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ORIGINAL RESEARCH

Safety of Primed Repetitive Transcranial Magnetic Stimulation and Modified Constraint-Induced Movement Therapy in a Randomized Controlled Trial in Pediatric Hemiparesis

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Abstract

Objective: To investigate the safety of combining a 6-Hz primed low-frequency repetitive transcranial magnetic stimulation (rTMS) intervention in the contralesional hemisphere with a modified constraint-induced movement therapy (mCIMT) program in children with congenital hemiparesis.

Design: Phase 1 randomized, double-blinded, placebo-controlled pretest/posttest trial.

Setting: University academic facility and pediatric specialty hospital.

Participants: Subjects (N=19; age range, 8–17y) with congenital hemiparesis caused by ischemic stroke or periventricular leukomalacia. No subject withdrew because of adverse events. All subjects included completed the study.

Interventions: Subjects were randomized to 1 of 2 groups: either real rTMS plus mCIMT (n=10) or sham rTMS plus mCIMT (n=9).

Main Outcome Measures: Adverse events, physician assessment, ipsilateral hand function, stereognosis, cognitive function, subject report of symptoms assessment, and subject questionnaire.

Results: No major adverse events occurred. Minor adverse events were found in both groups. The most common events were headaches (real: 50%, sham: 89%; $P=.14$) and cast irritation (real: 30%, sham: 44%; $P=.65$). No differences between groups in secondary cognitive and unaffected hand motor measures were found.

Conclusions: Primed rTMS can be used safely with mCIMT in congenital hemiparesis. We provide new information on the use of rTMS in combination with mCIMT in children. These findings could be useful in research and future clinical applications in advancing function in congenital hemiparesis.

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The doubly disabled adult brain after unilateral stroke is affected not only by the lesion itself, but also by exaggerated interhemispheric inhibition from the contralesional primary motor cortex (M1) acting on the ipsilesional M1.[1] In children with congenital hemiparesis, a similar inhibition may occur through developmental disuse, in which a child predominantly uses the less affected extremities, masking potential function in the affected extremities.[2] Low-frequency (inhibitory) contralesional repetitive transcranial magnetic stimulation (rTMS) has shown promising cortical effects by inhibiting the contralesional M1, thereby

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disinhibiting surviving neurons in the ipsilesional M1.[3-5] More studies are investigating the use of rTMS as an intervention to restore higher excitability in the ipsilesional M1.

Iyer et al[6] found that the effects of 1-Hz low-frequency stimulation can be enhanced through preceding the low-frequency session with a priming 6-Hz high-frequency session. The use of 6-Hz priming of low-frequency rTMS to the contralesional hemisphere in children with stroke may work by creating greater disruption of the exaggerated interhemispheric effects of the contralesional hemisphere on the ipsilesional hemisphere. In an effort to achieve improved outcomes, 6-Hz priming rTMS used immediately prior to the low-frequency rTMS can be used to capitalize on principles of homeostatic plasticity.[7] Homeostatic plasticity encompasses several mechanisms aimed at stabilizing neuronal activity to maintain synaptic specificity and prevent unconstrained synaptic plasticity from predominating in the system.[8] Importantly, homeoplastic plasticity depends on the previous history of synaptic activity.[9]

Therefore, excitatory priming stimulation biases the neural network to seek return to its baseline activity level. In combination, the low-frequency rTMS applied in the facilitated state yields a more pronounced inhibition compared with low-frequency rTMS that is not preceded by high-frequency rTMS.[6]

Distinct from rTMS, motor learning with use of constraint is an additional intervention with potent effects on brain reorganization.[10-12] Modified constraint-induced movement therapy (mCIMT) is defined as <3 hours of therapy per day using the techniques of shaping, repetition, and constraint.[13] The combining of electrophysiological and behavioral interventions provides a synergistic approach that may help to maximize the recovery of hand function. Both interventions are aimed at suppression of the exaggerated inhibitory interhemispheric effects, allowing increased contribution from the surviving neuronal networks within the ipsilesional hemisphere.

The important question of safety remains with such interventions. The safety of rTMS has been investigated to a much greater extent in adults with stroke than children; however, understanding the risks is paramount for all ages.[14-16] Kirton et al[17] demonstrated that 1-Hz low-frequency contralesional M1 rTMS was safe, with no serious adverse events (eg, seizure) in children with stroke. Although there are reports in adults with brain injury that using 6-Hz priming rTMS with 1 treatment[18] and multiple treatments[19] is safe, primed rTMS has not been explored in children with stroke. Because of the high-frequency nature of the priming and the greater potential risk of adverse events (eg, seizure), investigating the safety of a 6-Hz primed, 1-Hz low-frequency application of rTMS in combination with motor learning training should be thoroughly investigated.

The purpose of this article is to report on the safety of 6-Hz primed low-frequency rTMS combined with mCIMT specific to children with hemiparesis. We defined safety by physician assessment, cognitive status, a subject report of symptoms, and a questionnaire. Because the rTMS component of the intervention was delivered on the contralesional hemisphere, safety also included assessment of ipsilateral, unaffected, hand function.

List of abbreviations:

AMT	**active motor threshold**
mCIMT	**modified constraint-induced movement therapy**
MRI	**magnetic resonance imaging**
M1	**primary motor cortex**
RMT	**resting motor threshold**
rTMS	**repetitive transcranial magnetic stimulation**
TMS	**transcranial magnetic stimulation**

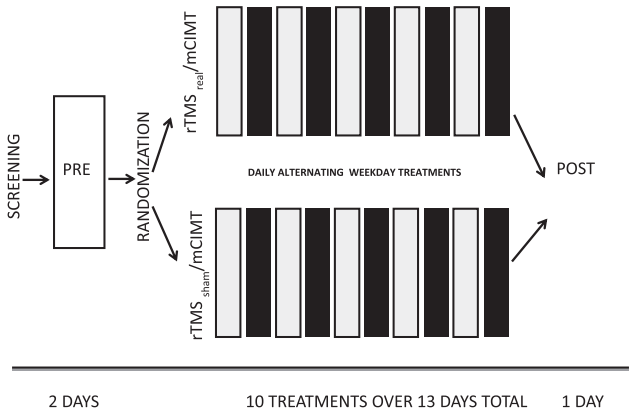

Fig 1 Study design. Screening was followed by a 2-day series of pretesting: imaging, physician assessment, and cognitive and motor testing. rTMS sessions (light blocks) were 20 minutes total: priming for 10 minutes at 6Hz at 90% of the RMT, followed by low-frequency 1-Hz rTMS for 10 minutes at 90% of the RMT. mCIMT (dark blocks) was performed for 2 hours with 1:1 therapist-subject treatments. The constraint cast was applied on treatment day 2 and was removed on treatment day 10 (13 days total wear, including weekends). Abbreviations: $rTMS_{real}$, real rTMS group; $rTMS_{sham}$, sham rTMS group.

Methods

This study was a randomized, controlled, blinded, pretest-posttest trial comparing active and placebo rTMS in combination with mCIMT in children with congenital hemiparesis. Subjects meeting our criteria were randomized into 1 of 2 groups: real rTMS plus mCIMT and sham rTMS plus mCIMT (fig 1). Specific exclusion and inclusion criteria guided subject enrollment and participation in stages (appendix 1). For example, during the initial screening, we excluded children with disorders of cellular migration and proliferation because exaggerated interhemispheric inhibition may not be present in these nonstroke disorders and our intervention may potentially not be applicable. Because children with perinatal stroke typically experience seizure within the first 48 hours after birth,[20] excluding any history of seizure would yield very few children to study. We limited seizure activity to none in the 2 years prior to the study because the study neurologist deemed this seizure-free period appropriate in regard to safety. At pretest, we obtained a fluid-attenuated inversion recovery scan sequence for assessment of the cerebral infarction and a gradient echo scan sequence for evidence of any prior hemorrhage. The study pediatric neurologist reviewed these results for each subject enrolled. Evidence of hemorrhage and subsequent presence of hemosiderin protein excluded any subjects because they may have been predisposed to seizure.[21,22] We allocated subjects using a random numbers table system. Researchers administering the rTMS interventions were unblinded. Testing researchers, physicians, caregivers, and subjects were blinded to treatment allocation.

Subjects were recruited through institutional review board–approved mailings, community- and school-based contacts, and diagnosis-specific website postings. The study's pediatric neurologist completed a magnetic resonance imaging (MRI) session with each subject, which included fluid attenuation inversion recovery