SI) [9] and can generate ambiguity. For instance, the indication of “25.000” as the total number of pulses for a depression treatment using a 10 Hz frequency could be interpreted as 25 or 25000. One may feel compelled, however, to assume the latter value, since the total number of pulses is an integer number and there would be no need to present it with three decimal digits.

The CFM’s recommendations [8] were then compared to the Consensus Statement published by Rossi et al. [2] and to a recently published discussion regarding magnetic stimulation dose [10] (Table 1). This comparison pointed out non-uniformities in terminology and in the set of parameters considered for the protocol report.

Table 1: Comparison between the CFM [8] and the international consensus recommendations [2].

Frequency (Hz)	Intensity (% of MT)		Duration of trains (s)	MDP (s)	Pulses per train	Pulses per MDP
	[8]	[2]				
10	110	110	5	5	50	50
5	120	120	10	10	50	50
1	80 or 100	90 or 100	1200	>1800	1200	>5000*

*For intensity of 90% of MT

The international meeting consensus mentions that an inter-train interval of 5000 ms is considered safe for stimulation frequencies of less than 20 Hz with groups of 10 trains [2]. Although the CFM recommends a higher number of trains it also allows for a much higher inter-train interval [8]. It then says that the maximum duration of pulses (MDP) for individual TMS trains should not exceed the values provided on the table.

Since one individual train corresponds to a group of pulses, the MDP would be readily comparable to the duration of trains shown in the CFM recommendations [8]. Indeed, these values agree, as can be seen in Table 1, in which CFM values for the pulses in one train are found by multiplying the frequency by the duration of the train. Values related to the maximum duration of pulses were taken from the international consensus [2]. Numbers preceded by the signal “>” are the longest values tested up to the point of the consensus meeting.

Since there were no indications for stimulations at 80% of motor threshold (MT), the closest comparable value of 90% was used in table 1, as it basically coincides with the values for 100%. The calculations also indicate that “Total number of pulses” in the CFM’s document refers to the entire treatment, and not to each individual session. While this is in agreement with the recently published reporting suggestions for magnetic stimulation dose [10], it also means that the total number of pulses is not a fixed value for all cases and should be recalculated whenever the number of treatment days was decided to be different from 20. It could be useful to stress that the quantity refers to the whole duration of the treatment.

The terminology used for the described parameters in the Brazilian CFM document is closer to the suggestions recently published in the literature [10] than to terms such as the MDP parameter considered in the 2008 international meeting consensus [2, 9]. While this points towards a harmonization in terminology, there are several other relevant parameters for reporting and reproducing research and clinical protocols that aren’t currently considered by CFM document to be informed. These include stimulus waveform related parameters such as a complete characterization of the coil current waveform encompassing pulse shape, amplitude, width and polarity as well as coil configuration related parameters such as the winding shape, diameter, number of turns in each winding, core dimensions and material and any parameters of auxiliary coils or windings [10].

Uniformity in reporting these stimulation parameters is paramount to ensure sufficient information so that doses can be reproducible, for both research and clinical purposes.

Reliability of TMS devices

Medical devices must undergo tests of compliance to relevant standards containing general and specific safety and performance requirements promulgated by the International Electrotechnical Commission (IEC) and others that apply, in order to be registered by Health Surveillance Agencies [6].

The most relevant standards that TMS devices must comply with include the IEC 60601-1, IEC 60601-1-2, IEC 60601-1-4, and, since, up to the present there is no specific standard for TMS, the choice is to meet the specific parameters of the IEC 60601-2-10 standard, which contains specific requirements for the safety and performance of nerve and muscle stimulators.

However, the IEC 60601-2-10 standard states that, among others, equipment destined for brain stimulation and for neurological research should specifically be excluded from that standard's fields of application. Namely, TMS devices fall under this category.

This denotes the lack of a specific standard for brain stimulation equipments, most notably for TMS ones, since the operation principles of magnetic stimulations that induce currents on nerves and those that directly deliver currents via electrodes are quite different and require different safety prescriptions.

For instance, taking into account the magnetic field exposure reference limits published by ICNIRP [3, 4, 5], specific requirements arise to be considered for TMS devices safety. Hazards regarding staff exposure to doses that surpass the recommended values by ICNIRP at distances of about less than 70 cm from the coil surface are pointed out by Kälstrom et al. [11].

Much more restrictive is the fact that the ICNIRP reference levels were determined for exposure conditions in which the variation of electromagnetic fields over the body is small [4]. It is further stated that often the field source is close to the body making the field non-uniform or very localized, and that standardization bodies have the task to give further guidance on the specific exposure situations in which space averaging over the body can be applied, as well as deriving new reference levels for special types of non-uniform exposures. It is likely that TMS falls into one of these cases, since the fields generated by the stimulation coils are notably not distributed uniformly in space.

The ICNIRP guideline mentions that all scientific data and their interpretation are subject to some degree of uncertainty, and that this is compensated for by reduction factors [4]. It also states, however, that there is insufficient information about all the possible sources of uncertainty to provide a rigorous basis for establishing reduction factors over the whole frequency range and for all modulation patterns [4]. The degree of caution to be applied when considering reduction factors for the available database would be, thus, a matter of expert judgment to a large extent.

In the recently published Directive 2013/35/EU [12], the European Commission undertakes the task of making available before July, 2016, non-binding practical guides that cover, among others, the aspects of spatial averaging of electric and magnetic fields, guidance for dealing with uncertainties in measurements and calculations and most notably guidance on demonstrating compliance in special types of non-uniform exposure in specific situations.

Lastly, quantities and unit symbols used in some user manuals for TMS systems do not follow the SI recommendations [9]. The use of the obsolete term "magnetic induction" for the quantity magnetic flux density and the use of the symbol Tl for the unit tesla, instead of T, are some examples of non-conformities of manuals' terminology with the SI.

In order to guarantee the metrological reliability of TMS devices, a particular standard establishing specific

criteria, in agreement with ICNIRP restrictions and SI terminology, and including the requisite of measurement uncertainty evaluation, should be elaborated.

Discussion

Given the described scenario, what seems like the most direct way of facilitating harmonization would be to use the same values, terminology and reporting framework of consensus reports and publications alike for the development of safety protocols, clinical and research reports, and other relevant documents [2, 10]. It could be also important to express the protocol limiting values as a function of parameters that can be directly adjusted on the devices, to avoid the need of further complicating calculations.

In particular for the CFM resolution, it would be valuable to reassess the used terminology to express safety parameters and the set of information required to be provided for dose protocol framework, in agreement with the international consensus and recent discussions in literature [2, 10]. For sufficiency of information, some other parameters concerning coil configuration and stimulus waveform should be included in the CFM document.

The absence of specific standards regarding TMS machines raises issues in ensuring different aspects of safety already discussed, and could hinder the reliability of the technique and its capability to assure the success of the therapeutic protocol.

Considering the current status of safety guidelines regarding exposure, it could also be argued that preliminary actions to better protect staff should be taken until proper dosage measurement guidelines for non uniformly distributed fields are published. In addition, research on the calculation and measurement of magnetic stimulation doses, as well as staff exposure, should be carried out to provide more data and allow for specific safety requirements definitions for a possible future particular standard for TMS. The inclusion of requirements of expression of measurement uncertainty among the criteria for conformity assessment of TMS devices is a crucial aspect in guaranteeing the proper dose delivering. Different physiological effects are produced by minor variations in the combinations of stimulation parameters, altering clinical outcomes.

Conclusion

This work analyzed and discussed relevant safety aspects concerning terminology of TMS protocols and the metrological device reliability.

The current status of TMS safety stimulation protocol presents non uniformities regarding terminology and set of parameters reported. In particular, comparing aspects of protocol reporting in the recently published Brazilian resolution of CFM with international literature and consensus indicated issues concerning terminology and lacking of relevant parameters for reporting clinical protocols that could

allow for ambiguities.

Considering the lack of a particular standard directed specifically at TMS devices, and the inadequacy of the standard used to substitute it, its metrological reliability demands for a future publication of a particular standard establishing specific criteria for TMS, in agreement with ICNIRP restrictions and SI terminology, and including the requisite of measurement uncertainty evaluation.

Moreover, some form of precaution should also be considered for the TMS staff while the updated guidelines for the proper dosimetry studies are not published.

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