Turk J Phys Med Rehab 2017;63(2):193-196
DOI: 10.5606/tftrd.2017.417

Review

Theta burst stimulation a new paradigm of non-invasive brain stimulation for post-stroke upper limb motor rehabilitation

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Received: April 2016 Accepted: July 2016

ABSTRACT

Objectives: The aim of this study was to perform a brief review of studies which investigated the effects of theta burst stimulation (TBS) as a new paradigm of non-invasive brain stimulation on the upper limb motor function in patients with stroke.

Materials and methods: We searched studies published between January 1990 and October 2015 at PubMed, Medline, Cochrane, and CINAHL databases using the following key words: stroke and theta burst stimulation.

Results: Eleven of 67 studies met the inclusion criteria. Of these, six studies used multiple sessions of TBS intervention. The results of the selected studies showed a significant improvement in the upper limb motor functions in nine studies, whereas one study did not show any change after the TBS intervention. One of the selected study showed a negative trend in motor functions after the application of TBS.

Conclusion: Our study showed that TBS had a positive effect on motor recovery in patients with stroke. Combination of both intermittent TBS to the ipsilesional hemisphere and continuous TBS to the contralesional hemispheres would be more effective than the single application of any one of these technique.

Keywords: Stroke rehabilitation; theta burst stimulation; transcranial magnetic stimulation.

Stroke is one of the major causes of death and leading cause of long-term disability in adults.[1] Several studies have shown that upper limb disability is a major concern on post-stroke patients, as it affects the activities of daily living.[2] Currently, physical therapy and occasional neurostimulation techniques are used for the treatment of stroke-induced hand motor deficits.[3]

In a post-stroke brain, the equilibrium of cortical excitability is altered, which shows a reduction in the cortical excitability of the ipsilesional hemisphere. On the other hand, there is an enhanced excitability of the contralesional hemisphere.[4] This altered equilibrium is due to the increased interhemispheric inhibition from the contralesional hemisphere to the ipsilesional hemisphere. This can be re-balanced by non-invasive cortical stimulation by repetitive transcranial magnetic stimulation (rTMS).[4]

Theta burst stimulation (TBS) is a method of applying rTMS in a patterned protocol (3 pulses given at 50 Hz which are applied at 5 Hz). Intermittent TBS (iTBS) in which a 2 sec train of stimulation (10 bursts) is followed by 8 sec pause significantly increases the motor cortex excitability, when applied to the ipsilesional hemisphere. Continuous TBS (cTBS) applied for 40 sec significantly suppresses motor cortex excitability, when applied to the contralesional hemisphere as demonstrated by Huang et al.[5]

However, several studies on TBS have not shown a long-lasting effect on the motor functions of post-stroke patients and no consensus in the application of TBS on post-stroke patients is available. Therefore, the aim of the present study was to evaluate the effect of TBS on upper limb motor recovery on patients with stroke in the light of literature data.

MATERIALS AND METHODS

We performed a computerized search using the search terms stroke and TBS at PubMed, Cochrane, CINAHL, and Medline databases, where shortlisted

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Cite this article as:
Khan F, Chevidikunnan F. Theta burst stimulation a new paradigm of non-invasive brain stimulation for post-stroke upper limb motor rehabilitation. Turk J Phys Med Rehab 2017;63(2):193-6.

for studies written in English and published between January 1990 and October 2015. The studies which met the following criteria were included: *(i)* patients diagnosed with stroke, *(ii)* adult patients, and *(iii)* TBS effects on the upper limb motor function in patients with stroke. Studies *(i)* done on animals, *(ii)* normal subjects *(iii)* which included combination of TBS and *(iv)* TMS effects on other variables rather than upper limb recovery, such as spasticity, neglect, and aphasia were excluded.

The search yielded a total of 67 citations and 11 met the inclusion criteria. Two studies recruited patients in the acute phase, one study from sub-acute phase, and the remaining eight studies on chronic phase.

RESULTS

The study design was double-blind, cross-over, sham-controlled in two studies; double-blind, randomized allocation in two studies; and randomized-controlled, triple-blind, pseudo-random allocation, and semi-randomized, placebo-controlled in one of each in the remaining studies. Table 1 shows the details of the studies included.

The studies used TBS interventions in different patterns of stimulation. Five studies used iTBS (facilitatory on the ipsilesional hemisphere) and cTBS (inhibitory on the contralesional hemisphere), three studies used iTBS alone in the ipsilesional hemisphere, and three studies used cTBS alone in the contralesional hemisphere. Six studies used sham as the control intervention. In five studies, intervention was applied only for one session, while, in four studies, intervention was applied for 10 sessions, and intervention was applied for three and 13 sessions in one study each.

Different outcome measures were used in the selected study. Neurophysiological variables such as motor-evoked potential (MEP), resting motor threshold (RMT), and active motor threshold (AMT) were used in eight studies. Reaction time was used in two studies, dynamometry and force assessment were used in five studies, and objective scales for hand function (Fugl Meyer Assessment [FMA], Wolf Motor Function Test [WMFT], Action Research Arm Test [ARAT], and Jebsen Taylor Test [JTT]) were used in seven studies. One study used functional magnetic resonance imaging (fMRI) and as the outcome measures.

Eight studies incorporated physical therapy/motor training along with the TBS interventions, one study incorporated occupational therapy as an additional intervention along with TBS, and two studies did not use any additional interventions.

DISCUSSION

The present study shows variability in the results of the different TBS studies on the upper limb motor functions of the patients with stroke. Six studies conducted by Meehan et al.,[6] Hsu et al.,[7] Talelli et al.,[8] Di Lazzaro et al.,[9] Yamada et al.,[10] and Ackerley et al.[11] used multiple sessions of TBS; the studies carried out by Di Lazzaro et al.,[9] Hsu et al.,[7] and Talleli et al.[8] applied 10 sessions of TBS intervention, and in the study of Meehan et al.,[6] the TBS intervention was given only for three sessions and in the study of Yamada et al.,[10] the TBS intervention was given for 13 sessions.

The results of the study conducted by Hsu et al.[7] where iTBS was applied to the ipsilesional hemisphere for 10 daily sessions showed that there was an increase in the upper extremity FMA and National Institute of Health Stroke Scale (NIHSS) scores after the intervention, whereas there was no change in the ARAT and in the other electrophysiological parameters. A similar study done by Talelli et al.[8] where TBS intervention was applied for 10 daily sessions and followed until 90 days post-intervention showed no improvement in any of the outcome measures after the intervention and until the end of follow-up. The results of the study done by Meehan et al.[6] showed that there was a significant change in the upper limb performance after three daily sessions of cTBS, when applied only to the contralesional hemisphere. The study carried out by Ackerley et al.,[12] where a crossover design was used, showed a positive trend toward the application of iTBS to the ipsilesional hemisphere, whereas there was a negative effect after the application of cTBS to the contralesional hemisphere. The results of the studies performed by Talelli et al.[13] and Di Lazzaro et al.,[14] where TBS (iTBS to ipsilesional and cTBS to contralesional hemisphere) was applied for a single session, showed a significant positive trend in both motor and electrophysiological outcomes. Similarly, the results of the study of Di Lazzaro et al.,[9] where cTBS versus sham intervention was used, showed an improvement in the ARAT and JTT scores in all patients for up to three months post-treatment. In addition, the ARAT scores significantly improved in both real and sham groups, although only patients receiving real TBS significantly improved on the JTT at three months after treatment. Yamada et al.[10] showed a significant increase in the FMA scores (from 46.6±8.7 to 51.6±8.2

Table 1. Details of included studies

Study	No. of participants	Age in years Mean±SD	Stroke duration Mean±SD	TBS protocol	Main outcome measures	Additional interventions
Talelli et al.[13]	6	57.7±14.9	31±37.9*	1. iTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 10 bursts × 20 trains, ITI=8s 2. cTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 100 bursts (300 pulses) 3. Sham (1 session)	SRT, CRT, BI, 9HPT, NIHSS, MI, ARAT, grip strength, AMT, RMT, MEP amplitude	
Di Lazzaro et al.[14]	12/12 controls	69.4±9.5 63.2±5.3	<10#	1. iTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 10 bursts × 20 trains, ITI=8s 2. cTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 200 bursts (600 pulses) (1 session)	AMT, RMT, MEP, amplitude, latency	
Ackerley et al.[12]	10	60±11	28±25*	1. iTBS 90% AMT, 1 burst with 3 pulses at 50 Hz, 10 bursts × 20 trains, ITI=8s 2. cTBS 90% AMT, 1 burst with 3 pulses at 50 Hz, 200 bursts (600 pulses) (1 session cross over)	Grip lift kinetics, ARAT, MEP amplitude	Motor training
Di Lazzaro et al.[16]	17	68.2±11.7	<10#	1. iTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 10 bursts × 20 trains, ITI=8s (1 session)	NIHSS, mRS, RMT, AMT, MEP amplitude	Physical therapy
Meehan et al.[6]	12 (4/4/4)	63±9 64±14 65±10	88±91* 69±47* 66±61*	1. cTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 200 bursts (600 pulses) (3 session)	WMFT, reaction time, movement time, kinematic analysis	Motor training
Hsu et al.[7]	12 (6/6)	56.8±6.8 62.3±8.5	22.0±5.3# 20.8±3.6#	1. iTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 400 bursts (1200 pulses) (10 session) 2. Sham	Upper extremity FMA, ARAT, NIHSS, AMT, MEP	Physical therapy
Talelli et al.[8]	41 12/12/13/12 Drop out	55.8±12.4 59.4±12.4 54.4±15.8 58.5±12.0	29.8±19.7* 49.6±76.9* 17.5±5.1* 38.5±57.2*	1. iTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 10 bursts × 20 trains, ITI=8s 2. cTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 200 bursts (600 pulses) 3. Sham iTBS, (4) Sham cTBS. (10 session)	9HPT, ROM, JTT, RASP, dyanamometry, ashworth	Physical therapy
Di Lazzaro et al.[9]	12 (6/6)	59.5±12.4 57.5±12.3	34.8±17.5* 30±27.6*	1. cTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 200 bursts (600 pulses) 2. Sham (10 session)	9HPT, ARAT, JTT, Dynamometry, AMT, MEP amplitude	Physical therapy
Yamada et al.[10]	10	62.0±11.1	95.7±70.2*	1. cTBS 80% AMT, 1 burst with 3 pulses at 50 Hz, 200 bursts (2400 pulses) (13 session)	FMA, WMFT, FAS	Occupational therapy
Ackerley et al.[15]	13	69±8	23±16*	1. iTBS 90% AMT, 1 burst with 3 pulses at 50 Hz, 10 bursts × 20 trains, ITI=8s 2. cTBS 90% AMT, 1 burst with 3 pulses at 50 Hz, 200 bursts (600 pulses) 3. Sham (cross over)	FMA, 9HPT, NIHSS, mRS, precision grip, sensory motor integration, MEP	Dexterity training
Ackerley et al.[11]	18	56.8±6.8 62.3±8.5	22.0±5.3# 20.8±3.6#	1. iTBS 90% AMT, 1 burst with 3 pulses at 50 Hz, (600 pulses) 2. Sham (10 sessions)	Upper extremity FMA, ARAT, NIHSS, mRS, MEP, fMRI	Physical therapy

* Months; # Days; 9HPT: 9-Hole Peg Test; AMT: Active motor threshold; ARAT: Action Research Arm Test; BI: Barthel index; CRT: Choice reaction time; cTBS: Continuous theta burst stimulation; FAS: Functional Ability Scale; FMA: Fugl Meyer assessment; fMRI: Functional magnetic resonance imaging; iTBS: Intermittent theta burst stimulation; ITI: Inter-train interval; JTT: Jebsen Taylor Test; MEP: Motor-evoked potential; MI: Motoricity index; mRS: Modified Rankin scale; NIHSS: National Institute of Health Stroke Scale; RASP: Rivermead Assessment of Somatosensory Performance; RMT: Resting motor threshold; ROM: Range of motion; SRT: Simple reaction time; WMFT: Wolf Motor Function Test.

points, $p<0.01$) and shortened the log performance time of the WMFT (from 2.5±1.1 to 2.2±1.2 s, $p<0.01$) in which a 13-day protocol of cTBS combined with intensive occupational therapy was applied to post-stroke patients. The results of the studies performed by Ackerley et al.[15] also showed improvements in paretic grip-lift performance accompanied by an immediate facilitation of ipsilesional M1 excitability after iTBS to the ipsilesional motor area. In another study, the aforementioned authors showed improvements in the ARAT after the 10 sessions of intervention period, when therapy was primed with real iTBS, but not sham, and were maintained at one month.[11] The improvements in the ARAT at one month were related to balanced corticomotor excitability and increased ipsilesional premotor cortex activation during paretic hand grip. Di Lazzaro[16] also demonstrated that iTBS produced a significant increase in the MEP amplitude for ipsilesional hemisphere, which was significantly correlated with recovery in 17 stroke patients.

In the present study, we found variable results for the application of TBS for the upper limb rehabilitation of post-stroke patients. Although few studies reported non-significant results, the majority of the studies showed a positive trend toward the therapeutic application of TBS. In addition, the recent studies reported significant effects of TBS on the upper limb rehabilitation of patients with stroke.[10,15] As TBS is a new paradigm of application of repetitive rTMS in a high frequency with a burst and with low intensity, it seems to be safe and comfortable for the patients. According to the literature data, there is a need for setting a protocol with the most evident parameters for the application of TBS and its long-term effects should be studied.

The main limitations of the present study are limited data on TBS interventions on the upper limb in patients with stroke and lack of long-term follow-up studies after TBS interventions. Therefore, further, large-scale, well-designed studies are necessary to confirm the effect of TBS on the upper limb motor outcomes and their effect on cortical plasticity for patients with stroke.

In conclusion, TBS showed a positive trend in the upper limb motor recovery in post stroke patients.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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