Title: Combined effects of rTMS and botulinum toxin in benign essential blepharospasm: A novel approach

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BACKGROUND:

Benign essential blepharospasm (BEB) is a focal dystonia characterized by excessive involuntary closure of the eyelids.[1] BEB is a functionally disabling disorder with significant impact on the quality of life.[2] Due to repeated involuntary closure of eyes, in severe cases, patients become functionally blind despite a normal visual acuity. Chemodenervation with botulinum neurotoxin (BoNT) injections administered every 12 weeks has emerged as an effective first-line therapy for the treatment of BEB. However, the treatment is purely symptomatic and does not modify the disease pathophysiology.[3] Importantly, the clinical benefits are temporary with most patients reporting benefits lasting only about 8-10 weeks.[4, 5] We conducted a retrospective analysis of BEB patients at our movement disorders center that has followed over 250 patients (manuscript submitted) and found that the average duration of benefits from BoNT injections was about 9.5 weeks which is consistent with other studies. Thus BoNT therapy although a first-line therapy for BEB shows suboptimal benefits in many patients. Therefore, there is a clear merit in exploring other options that can potentiate and possibly prolong the effects of BoNT injections.

rTMS refers to application of repetitious transcranial magnetic stimulation (TMS) pulses to a specific brain target at predefined stimulation parameters. We propose a **novel approach** of combining rTMS therapy with BoNT injections in BEB. The **primary goal** of this study is to compare the standard treatment with BoNT versus BoNT combined with a two week course of rTMS therapy. The **central hypothesis** is that rTMS therapy potentiates and prolongs the effects of BoNT therapy in BEB. rTMS therapy has shown beneficial results in many neurological and psychiatric conditions.[6,7] rTMS therapy is noninvasive and is FDA approved for treatment of medication refractory depression when delivered to the prefrontal cortex.[8] In our study we will select the anterior cingulate cortex (ACC) as the target of stimulation. ACC has been proposed by many studies as the main sites of pathology in BEB. Anatomically in monkey studies, the ACC has been shown to have clear projections to the upper facial muscles.[9] In BEB patients, PET study has shown there is an increased glucose uptake in the ACC.[10,11] fMRI study has also shown an increased brain activity in the rostral ACC in relation to the eye-closure.[12, 13] Kranz et al in collaboration with Dr Hallett's lab tested the effects of rTMS of the ACC in BEB. So far to date this is the only rTMS study that is available for review in literature. These investigators found that a single session of low frequency rTMS delivered to the ACC had positive clinical benefits though lasting only for about one hour.[14]

The fundamental mechanism of action for rTMS is modulation of brain excitability.[15] rTMS at frequencies of 5-Hz and higher has been found to transiently enhance the excitability,[16] whereas rTMS at frequencies of 1-Hz and lower has been found to depress the cortical excitability.[17] Many rTMS studies have also shown that repeated sessions of rTMS therapy results in cumulative persistent benefits that can last several weeks. For example, in a recent double blind randomized controlled study, low frequency rTMS delivered over eight weeks to Parkinson's disease patients showed positive clinical benefits that lasted 12 weeks beyond the last rTMS session.[18] In this proposal we plan to employ a two week course of rTMS therapy to achieve sustained benefits. With standard BoNT treatment, the peak-dose benefits are seen at about 4-6 weeks after the administration of injections. We plan to introduce rTMS during this peak-dose period (about 6 weeks after BoNT or **T1**). We will examine the effects of combined therapy at about 10 weeks after BoNT injections (**T2**) and at about 12 weeks after BoNT injections (**T3**). We will also measure the physiological effects at these time points. We will use the blink reflex recovery (BRR) curve that reflects the brain stem excitability. An increased BRR indicates that there is increased excitability of facial motor neurons and bulbar interneurons. BRR has been shown to be increased in a significant proportion of patients with BEB.[19,20] According to the animal model of blepharospasm, one of the underlying mechanisms for increased BRR is that a loss of dopamine-containing neurons in the substantia nigra pars compacta causes a decreased inhibition in the blink circuit.[21]

In summary, BEB is a functionally disabling focal dystonia. BoNT therapy is suboptimal in many BEB patients. rTMS therapy is a promising noninvasive therapy and has shown positive benefits in BEB. rTMS therapy can be

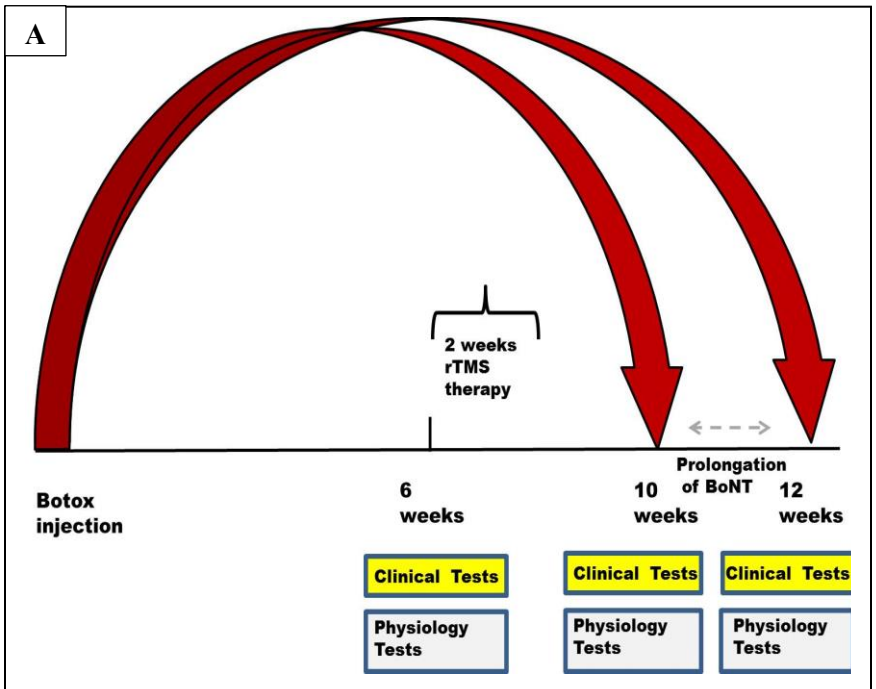
easily combined with BoNT injections to enhance the effects of BoNT in BEB. We plan to collect pilot data on this novel approach in this one year application. The specific aims for the proposal are:

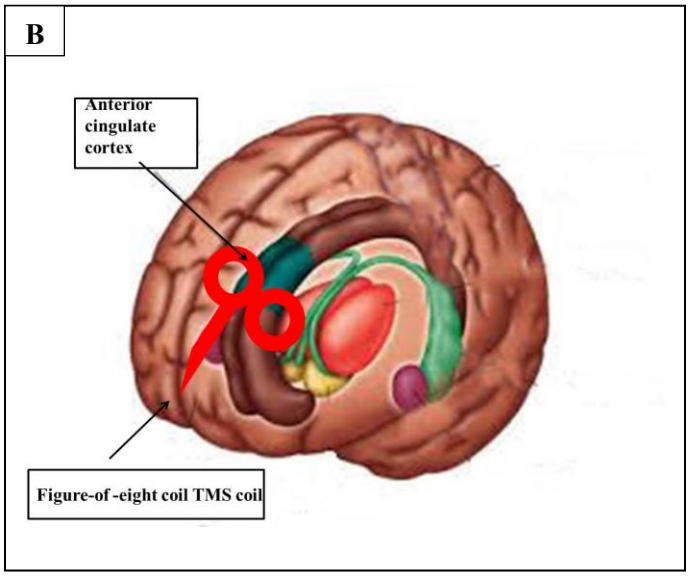
<u>Aim 1:</u> Clinical impact of rTMS therapy in BEB.
We will determine the clinical effects of 0.2 Hz rTMS therapy of the ACC when combined with BoNT injections in BEB. Comparisons will be drawn between the T1, T2 (about 10 weeks after BoNT) and T3 (about 12 weeks after BoNT) assessments in the clinical scoring of BEB symptoms and patient rating of quality of life. We hypothesize that in comparison to T1 assessment; there will be an increased control of BEB symptoms and patient rating of quality of life at T2 follow-up. These benefits will remain sustained at T3 follow-up though to a lesser extent.

<u>Aim 2</u>: Physiological impact of rTMS therapy in BEB

Aim 2a: We will determine the physiological effects of 0.2 Hz rTMS therapy of the ACC when combined with BoNT injections in BEB. We will record the time course of effects on BRR at T1, T2 and T3 assessments. We hypothesize that in comparison to T1 assessment, BRR will be reduced and reach physiological levels at T2 follow-up. BRR will continue to remain at physiological levels at T3 follow-up though to a lesser extent than at T2.

Aim 2b: We will determine if the effects of 0.2 Hz rTMS therapy on BRR will correlate with clinical scoring of BEB symptoms. We hypothesize that the change in BRR at T2 and T3 will show positive correlation with the improvement in BEB symptoms at these time points.





rTMS will be delivered over the ACC with a figure-of-eight coil.

Figure 1:
A shows the schedule for rTMS intervention and monitoring of clinical and physiological outcomes
B shows the target in the brain for rTMS intervention

METHODS

Study design: We propose a blinded control study of real and sham rTMS with a goal of enrolling about eight subjects (age range 21–80 years) in each treatment arm and ten healthy control subjects for normative physiological data (total 26 16). Subjects diagnosed with blepharospasm or cranio-cervical dystonia who receive BoNT therapy at our center will be approached. The BoNT clinic at our center follows more than 250 subjects with dystonia. Subjects followed at our center regularly fill out a self-reported form to document if they have responded to BoNT and the duration of benefits perceived with BoNT therapy. We will enroll only those subjects who report experiencing positive benefits with BoNT but lasting about 10 weeks or less. We will exclude subjects if they report 1) pregnancy; 2) active seizure disorder; 3) significant cognitive impairment; 4) exposure to neuroleptics; and 5) presence of a metallic body such as pacemaker, implants, prosthesis, artificial limb or joint, shunt, metal rods and hearing aid.[14] We will enroll about 10 healthy age and sex-matched subjects controls for normative electrophysiological data. Controls will be recruited through fliers placed across the campus. All controls will be examined by Dr. Wagle Shukla to ensure that they are neurologically healthy.

We will invite all eligible subjects to an introductory session. During this session the procedures outlined for the study will be explained in detail. We will then obtain an IRB approved informed consent. We will perform medical history and neurological examination using the NINDS Common Data Elements. Each subject will be randomized to receive either real or sham stimulation. We will record the demographics and severity of BEB using the blepharospasm severity scale.[22] The BEB subjects followed at our center are scheduled for BoNT treatment about every 12 weeks as per the standard of care. We will start rTMS therapy at about 6 weeks after they have received the BoNT injections. We have chosen this timeframe to coincide the rTMS therapy with the peak-dose effects of the BoNT injections. We will do our best to make sure that the patients are accompanied to the laboratory facility by a friend, relative, or spouse, or we will arrange transportation. Although the physician administering TMS will be aware of the status of the subject in terms of real TMS versus sham-TMS, this physician will play no role in any of the outcome measures, and will not be present during any of the outcome measure assessments. Similarly, the investigators who perform the outcome measures will not be present during any of the TMS sessions, and therefore will remain blinded to the status of the patients with respect to real-TMS versus sham-TMS.

Outcome measures: The primary clinical outcome will be the percentage change in physician rating of BEB symptoms. We will record 5 minute videos of eye blinks for the eye blink rate, number of sustained blinks, and time of eye closure. These videos will be scored by a blinded rater. We will then use the Jankovic rating scale and blepharospasm disability index to rate the improvements. We have IRB approved consent to obtain videos of most patients presenting to our center but the ICF will include a video consent section. The secondary outcome for the study will include the subjective rating by the patients. We will record blink reflex recovery (BRR) as the physiological outcome of rTMS. We will determine the time course effects of rTMS on physiological outcome. We will also determine if the physiological effects correlate with the clinical outcome measures.

Clinical measures:

Physician rating: We will score the eye blink rate, number of sustained blinks, and time of eye closure. An eye blink will be defined as any visible, bilateral, and synchronous contraction of the orbicularis oculi (OO muscle), causing eyelid drop. Blink rate will be expressed as blinks per minute. Sustained spasms of the OO muscle will not be considered blinks and will be counted separately. The time (seconds) of eye closure whenever blinks cause prolonged eye closure (eyes shut > 2 seconds) will be recorded with a stopwatch.[14]

Patient rating: We will administer the Craniocervical Dystonia Questionnaire Description for quality of life assessment. The Craniocervical Dystonia Questionnaire (CDQ-24) is a patient-rated health related quality of life (HR-QoL) measure for craniocervical dystonia. It was developed based on issues that are relevant to patients with BEB. It has been validated for use in clinical research. The CDQ-24 measures the impact of Craniocervical

Dystonia on 5 HR-QoL domains. It is composed of 24 items, forming 5 subscales: stigma, emotional well-being, pain, activities of daily living, and social/ family life. Items are rated on a 5-point scale.[23] Each item consists of five statements representing increasing severity of impairment, scored from 0 to 4. Subjects will be instructed to indicate how they have felt during the past two weeks because of dystonia by selecting one of the five statements for each item. Subjects will also rate their symptoms before and after stimulation using a 7-point nominal scale: 1) excellent, 2) very good, 3) good, 4) average, 5) slightly worse than usual, 6) bad or 7) very bad.

Physiological Measure:

Blink reflex recover: We will record surface EMG recordings for both eyes separately from the orbicularis oculi (OO) muscle using Ag-AgCl surface electrodes. The EMG signals will be amplified using D360 amplifiers (Digitimer, Welwyn, UK), band pass filtered (5–2,500 Hz), analog-to-digital-converted using a 1401 AD converter (CED, Cambridge, UK) at a sample rate of 5,000 Hz, and will be collected on a computer. Electrical stimulation will be applied to the supraorbital nerve in the supraorbital notch with a bipolar stimulating electrode and a constant current generator (Digitimer). Single and paired electrical stimuli (conditioning and test) will be delivered and EMG amplitudes will be recorded from the OO muscle. All stimuli will be 0.2 msec in duration and stimulus intensity will be set at 3 times the R2 threshold (lowest intensity that gives an R2 response in at least 5 out of 10 trials). Subjects will be studied at rest, with eyes gently closed. The blink reflex in response to paired stimulation will be assessed at multiple inter stimulus intervals of about 200 msec (6 trials of test and paired stimulus each, pseudo randomized.). Pairs of stimuli will be separated by varying time intervals of 20–40 seconds to minimize habituation. Trials with excessive EMG artifact will be rejected online. Data will be analyzed offline using Signal software (Cambridge Electronic Design, UK). The raw blink recordings will be DC-corrected, rectified, and averaged. The onset latency and duration of R1 and R2 responses will be determined by manual cursor marking of the beginning and end of responses. Peak amplitude of R2 will be calculated within a window from 30 to 60 msec to avoid stimulation artifacts. We will obtain R2 recovery values by dividing the size of R2-test [R2T] by the size of conditioning response [R2C]. [19]

rTMS therapy:

Real stimulation: rTMS will be delivered over each anterior cingulate cortex, using a figure-of-eight coil connected to a Magstim machine (Magstim Company, Dyfed, UK). We will apply rTMS with 0.2 Hz frequency to the ACC. We will deliver 180 stimuli (around 15 min) with a stimulator output of 100% active motor threshold (AMT). AMT will be assessed at the tibialis anterior muscle with the figure-of-eight coil. The AMT will be defined as the lowest stimulation intensity required to evoke a 150 μV potential in the target muscle. To determine the stimulation site for ACC, the figure-of-eight/double cone coil will be placed over Fz and then moved over the midline of the brain in 0.5-cm steps anteriorly, until the point of maximum motor evoked potential in the orbicularis oculi (OO) muscle (with a latency of 6–8 msec) is reached (about 3.5 cm medial and 5.5 cm anterior to motor cortex).[14] The coil position will be marked on the skin. Constant coil position will be continuously monitored during the experiment. These rTMS sessions will be repeated on a daily basis over 10 days. During rTMS, all patients will wear ear plugs in order to protect the ears from the acoustic artefact associated with the discharge of the stimulation coil.

Sham Stimulation: During sham rTMS, subjects will undergo the same procedure for identifying stimulus location as used in patients receiving real rTMS. Sham rTMS will be administered using the same Magstim coil as used in real stimulation. This coil will be placed on the patient's head in an identical manner however will not be connected to the Magstim device. Instead another coil will be connected to provide stimulation sound. In each stimulation condition, the Magstim will be placed behind the patient and not visible to him or her. Placebo sham coil which produces discharge noise and vibration similar to a real coil without stimulating the cerebral cortex. During rTMS, all patients will continue to wear ear plugs as instructed during the real stimulation sessions.

***Safety of rTMS**:* Repetitive TMS can have undesired side effects. Guidelines for the safe use of rTMS were formulated at the 1st International Workshop on the Safety of TMS.[24] These were adopted by the International Federation for Clinical Neurophysiology and subsequently updated.[25] The proposed study will use TMS parameters well within the published safety guidelines. We will conduct careful monitoring of the participants and follow all recommended precautions for the application of TMS. Subjects will have a urine pregnancy test done on the first day of the scheduled rTMS visit before rTMS is done.

There will be a potential for direct benefit if the study stimulation helps subject's blepharospasm symptoms. Risks include a neck ache or headache. The study procedure may also cause the nearby scalp muscles to twitch. Although TMS has been used for over 20 years, there is a possibility of unknown risks due to TMS.

Data Safety Monitoring Plan

The principal investigator monitors the patient safety and data collection of each study visit. If she feels there is possible harm to subject safety or the possibility of, any harm due to something new that was learned during the study, she will convene a multi-disciplinary committee of at least 2 health professionals to perform a thorough review of the study details.

Patient Stipends

Payments for mileage reimbursement will be paid to study subjects with blepharospasm. If a hotel visit is required, the study team will make the hotel arrangements for the subjects and the cost will be pre-paid.

Control subjects will be paid a flat rate of $20 or can be paid for mileage, whichever is greater. If you are paid more than $75, we will need to collect your social security number.

SAMPLE SIZE, EXPECTED OUTCOME AND STATISTICAL ANALYSIS: With an expected difference of 30% in the primary outcome measure[14] between before (T0) and after rTMS therapy (T1), a standard deviation of 20%, type I error of 5% and power of 80%, the necessary sample size for each group has been determined. In this one year pilot study we propose to enroll a total of 16 BEB subjects with eight subjects in each treatment arm and 16 healthy controls for normative physiological data. Descriptive statistics will be used for the demographic data. Data will be presented as mean (SD) unless otherwise indicated. We will examine each of the dependent measure separately. These include the eye blink rate, number of sustained blinks, the time of eye closure, patient rating of blepharospasm and the BRR cycle. For Aim 1 and Aim2a, each dependent measure will be examined using the following statistical approach. We will conduct a mixed model analysis using time and stimulation arm as repeated factors adjusted for baseline values, and subjects as the random factor. The model will include 2 within-subject factors: treatment (2 levels: active vs sham) and time (3 levels: T1, T1, and T3). If the interaction effects between stimulation arm and time are found as non-significant, they will be dropped. In case of significant main effects, post hoc pairwise comparisons will be corrected using Fisher least significant difference procedure in accordance with the closed test principle; i.e., post hoc comparisons will be declared non-significant if the global *p* value of the main effect (testing equality of all 2 stimulation arms simultaneously) are non-significant, but will be carried out without further correction in case of a significant global main effect. SPSS version 15.0 for Windows will be used for statistical computations. The 2-tailed significance level will be set at 0.05. For Aim 2b, we will use Spearman correlation test to determine the relation between the change in BRR and change in clinical scores at T2 compared to T1 and at T3 compared to T1.

POTENTIAL PROBLEMS

1. Subjects may not meet the criteria, may not tolerate the rTMS therapy or drop out of the study. We will factor in these considerations during recruitment. We propose a sample size of eight subjects in each treatment arm (total 16). We have an IRB approved database of patients followed at our center. In order to meet our target sample, while conducting the retrospective analysis we preemptively identified the BEB subjects that receive suboptimal benefits (36 subjects).
2. Quality assurance (QA) on the Magstim machine will be constantly monitored.
3. Quality of EMG recordings: The EMG recordings (Delsys, Inc., Boston, Massachusetts) are reliable with high signal-to-noise ratio. We will reduce the noise of the EMG signals by cleaning and lightly abrading the skin.

The University of Florida nor the Principal Investigator hold a patent or license for any material, object or process used in this study. There is no license pending or under consideration or is there any intention to file a patent application at a later date.

Computer-based files will only be made available to personnel involved in the study through the use of access privileges, passwords and encryption. Passwords and encryption are used to ensure that the electronic data is secure and housed in a locked room.

References

1. Hallett M, Evinger C, Jankovic J, Stacy M, BEBRF International Workshop. Update on blepharospasm: Report from the BEBRF international workshop. Neurology 2008;71:1275-1282.

2. Wenzel T, Schnider P, Griengl H, Birner P, Nepp J, Auff E. Psychiatric disorders in patients with blepharospasm - a reactive pattern? J Psychosom Res 2000;48:589-591.

3. Costa J, Espirito-Santo C, Borges A, et al. Botulinum toxin type A therapy for blepharospasm. Cochrane Database Syst Rev 2005;(1):CD004900.

4. Ainsworth JR, Kraft SP. Long-term changes in duration of relief with botulinum toxin treatment of essential blepharospasm and hemifacial spasm. Ophthalmology 1995;102:2036-2040.

5. Streitova H, Bares M. Long-term therapy of benign essential blepharospasm and facial hemispasm with botulinum toxin A: Retrospective assessment of the clinical and quality of life impact in patients treated for more than 15 years. Acta Neurol Belg 2014.

6. Gironell A, Kulisevsky J, Lorenzo J, Barbanoj M, Pascual-Sedano B, Otermin P. Transcranial magnetic stimulation of the cerebellum in essential tremor: A controlled study. Arch Neurol 2002;59:413-417.

7. Hallett M. Transcranial magnetic stimulation: A primer. Neuron 2007;55:187-199.

8. Lefaucheur JP, Andre-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014.

9. Morecraft RJ, Louie JL, Herrick JL, Stilwell-Morecraft KS. Cortical innervation of the facial nucleus in the non-human primate: A new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression. Brain 2001;124:176-208.

10. Kerrison JB, Lancaster JL, Zamarripa FE, et al. Positron emission tomography scanning in essential blepharospasm. Am J Ophthalmol 2003;136:846-852.

11. Ceballos-Baumann AO, Sheean G, Passingham RE, Marsden CD, Brooks DJ. Botulinum toxin does not reverse the cortical dysfunction associated with writer's cramp. A PET study. Brain 1997;120 (Pt 4):571-582.

12. Hanakawa T, Dimyan MA, Hallett M. The representation of blinking movement in cingulate motor areas: A functional magnetic resonance imaging study. Cereb Cortex 2008;18:930-937.

13. Dresel C, Haslinger B, Castrop F, Wohlschlaeger AM, Ceballos-Baumann AO. Silent event-related fMRI reveals deficient motor and enhanced somatosensory activation in orofacial dystonia. Brain 2006;129:36-46.

14. Kranz G, Shamim EA, Lin PT, Kranz GS, Hallett M. Transcranial magnetic brain stimulation modulates blepharospasm: A randomized controlled study. Neurology 2010;75:1465-1471.

15. Wagle Shukla A, Vaillancourt DE. Treatment and physiology in parkinson's disease and dystonia: Using transcranial magnetic stimulation to uncover the mechanisms of action. Curr Neurol Neurosci Rep 2014;14:449-014-0449-5.

16. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117 (Pt 4):847-858.

17. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398-1403.

18. Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y, Research Committee on rTMS Treatment of Parkinson's Disease. Supplementary motor area stimulation for parkinson disease: A randomized controlled study. Neurology 2013;80:1400-1405.

19. Quartarone A, Sant'Angelo A, Battaglia F, et al. Enhanced long-term potentiation-like plasticity of the trigeminal blink reflex circuit in blepharospasm. J Neurosci 2006;26:716-721.

20. Eekhof JL, Aramideh M, Bour LJ, Hilgevoord AA, Speelman HD, Ongerboer de Visser BW. Blink reflex recovery curves in blepharospasm, torticollis spasmodica, and hemifacial spasm. Muscle Nerve 1996;19:10-15.

21. Schicatano EJ, Basso MA, Evinger C. Animal model explains the origins of the cranial dystonia benign essential blepharospasm. J Neurophysiol 1997;77:2842-2846.

22. Lindeboom R, De Haan R, Aramideh M, Speelman JD. The blepharospasm disability scale: An instrument for the assessment of functional health in blepharospasm. Mov Disord 1995;10:444-449.

23. Jankovic J, Kenney C, Grafe S, Goertelmeyer R, Comes G. Relationship between various clinical outcome assessments in patients with blepharospasm. Mov Disord 2009;24:407-413.

24. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, june 5-7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1-16.

25. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008-2039.