First repetitive transcranial magnetic stimulation for treatment of Drug Induced Tardive Syndromes: double randomized clinical trial

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Abstract

***Background*.** Repetitive transcranial magnetic stimulation (rTMS) has become widely used as a therapeutic tool in parkinson's disease. Late-onset (tardive syndromes) movement disorders typically manifest three months or later (this varies) after the exposure to antipsychotic drugs, and unfortunately have no satisfactory medical treatment. The aim of this study was to evaluate the efficacy of repetitive transcranial magnetic stimulation (rTMS) on drug induced tardive syndromes.

***Material and Methods*:** Twenty patients with Tardive syndromes were allocated to receive real or sham rTMS. Each patient received 2000 rTMS pulses (20 Hz at 100% rMT) over the hand motor area area for 10 consecutive days. The Abnormal involuntary movement scale (AIMS), and cortical excitability of all patients were measured before, and immediately after the 10 sessions,.

***Results*.** At baseline, there was no significant difference between the groups in age, sex distribution, duration of illness, and treatment. The offending antipsychotic drugs that induced TS and the current treatment were similar in both groups, and no significant differences in clinical rating scale and their subitems nor in cortical excitability between groups. However, there was a significant improvement in the AIMS score (pre versus post sessions with p= 00001) in the real rTMS group compared with the sham group (P = 0.03). A repeated-measures ANOVA that showed a significant Time (pre, post session) × Group (real vs sham) interaction (P = .0001). The same trends were observed in the clinical subscales with significant improvement in real group and no effect the sham group. There were no significant changes in cortical excitability in either group.

***Conclusion*.** This is the first clinical trial study of bilateral hemispheric rTMS in patients with tardive syndromes. Bilateral hemispheric high frequency rTMS might be a feasible treatment for tardive syndromes resistant to medical treatment; further multicenter studies are needed to confirm this result.

Introduction:

Tardive syndrome (TDS) is a potentially permanent and irreversible hyperkinetic movement disorder caused by exposure to dopamine receptor blocking agents. DSM-5 diagnostic criteria for TDS include a history of more than 3 months cumulative exposure to dopamine receptor blocking agents (DRBAs), except in elderly patients in whom 1 month is adequate (American). The causative agents are usually typical or atypical antipsychotic drugs (APDs). Recent reports, however, suggest that TDS could also be caused by a wide variety of psychotropic drugs, such as antidepressants and antiparkinsonian medications (Lerner, Miodownik 2011 (). Tardive syndrome can manifest heterogeneous features of Abnormal involuntary movements (AIMs) that comprise dystonia, chorea, athetosis, akathisia, myoclonus, stereotyped behavior, tremor, and tourettism or tics (Dauer et al 1998, Aia et al 2011, Lerner, and Miodownik 2011, Aquino and, Lang 2014). Orofacial dyskinesia is the most common symptom in less severe cases, while generalized hyperkinetic movements with predominance of axial dystonia also occur in severe cases (Thobois et al 2008). These abnormal movements can persist for years despite discontinuation of the offending drug. In many cases, tardive dyskinesia (TD) can be an irreversible condition, resistant to pharmacological treatment.

Although the pathophysiology of TD is not well understood, it is hypothesized that central dopamine blockade plays a role in the pathogenesis of this condition. Striatal dopamine receptor supersensitivity has so far been the most plausible explanation for development of TDS. Chronic exposure to DRBAs can induce upregulation of postsynaptic dopamine receptors, particularly of the D2 subclass, in the striatum (Loonen and, Ivanova 2013). Teo et al. (2012) hypothesized that hypersensitivity of D2 receptors could cause maladaptive plasticity in the cortico-striatal transmission, resulting in an inability to normalize the miscoded motor program in patients with TDS . Trugman et al. hypothesized that the D2 receptor blockade concomitant with repetitive activation of the D1 receptors could be a fundamental cause of TDS (Trugman et al 1994). This hypothesis might be consistent with the delayed onset of TDS after exposure to neuroleptics and the persistence of TDS even after withdrawal from them (Trugman et al 1994). In addition, maladaptive changes in non-dopaminergic neurotransmitter systems, such as those involving opioids (enkephalin and dynorphin), glutamate, and acetylcholine, have also been reported in patients with TDS (Tsai et al 1998)

Accumulating evidence suggests that TDS might result from abnormal plasticity in the motor circuit that links with the basal ganglia (Thobois et al 2008, Trugman et al 1994). Consistent with this concept, TDS was successfully treated with DBS of the GPi, which is the major basal ganglia

output nucleus. Evidence that GPi-DBS could influence the brain CBF levels in the primary motor cortices has also been reported (Thobois et al 2008). It has also been noted that not only the GPi but also the STN and thalamus could be targets for DBS in the treatment of TDS (Zhang et al 2006, Sun et al 2007). These observations indicate that TDS might be a network disorder involving cortico-thalamo-basal ganglia motor circuitry. Multiple single case reports (Nandi et al 2002, Trottenberg et al 2001) and open-labeled small case series (Franzini et al 2005, Sako et al 2008, Shaikh et al 2014) have shown that GPi-DBS could be highly effective in the treatment of patients with medically intractable TDS. Multiple case reports document that TDS-associated motor symptoms could be alleviated immediately or within a few days after the GPi-DBS was initiated (Franzini et al 2005, Trottenberg et al 2001). Prospective studies with blind assessments also showed that GPi-DBS could alleviate TDS symptoms regardless of their subtypes (e.g., chorea and dystonia) or body distributions (Damier et al 2007, Pouclet-Courtemanche et al 2016).

The present study was prompted by our experience with a female patient, 24 years old who was admitted in ICU with severe Neuroleptic malignant syndrome after receiving long-acting haloperiodol injection 50mg/2 weeks. She developed abrupt symptoms including hyperthermia (> 38ºC), mental status change, muscle rigidity, tremors, facial dyskinesia, skeletal muscle hyperonicity, loss of consciousness, autonomic lability, pallor, sweating, tachycardia, arrhythmia with creatinine phosphokinase 2500 after admission. She received conventional treatment for neuroleptic malignant syndrome in the form of muscle relaxant (baclofen), anticholinergic agents (akinetone), Beta-blockers (propranolol), dopaminergic drugs, dopamine agonist, paracetamol, and benzodiazepines, without improvement. As a last option we applied repeated sessions of high frequency rTMS (2000 pulses for each hemisphere every day). She received 25 sessions comproising 10 trains of rTMS at 25 Hz (200 pulses each train at 80% of resting motor threshold) with a 40 s intertrain interval (five sessions /weeks for 4 weeks). She completely recovered after 25 sessions (case report not published) with normal gait normal CPK and normal temperature.

Based on this experience, and the success of deep brain stimulation as well as because TDs are often refractory to all therapeutic modalities; the aim of the present study was to evaluate the therapeutic effect of repeated sessions of high frequency rTMS applied over motor area of both hemispheres for patients with drug induced TDs.

Material and methods

According to the diagnostic and statistical manual of mental disorders, fourth edition (DSM IV) (American Psychiatric Association ,2000), the spectrum of Tardive dyskinesia (TD) includes involuntary movements of the tongue, jaw, trunk, or extremities, and may be choreiform, athetoid, or stereotypic in nature. Abnormal movements should appear during exposure or within 4 weeks of withdrawal from oral antipsychotics or 8 weeks from depot formulations. The minimal exposure to antipsychotics should be 3 months, except for patients older than 60, who can develop TD after using antipsychotic drugs for 1 month. Finally, the movements should be present for at least 1 month to fulfil the criteria for TD. Based on the phenomenology, tardive syndromes subtyped as: tardive dyskinesia, tardive stereotypy, tardive dystonia, tardive tremor, tardive akathisia, tardive myoclonus and tardive tourettism (Bhidayasiri and Boonyawairoj, 2011).

Twenty patients with drug induced Tardive syndromes (12 males and 8 females, mean age 41.15 $\pm$ 16.8 years; range, 21-79 years) were recruited from the outpatient clinic of Aswan University Hospital. The duration of tardive syndromes was 18.35 + 30.8 months ranging from 1 month to 120 months. The duration of medical treatment for management of TS was 6.06 $\pm$ 8.8 months. None of the patients suffered from any other clinically relevant disorders.

Their previously diagnosed psychiatric disorders were as follows: 8 had schizophrenia, 10 mood disorders, 2 dementia with psychotic features. They received typical or atypical antipsychotic drugs (15 patients received Haloperidol 50 mg/ 2-4 weeks, and 5 patients received respiredone and aripeprazole. The duration of treatment (antipsychotic drugs) was ranging from to 12- 30 months. Tardive syndromes included; tardive dyskinesia in 5 patients, tardive stereotypy, tardive dystonia 2 patients, tardive tremors, bradykinesia and rigidity 13 patients). Demographic and clinical data are given in table 1.

Each patient was assessed with the abnormal involuntary movement scale (AIMS) (Guy 1976). The entire test can be completed in about 10 minutes. The AIMS test has a total of twelve items rating involuntary movements of various areas of the patient's body. These items are rated on a five-point scale of severity from 0–4. The scale is rated from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe). Two of the 12 items refer to dental care. The remaining 10 items refer to body movements themselves.

Experimental Setup and Design

Subjects sat in a comfortable chair. Electromyographic (EMG) recordings (Nihon Kohden 9400, Japan) from the abductor digiti minimi muscle of

right hand was acquired with silver–silver chloride surface electrodes, using a muscle belly–tendon set-up, with a 3-cm-diameter ground electrode placed on the wrist. The EMG parameters included a bandpass of 20 to 1000 Hz and a recording time window of 200 ms. TMS was performed with a 90-mm figure-of eight coil connected to Magstim (UK) super rapid magnetic stimulator. Motor thresholds (MT) were determined after localization of the motor "hot spot" for the abductor digiti minimi muscle in left hemisphere as described in previous reports (Khedr et al., 2015, 2016 a, 2016b).EMG signals were monitored and recorded for 20 ms before stimulation. RMT, AMT, cSP and iSP were evaluated as previously reported by Khedr et al.(2006, 2015, 2016a, 2016b) and Werhan et al (2007).

Randomization

The patients were classified into two groups (10 patients for each group):1st group received real 20 Hz-rTMS at 100% RMT (a total of 2000 pulses to each hand area consisting of 10 trains of 200 pulses with intertrain interval 30 s), and the 2nd group received sham stimulation with the same pulse delivery as the 1st group but with the coil placed perpendicular to the scalp.

Repetitive transcranial magnetic stimulation (rTMS) procedure:

TMS was performed with a commercially available 70mm figure of eight coil connected to a high frequency Magstim stimulator. The primary motor areas of the hand of both hemispheres were determined as previously reported (Khedr et al Khedr et al.(2006, 2015). During rTMS, all patients wore ear plugs in order to protect the ears from the acoustic artifact associated with the discharge of the stimulation coil. For each patient 10 sessions were administered once per day for 5 consecutive days each week for two weeks. All patients were assessed before rTMS and immediately after the end of the 10 sessions. The patients did not know which type of stimulation they received and to ensure that the study was double blinded the doctor who assessed the patients didn't know which type of stimulation the patients received. None of the patients had had rTMS before and were unaware of the type of stimulation.

Follow up

The Aims scale and different parameters of cortical excitability were assessed before and after the end of session treatment.

The primary outcome was change in Aims score at the end of the last session and then one month after treatment.

Secondary outcome was change in cortical excitability parameters after the last session of treatment.

All patients provided fully informed consent. The local ethics committee had approved the experimental protocol.

Statistical analysis

Baseline values (ie, before rTMS) of the Aims scale in each group were compared using one way Anova for independent samples. Means ± standard deviation (SD) were used to represent data. The level of significance was set at $P<0.05$. Changes in AIMS in the two groups overtime were analysed with a two factor repeated measures analysis of variance (ANOVA) with "treatment" (real versus sham rTMS) and "time" (before, versus after the end of last treatment session), as the main factors. When necessary, a Greenhouse–Geisser correction was applied to correct for non- sphericity. Post hoc unpaired t tests were carried out for comparisons pre versus post sessions.

Results

At baseline, there was no significant difference between the groups in age, sex distribution, duration of illness, and treatment. The offending antipsychotic drugs that induced TS and the current treatment were similar in both groups. The mean value ± SD of Abnormal involuntary movement scale (AIMS) and their sub-items (overall severity, incapacitation and awareness were similar with no significant differences between both groups (Table 1). There were no significant differences between groups in any of the neurophysiological parameters including rTMT, AMT, cSP at different intensities, Input-output curve and iSP, (table 2).

However, there was a significant improvement in the AIMS score in the real rTMS group compared with the sham group. The AIMS in the real group decreased by a mean of 8.5±1.7; P= 0.005), while in sham group there was a much smaller and less signficant reduction of 1.3 ± 3.3 points ($p = 0.03$). The repeated-measures ANOVA that showed a significant Time (pre, post session) × Group (real vs sham) interaction (Df=1,f=42.632, and P = .0001), indicating that the reduction in the real group was greater than that in the shame group. The same trend was observed in all the subscales (overall severity,

incapacitation, and awareness) with significant improvement in real group while there were no significant changes in the sham group (table 3 and figure 2).

There were no significant changes in cortical excitability in any group. This was confirmed in a repeated-measures ANOVA that showed no significant interaction between groups, Time (pre, post session) × Group (real vs sham), and no main effect of Time (table 4).

Discussion

The main finding in the present study was the dramatic effect of high frequency rTMS in ameliorating the symptoms of medically refractory TS. It is the first clinical trial to suggest that rTMS may offer a possible treatment for TS.

We can only speculate on the mechanism of action of high frequency rTMS in the present patients. Neuroleptic-induced extrapyramidal syndromes may result primarily from blockade of dopamine receptors in the striatum, leading to imbalance between acetylcholine and dopamine systems in this area. Some reports in the literature show that high frequency rTMS can increase levels of dopamine, and perhaps this could contribute to improvement in symptoms. For example, Strafella et al (2001, 2003) found an increase in dopamine release in the striatum after 10 Hz rMS of prefrontal and motor cortex. Similarly in rats, frontal 20 Hz rTMS has been found to increase the extracellular concentration of dopamine in the dorsal hippocampus, nucleus accumbens septi and dorsal striatum.5 Khedr et al 2008 measured serum plasma levels in patients with Parkinson's disease pre and post six sessions of 25 Hz rTMS and found that the improvement in symptoms was paralleled by an increase in plasma levels of dopamine and that these levels correlated with clinical status before and after treatment. Another possible explanation is that the improvement may be related to neuroplasticity as Teo et al[2] have suggested that neuroleptic treatment interacts with the NMDA receptor which is known to play a critical role in synaptic plasticity. They proposed that this could lead to maladaptive plasticity similar to that observed in many other hyperkinetic movement disorders. However there were no changes in the cortical excitability parameters after rTMS in the present study so that this explanation seems less likely.

Conclusion and recommendation

Bilateral hemispheric high frequency rTMS might be a feasible treatment for tardive syndromes resistant to medical treatment; further multicenter studies are needed to confirm this result. More well-designed double-blind trials of large number of patients are needed. In particular, it is important to clarify specific inclusion criteria for patient selection, best stimulation parameters, follow up of long duration.

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Table 1: Demographic and clinical data of studied groups

Demographic and clinical parameters	Real group N= 10 Mean ±SD	Sham group N=10 Mean ±SD	P valu e
Age (Years)	44.7±21.2	39.7±13.3	0.53
Sex male/female	7/3	7/3	1.00
Duration of tardive syndromes (months)	22.3 ±17.8	25.7±40.9	0.31
Duration of treatment of tardive syndromes (months)	6.3±10.7	5.8±7.8	0.90
Offending antipsychotic	Haloperidol depot (2 patients) resperidone (4 patients) Haloperidol depot and resperidone (2patients) Clopexol depot (1 patient) Resperidone and aripiprazole (1 patient)	Haloperidol depot (2patient) Haloperidol and resperidone (3patient) Haloperidol and stellasil (1patient) Clopexol depot and resperidone (2patient) Clopexol depot and aripiprazole (1patient)	
Current treatment with failure to improvement	Amantadine, benzotropine and Biperiden	Amantadine, benzotropine, levodopa and Biperiden	
Types of Tardive Syndromes	Tardive dyskinesia (1patient) Orolingual dyskinesia (2 patients) Parkinsonian tremors and rigidity (5 patients) Dystonia and oculogyric crisis (1patient)	Tardive dyskinesia (1patient) Orolingual dyskinesia (1patient) Parkinsonian tremors and rigidity (5 patients (7patient)	
Abnormal involuntary movement scale (AIMS)	13.5±1.7	11.4±3.7	0.12
Overall severity	2.5±0.5	2.3±0.7	0.47
Incapacitation	2.6±0.5	2±0.8	0.06
Awareness	2.4±1.2	2.2±0.8	0.66

Table 2: Baseline Cortical excitability parameters among real and sham groups

Neurophysiological parameters	Real group N= 10 Mean ±SD	Sham group N=10 Mean ±SD	P value
Resting motor threshold (RMT)	39.8±4.98	42.6±7.5	0.340
Motor active threshold(AMT)	32.9±5.2	36.9±6	0.128
Amplitude of MEP in output curve(Uv)			
110%	220.3±214.3	182.4±126.1	0.637
120%	603.3±702.3	440.2±267.9	0.506
130%	985.2±1287.3	882.6±692.2	0.828
140%	1148.5±1292.8	1430.3±1115.6	0.608
150%	1293.9±1231.7	1790.80±1223.9	0.377
Cortical silent period duration in output curve (ms)			
110%	81.5±38.1	92.7±27.6	0.465
120%	112.3±48.8	134.3±47.4	0.320
130%	127.5±63.1	154.5±53.5	0.316
140%	138.9±57.4	178.9±62.8	0.155
150%	148.5±59.9	180.4±70.2	0.289
Transcallosal inhibition duration(ms)	28.1±9.6	31.9±5.8	0.28

Table 3: CLINICAL parameters in pre-sessions and post-sessions among real and sham groups

	Pre-session N= 10 Mean ±SD	Post-session N=10 Mean ±SD	Paired test	P value 2way ANOVA Time X groups
AMIS				Df=1,f=42.632,
Real group	13.5±1.7	4.9±2.4	0.005	P=0.0001
Sham group	11.4±3.7	10.1±4.6	0.034	
Overall severity				Df=1,f=46.091, p=0.0001
Real group	2.5±0.5	1.1±0.3	0.004	
Sham group	2.3±0.7	2.2±0.6	0.317	
Incapacitation				Df=1,f=76.800,
Real group	2.6±0.5	0.9±0.7	0.004	p=0.0001
Sham group	2±0.8	1.9±0.73	0.317	
Awareness				Df=1,f=10.800,
Real group	2.4±1.2	1±0.0.5	0.014	P=0.004
Sham group	2.2±0.8	2±0.8	0.157	

Table 4: Cortical excitability parameters pre-sessions and post- sessions among real and sham groups

	Pre-session N= 10 Mean ±SD	Post-session N=10 Mean ±SD	Paired test	P value Time x group
Resting motor threshold (RMT) Real group Sham group	 39.8±4.98 42.6±7.5	 37.9±5.8 43±9.4	 0.211 0.959	 DF =1, F=1.089 P=0.311
Motor active threshold(AMT) Real group Sham group	 32.9±5.2 36.9±6	 31.8±4.5 36.5±7.6	 0.721 1.000	 DF=1, F=0.095 P=0.760
Amplitude of MEP in output curve(Uv) Real group in 110% Sham group in110% Real group in 120% Sham group in120 Real group in 130% Sham group in130% Real group in 140% Sham group in140% Real group in 150% Sham group in150%	 220.3±214.3 182.4±126.1 603.3±702.3 440.2±267.9 985.2±1287.3 882.6±692.2 1148.5±1292.8 1430.3±1115.6 1293.9±1231.7 1790.80±1223.9	 285.1±213.1 93.2±50.8 288±846 359.4±284.7 1511.8±1423.2 1131.3±1275.6 1692.5±1391.4 1712±1472.2 2764.3±2582.2 2402±1959.4		 Df=1, F=1.047, P=0.320
Cortical silent period duration in output curve (ms) Real group in 110% Sham group in110% Real group in 120% Sham group in120% Real group in 130% Sham group in130% Real group in 140% Sham group in140% Real group in 150% Sham group 150%	 81.5±38.1 92.7±27.6 112.3±48.8 134.3±47.4 127.5±63.1 154.5±53.5 138.9±57.4 178.9±62.8 148.5±59.9 180.4±70.2	 83.6±43.1 109.1±35.2 93.3±37.4 130.1±35.5 113.3±31.9 149.8±32.6 145.4±31.5 168.7±39.2 160.9±45.2 187.4±47.1		 Df=1, F=0.038 P=0.847
Transcallosal inhibition duration(ms) Real group Sham group	 28.1±9.6 31.9±5.8	 32.2±8.3 33.4±6.9	 0.28 0.74	DF=1,F=1.903 P=0.185

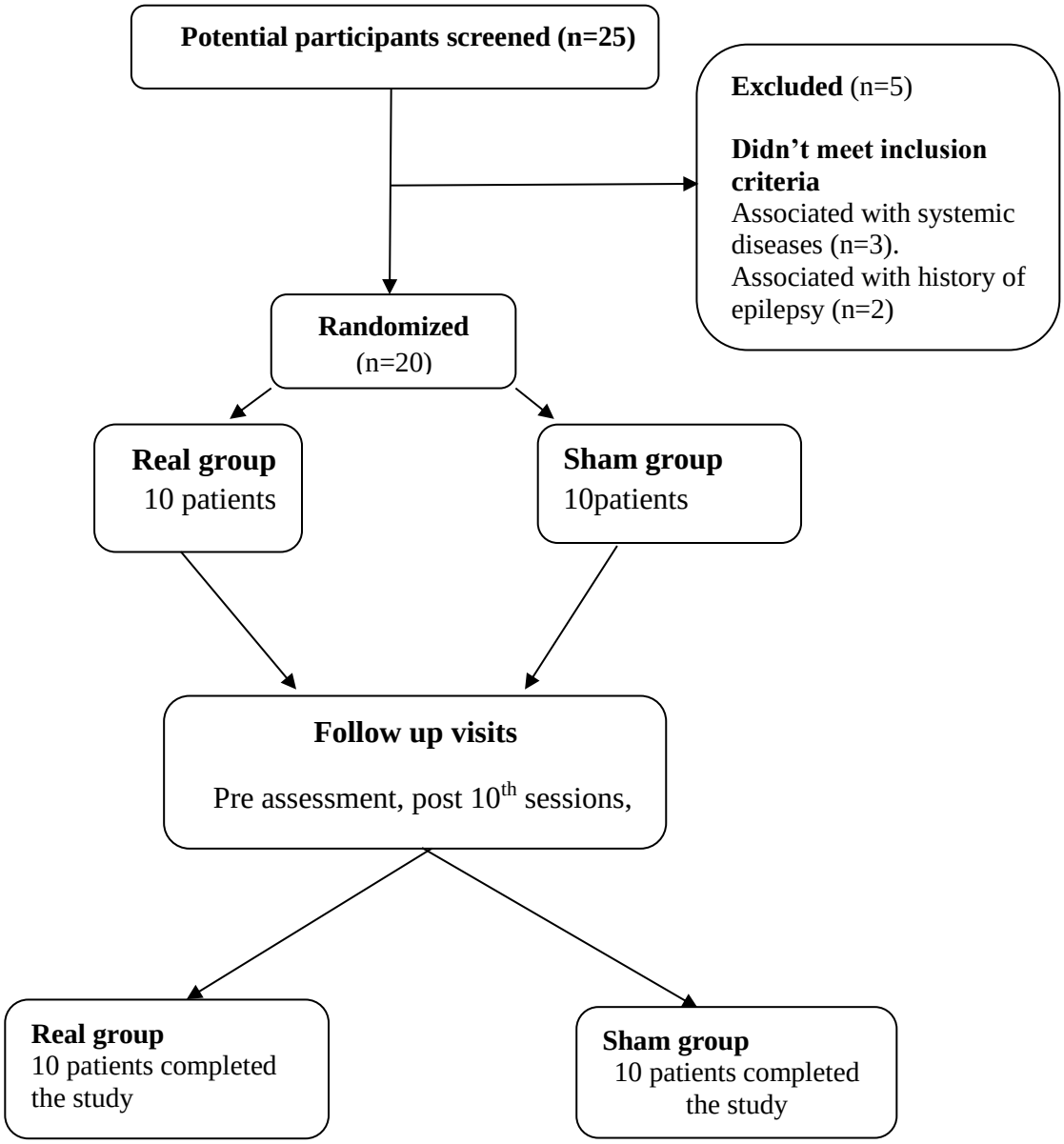

Figure 1

Flow chart

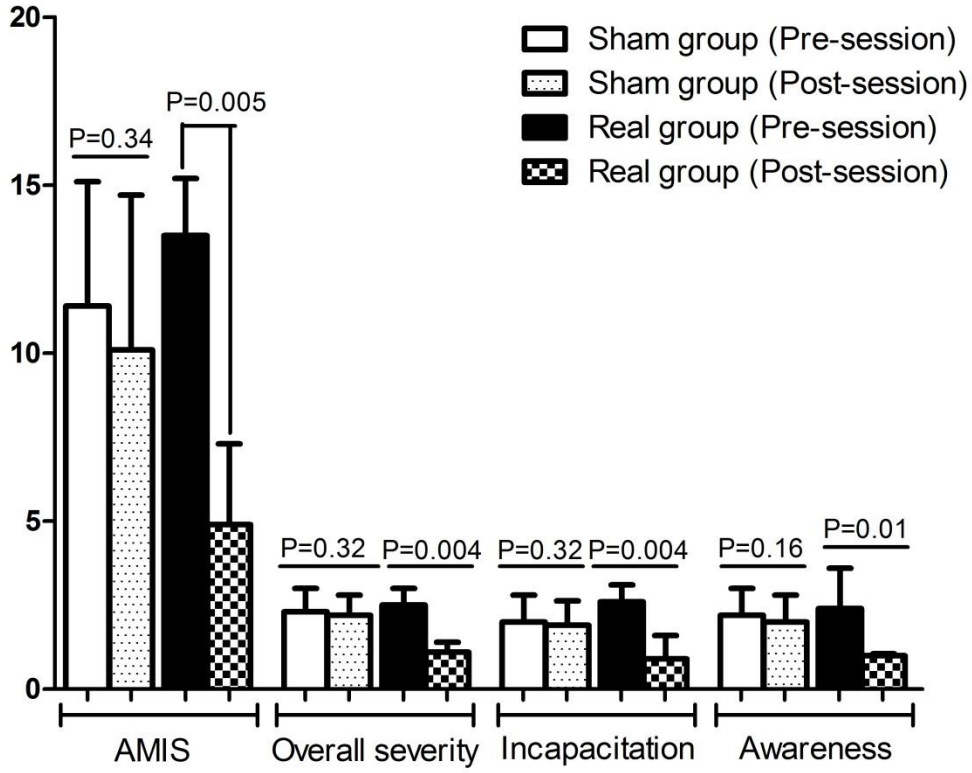
20
15
10
5
0
Sham group (Pre-session)
Sham group (Post-session)
Real group (Pre-session)
Real group (Post-session)
P=0.34
P=0.005
P=0.32
P=0.004
P=0.32
P=0.004
P=0.16
P=0.01
AMIS
Overall severity
Incapacitation
Awareness

Figure 2