The effect of high frequency repetitive transcranial magnetic stimulation on advancing Parkinson's disease with dysphagia: double blind randomized clinical trial

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Abstract

We investigate if rTMS has a therapeutic role in the treatment of dysphagia in patients with PD.

Material and methods: 33 patients with PD and dysphagia were randomly classified with ratio 1:2 to receive sham or real rTMS (2000 pulses; 20 Hz; 90% RMT; 10 trains of 10s with 25s between each train) over the hand area of each motor cortex (5 min between hemispheres) for 10 days (5 days /week) followed by 5 booster sessions every month for 3 months. Assessments included the Unified Parkinson's Disease Rating Scale part III (UPDRS), Instrumental activity of Daily Living (IADL), and Arabic-dysphagia Handicap Index (A-DHI) before, after the last session, and 3 months later. Video-fluoroscopy measures of pharyngeal transit time (PTT) and time to maximal hyoid elevation (H1-H2) were taken before and after the treatment sessions.

Results: There were no significant differences between groups. There was a significant improvement on all rating scales (ANOVA) after real rTMS with a significant time X group interaction. In particular there was a significant and long-lasting (3 months) effect of time on all sub-items of the A-DHI (functional: P = 0.0001; physical: P = 0.0001; emotional: P = 0.02) but not in the sham group. This was associated with significant improvement in H1-H2 (P = 0.03) and PTT (P = 0.01) during solid swallows in the real rTMS but not the sham group.

Conclusion: Real rTMS improves dysphagia in Parkinson's disease as documented by A-DHI scores and by video-fluoroscopy.

Introduction:

Swallowing dysfunction is common in idiopathic Parkinson's disease (PD), being symptomatic in up to 54.5% of patients especially in patients with predominantly akinetic rigidity [1] but seen in more than 90% using video-fluoroscopy [2-4]. It is

usually considered multifactorial with abnormalities documented in all phases of swallowing [3]. The underlying neurogenic mechanisms of swallowing dysfunction in PD are not well established although involvement of non-dopaminergic mechanisms has been suggested [5]. Indeed, even though levodopa treatment improves limb symptoms in PD [6] deglutitive dysfunction may fail to respond [7, 5, 8], and may even occasionally deteriorate [9].

Current dysphagia management in PD patients is unsatisfactory. A number of approaches including dietary modification and swallowing maneuvers [10], dopaminergic and anticholinergic pharmacotherapy [11], expiratory muscle strengthening [12], video based biofeedback therapy [13], cricopharyngeal myotomy [14] and cricopharyngeus botulinum toxin injection [15] have all been utilized with variable outcomes.

More recently there have been a number of trials testing possible neuromodulatory techniques in PD patients with dysphagia. One of these studies recruited 90 patients with PD and applied surface electrical stimulation over the submental region. At the end of the study there was significant improvement in the treated groups [16]. Dysphagia in other groups of patients has been treated with non-invasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). A meta-analysis found that rTMS has a positive effect on dysphagia after stroke although the best frequency (low v high frequency) and site (affected, unaffected or bilateral hemispheres) has yet to be resolved [17-20]. However, there have been no studies of the effects of brain stimulation methods for dysphagia in patients with Parkinson's disease.

Given that rTMS has been shown to have beneficial effects on limb motor control in PD [21], we decided to conduct a trial to test its effectiveness on dysphagia. Given the proximity of the hand area of M1 (5 cm lateral to Cz and 1 cm anterior to Cz) to the esophageal motor area (6.6cm lateral to Cz and 3.0 anterior to Cz) [19], we hypothesized that we might achieve beneficial effects on both dysphagic and limb symptoms.

Patients and Methodology:

Patients:

90 PD patients with dysphagia using UK brain bank criteria for PD [22] were recruited from the outpatient clinic in Assiut University during the period from May 2016- Jan 2018. Each patient was aged between 50-75 years and all fulfilled the UK brain bank criteria for PD. Patients were excluded if they had a history of repeated head injury, cerebrovascular strokes, encephalitis, oculogyric crisis, supranuclear gaze palsy, drug intake as antipsychotics or MPTP exposure, severe dementia, (MMSE $\leq$ 23) [23], severe depression (HAM-D) [24], severe dysautonomia, cerebellar signs, Babiniski sign, strictly unilateral features after 3 years, hydrocephalus or intracranial lesion on neuroimaging. To allow delivery of rTMS patients were also excluded if they had intracranial metallic devices or with pacemakers or any other device. Patients who were unable to give informed consent were also excluded. Treatment was maintained constant throughout the trial with no change in dosage. All received levodopa (Sinemet 250/25; ½ tablet three times per day) and anticholinergic (cogenitol ½ tablet three times per day). The sample size was calculated using G power software based on the following assumptions: proportion of expected outcome in the intervention group=30% (according the previous study), proportion of the expected outcome in the placebo group=1%, alpha level=0.05, power=0.80 with allocation ratio N2/N1=1, using a one tailed test.

Methods:

All cases were assessed with modified Hoen and Yahr staging [25], Unified Parkinson's Disease Rating Scale (UPDRS) part III [26], instrumental daily living activity [27], Self-Assessment scale [28], Swallowing Disturbance Questionnaire (SDQ) for dysphagia for diagnosis of dysphagia [29], and Dysphagia Handicap Index (DHI) [30]. Video-fluoroscopy examination while patients were on levodopa therapy was performed for 9 patients in the real rTMS group and 6 from the sham group.

The Swallowing Disturbance Questionnaire consists of five questions related to the oral phase of swallowing and 10 questions related to the pharyngeal phase. Fourteen questions were rated on a four-point (0–3) scale (0 for no disability and 3 for severe disability) and one was a “yes/no” question (yes was scored 2.5 and

no was scored 0.5). A score on the swallowing disturbance questionnaire (SDQ) of more than or equal to 11 indicates dysphagia.

A-DHI is a patient-administered, 25 item questionnaire, in which the patient can assign three responses for each question (never, sometimes, and always), adding a value to each response (0, 2 and 4, respectively) and reaching a score ranging from 0 to 100. Moreover, each patient performs a self-evaluation of their dysphagia, assigning a score from 0 (normal) to 7 (severe difficulty) [31] The DHI has 9 questions in the functional subscale, 9 question in the physical subscale, and 7 questions in the emotional subscale [32]

Randomization (Parallel Design)

Out of 90 PD patients 33 patients had dysphagia and participated in the study (see flow chart figure 1). Group allocations (real or sham with ratio 2:1) were placed in serially numbered opaque closed envelopes. Each patient was placed in the appropriate group after opening the corresponding sealed envelope.

Measuring resting motor threshold

Resting motor threshold was measured with a monophasic magnetic stimulator (Magstim model 200; Magstim, Whitland, UK) connected to a 90-mm outer diameter figure- of-8 coil, which had a maximal output of 2.2 Tesla. We located the optimal scalp location of each hemisphere from which TMS evoked motor-evoked potentials of greatest amplitude by moving the figure-of-8 coil systematically in 1-cm steps to determine the site of maximum peak-to-peak motor-evoked potentials in the first dorsal interosseous for each hemisphere. We used silver–silver chloride surface electrodes, using a muscle belly-tendon montage, with a 3-cm diameter circular ground electrode placed on the wrist. A Nihon Kohden Machine model 9400 (Tokyo, Japan) was used to amplify and record the signals.

Repetitive Transcranial Magnetic StimulationProcedure

Real rTMS was applied for 10 sessions (5 days per week) using a figure-of-8 coil (9-cm diameter loop) positioned over the hand area. A session of stimulation consisted of sequential stimulation of each hemisphere (right then left hemisphere) with 10 trains of 20-Hz stimulation, each lasting for 10 seconds with

an intertrain interval of 25 seconds. The intensity of stimulation was set at 90% of the rMT for the first dorsal interosseous of the contralateral hand with a total 2000 pules for each hemisphere. Given our previous experience in treating PD (Khedr et al., 2006) we decided to give 5 booster sessions every month for 3 months follow-up. Sham rTMS was applied using the same parameters, but with the coil held so that the edge was in contact with the head perpendicular to the scalp while the remainder was rotated 90° away from the scalp in the sagittal plane to reproduce the noise of the stimulation.

Video-fluoroscopy examination (pre and post 10 sessions).Video-fluoroscopy (VFS) was performed before and after rTMS sessions while patients were on levodopa therapy using a GE Prestiage II- USA machine. The examination was performed in an upright lateral position. The field of examination involved the oral cavity and extended down to the upper oesophagus. 5 ml of three different consistencies of barium-sulphate (fluid- semisolid- solid) were given to patients by a spoon. Cocoa was added to the barium to improve its flavour. Patients were requested to hold the barium in their mouth and only start to swallow when asked by the clinical investigator.

Assessment:

Examinations were recorded and assessment was further performed in slow motion in addition to the frame by frame analysis.

Temporal Measures:

The pharyngeal transit time (PTT) was measured, in seconds, from the point where the bolus head moved from the hold position and passed the posterior nasal spine until it fully entered the oesophagus after the closure of the upper oesophageal sphincter. The time of the first superior-anterior movement of the hyoid bone was assigned as H1, and the time when the hyoid bone reached its maximum elevation was assigned as H2. The time required for maximum elevation of the hyoid bone was therefore H2- H1. The temporal measures of the hyoid bone movement have been previously described [33].

Scoring Measures:

Penetration (passage of the bolus into the larynx, above the level of the vocal cord) and aspiration (passage of the bolus into the larynx, below the level of the vocal cord) were assessed using the previously validated 8-point penetration-aspiration scale [34]. Finally, post-swallow residue was scored as follows: patients with no residue after swallowing were given a score of zero, those who had residue either in the vallecular or in the pyriform sinus were given a score of 1, while those who had had residue both in the vallecula and pyriform sinus were scored 2.

Follow up

At the end of the therapy, patients were asked whether they thought they had real or sham rTMS. We followed up the patients clinically after the end of the 10th session, 1, 2, 3 months later after the end of booster sessions using the Dysphagia Handicap Index (DHI) as a primary outcome. The secondary outcome measures were changes in video fluoroscopy after the 10th session.
Assessment of the different scales (A_DHI and UPDRS and other) were performed by an assessor who was unaware of the type of stimulation. Likewise, the patients also did not know which type of stimulation they received.
We also asked patients specifically whether they experienced any of the common side effects of rTMS. Three patients of the real group refused to complete the sessions: one developed headache and insomnia and the other two refuse to stay in the hospital.

Ethics:

Informed consent was obtained from all subjects and the methodology was approval by the faculty of medicine ethical committee.

Statistics: Statistical analysis

All data were analyzed with the aid of the SPSS ver.16. The results were expressed as mean ± SD. Since some measures were not distributed normally at baseline, age, duration of illness and scores on different rating scales in each group were compared using the non-parametric Mann-Whitney test. Spearman correlations between base line scores were also performed. Statistical analysis of the scores in each test was performed with repeated measures analysis of variance (ANOVA) with TIME, as the within-subject factor, and treatment condition (real, and sham rTMS) as the between subject measure. Greenhouse–Geisser degree of freedom corrections were applied to correct for the non-sphericity of the data. $P<0.05$ was considered significant for all statistical analysis. Spearman correlation between the changes in the total UPDRS III (Pre-Post 10th sessions) and the changes in DHI (Pre-Post 10th sessions).

Results:

Clinical characteristics are summarised in Table 1. There were no significant differences between groups in age, sex, duration of illness, and total scores in the UPDRS III, IADL, Self-Assessment scale and dysphagia scales. There was a significant positive correlation between UPDRS Part III and SDQ and total A-Dysphagia Handicap Index at baseline with r= 0.77 (P = 0.0001) and r =0.79 (P = 0.0001) respectively.

Clinical scores (UPDRS III, Self-assessment scale and Instrumental Daily living activity) (table 2a)

One way repeated measures ANOVA (pre, post treatment and one, two and three months later) showed a significant effect of time on all rating scales (UPDRS III, IADL, self-assessment) in the real group while no such changes were observed in the sham group. Two-way repeated measures ANOVAs on the scores for each rating scale, with treatment CONDITION (real and sham) and TIME (baseline, post treatment, one, two and three months later) as main factors revealed a significant interaction effect for UPDRS III and Self-Assessment scores. There was no significant interaction for IADL. The mean change in UPDRS III (Pre-Post 10th session) was significantly higher in the real group (22.0$\pm$ 9.9) than in the sham group (2.3$\pm$ 5.4; P= 0.0001).

Dysphagia scores (A-Dysphagia Handicap Index) (table 2b and figure 2).

One way repeated measures ANOVA (pre, post treatment and one, two and three months later) showed a significant effect of time on all sub items (functional, physical, and emotional) as well as the total score of the Arabic-Dysphagia Handicap index in the real group while no such changes were observed in the sham group. Two-way repeated measures ANOVAs on the scores for each rating scale, with treatment CONDITION (real and sham) and TIME (baseline, post treatment, one, two and three months later) as main factors revealed a significant interaction effect for A- DHI sub-items and total scores. The mean reduction in the A-DHI (Pre-Post 10th session) was significantly greater (good improvement) in the real group (14.4 $\pm$ 9.9) than the sham group (0.9$\pm$ 3.0) (P= 0.0001). There was a significant positive correlation between the changes of UPDRS III and the changes in DHI Score (r= 0.68 and P= 0.0001).

Video-fluoroscopy (table 3, figure 3a and b)

Two-way ANOVA showed significant Time (pre, post) X Group (real, sham) interaction between groups for solid swallows (P= 0.007, 0.03 respectively), due to a significant improvement in the real rTMS group but not sham. There were no significant interactions for fluid or semisolid swallows. However, paired t-tests showed a significant improvement in H1-H2, and PTT for fluid swallowing in the real rTMS group (P= 0.04, and 0.03 respectively) while no such changes were observed in the sham group. There was no difference between groups in the scores of penetration/aspiration or residue.

Discussion

The mechanisms of dysphagia in PD are still unclear and this has limited progress in the management dysphagia. Levodopa treatment generally is accepted to have little effect on dysphagia in PD [8], and there are even a few (small-sized) studies

with formal assessments reporting that levodopa has an unfavorable effect on swallowing [5, 35]. Here we explored the possibility of employing new neuromodulatory methods to tackle dysphagia in PD. As noted in the Introduction, several previous studies have shown that rTMS can have beneficial effects in post-stroke dysphagia as well as dysphagia following a lateral medullary syndrome [36, 37]. rTMS has also been reported to have beneficial effects on limb movement symptoms in PD. Thus a logical progression is to assess the effect of rTMS in treating dysphagia in PD. Applying rTMS approaches to different disease aetiologies will provide us further information about the endogenous plastic changes in humans with regard to swallowing function.

In the present study we applied bilateral high frequency rTMS to treat dysphagia in PD. The rationale was that our previous work had shown that high frequency rTMS increases the excitability of M1 in healthy volunteers [38] and improves motor performance in patients with PD [39]. This was confirmed by Lomarev et al [40] who applied high frequency rTMS bilaterally (4 cortical targets: left and right motor and dorsolateral prefrontal cortex) in 18 PD patients and also reported that times for executing walking and complex hand movement tests gradually decreased [40]. Since we have shown that high frequency rTMS can improve post-stroke dysphagia, we chose to use the same parameters in the present study, reasoning that if we applied the TMS over motor cortex we would achieve a positive effect on movement control as well as dysphagia. Indeed, we found that rTMS over the motor hand area improved both dysphagia and motor scores as measured by A-DHI rating scores, UPDRS III, and SA respectively, whereas there was no effect of sham. Our results were confirmed by video-fluoroscopy, at least for solid swallows.

The rigidity, hypertonia, bradykinesia and involuntary movements in PD can interfere in the motor control of swallowing, increasing the risk for penetration and laryngeal aspiration. It has been suggested that rigidity and bradykinesia of may compromise the oral preparatory phase, which is under volitional motor control. These are the symptoms most likely to be ameliorated by rTMS, and it therefore would seem logical to have some improvement of swallowing. However, whether these are the most important factors in producing the improvement we observed is unclear since treatment with levodopa, which has good positive effects on

bradykinesia and rigidity is usually reported to have little or even an unfavorable effect on swallowing [5, 8, 35].

Although we targeted the hand/arm area of motor cortex, its close proximity to structures including the esophageal motor area cannot fully exclude the possibility that the after-effects we saw were due to excitability changes at esophageal motor cortex which might have more direct effects on corticobulbar activity and excitability.

In recent years, neuroimaging and neurostimulation studies have provided insights into the activation patterns of the swallowing sequence [41, 42]. A meta-analysis of imaging studies on swallowing [43] showed that the most consistent areas that are activated in these neuroimaging studies include the primary sensorimotor cortex (M1/S1), sensorimotor integration areas, the insula and frontal operculum, the anterior cingulate cortex and supplementary motor areas. In the present study stimulation of M1 could enhance the functional connectivity of swallowing network and interactions of involved brain regions as it has been described for resting state and during swallowing [44-46].

Videofluoroscopy is an objective measure of swallowing function but was only available in about half of the patients, limiting the statistical power. Nevertheless we observed a significant difference in the effect of real v sham rTMS on the PTT and H1-H2 times for solid swallows. Interestingly, both measure movement speed and are related to the bradykinesia and hypokinesia of limb movement [47]. A similar result could be seen in fluid swallows but this was not significant, perhaps because this is more difficult to quantify in the absence of computerized methods of assessment. However despite this improvement in speed of transit of the food bolus through the pharyngeal cavity there was no difference in the P/A or residue scores. The pharyngeal residue reflects impairment of pharyngeal muscle contractility and the subsequent weak propulsion of the bolus [48]. The small size of the bolus used in our study might have contributed to the lack of the difference in the residue scores. The mild degree of penetration reported in our population, might explain the lack of effect on P/A scores.

Limitations

Small sample size limits the power of this study and a larger sample size is recommended for future investigations. In addition, obtaining an adequate sham for rTMS is tricky. However, given that our participants had not received any TMS previously we do not think they would have perceived they were being given sham treatment. A possible solution in future trials might be to consider active stimulation at an inactive scalp site as we have done in previous study [39]. Another limitation was the absence of a healthy control arm for videofloroscopy.

Conclusions

The main conclusion is that real rTMS improves dysphagia in Parkinson's disease as documented by A-DHI scores and by video-fluoroscopy. The effect can be seen immediately following the last treatment session and up to 3 months later. However, it should be noted that over that three month follow-up period, patients were receiving a "top-up" treatment of 5 rTMS sessions every month, and this may have been instrumental in maintaining the effect.

References:

1. Khedr EM, Al Attar GS, Kandil MR, Kamel NF, Elfetoh NA, et al. (2012) Epidemiological study and clinical profile of parkinson's disease in the assiut governorate, egypt: A community-based study. Neuroepidemiology. 38(3): 154-163.
2. Eadie MTyrer J (1965) Alimentary disorder in parkinsonism. Australasian annals of medicine. 14(1): 13-22.
3. Edwards LL, Quigley EMPfeiffer RF (1992) Gastrointestinal dysfunction in parkinson's disease: Frequency and pathophysiology. Neurology. 42(4): 726-32.

4. Stroudley JWalsh M (1991) Radiological assessment of dysphagia in parkinson's disease. The British Journal of Radiology. 64(766): 890-893.
5. Hunter PC, Crameri J, Austin S, Woodward MCHughes AJ (1997) Response of parkinsonian swallowing dysfunction to dopaminergic stimulation. J Neurol Neurosurg Psychiatry. 63(5): 579-83.
6. Logemann JA (1998) The evaluation and treatment of swallowing disorders. Current Opinion in Otolaryngology & Head and Neck Surgery. 6(6): 395-400.
7. Calne DB, Shaw DG, Spiers ASDStern GM (1970) Swallowing in parkinsonism. The British Journal of Radiology. 43(511): 456-457.
8. Menezes CMelo A (2009) Does levodopa improve swallowing dysfunction in parkinson's disease patients? Journal of Clinical Pharmacy and Therapeutics. 34(6): 673-676.
9. Bushmann M, Dobmeyer SM, Leeker LPerlmutter JS (1989) Swallowing abnormalities and their response to treatment in parkinson's disease. Neurology. 39(10): 1309-14.
10. Robbins J, Gensler G, Hind J, Logemann JA, Lindblad AS, et al. (2008) Comparison of 2 interventions for liquid aspiration on pneumonia incidence: A randomized trial. Ann Intern Med. 148(7): 509-18.
11. Jost WH (2010) Gastrointestinal dysfunction in parkinson's disease. Journal of the Neurological Sciences. 289(1-2): 69-73.
12. Troche MS, Okun MS, Rosenbek JC, Musson N, Fernandez HH, et al. (2010) Aspiration and swallowing in parkinson disease and rehabilitation with emst: A randomized trial. Neurology. 75(21): 1912-1919.
13. Manor Y, Mootanah R, Freud D, Giladi NCohen JT (2013) Video-assisted swallowing therapy for patients with parkinson's disease. Parkinsonism & Related Disorders. 19(2): 207-211.
14. Born LJ, Harned RH, Rikkers LF, Pfeiffer RFQuigley EMM (1996) Cricopharyngeal dysfunction in parkinson's disease: Role in dysphagia and response to myotomy. Movement disorders. 11(1): 53-58.
15. Restivo DA, Palmeri AMarchese-Ragona R (2002) Botulinum toxin for cricopharyngeal dysfunction in parkinson's disease. New England Journal of Medicine. 346(15): 1174-1175.
16. Baijens LW, Speyer R, Passos VL, Pilz W, Van Der Kruis J, et al. (2013) Surface electrical stimulation in dysphagic parkinson patients: A randomized clinical trial. The Laryngoscope. 123(11): E38-E44.
17. Hamdy S, Jilani S, Price V, Parker C, Hall N, et al. (2003) Modulation of human swallowing behaviour by thermal and chemical stimulation in health and after brain injury. Neurogastroenterology & Motility. 15(1): 69-77.
18. Hamdy S, Rothwell JC, Aziz QThompson DG (2000) Organization and reorganization of human swallowing motor cortex: Implications for recovery after stroke. Clinical science. 99(2): 151-157.
19. Khedr EM, Abo-Elfetoh N, Ahmed MA, Kamel NF, Farook M, et al. (2008) Dysphagia and hemispheric stroke: A transcranial magnetic study. Neurophysiologie Clinique/Clinical Neurophysiology. 38(4): 235-242.

20. Liao X, Xing G, Guo Z, Jin Y, Tang Q, et al. (2017) Repetitive transcranial magnetic stimulation as an alternative therapy for dysphagia after stroke: A systematic review and meta-analysis. Clinical Rehabilitation. 31(3): 289-298.
21. Siebner HR, Mentschel C, Auer CConrad B (1999) Repetitive transcranial magnetic stimulation has a beneficial effect on bradykinesia in parkinson's disease. Neuroreport. 10(3): 589-594.
22. Hughes A, Ben-Shlomo Y, Daniel SLees A (1992) Uk parkinson's disease society brain bank clinical diagnostic criteria. J Neurol Neurosurg Psychiatr. 55(181): e4.
23. Kurlowicz LWallace M (1999) The mini-mental state examination (mmse). Journal of gerontological nursing. 25(5): 8-9.
24. Sharp R (2015) The hamilton rating scale for depression. Occupational Medicine. 65(4): 340-340.
25. Zhao YJ, Wee HL, Chan YH, Seah SH, Au WL, et al. (2010) Progression of parkinson's disease as evaluated by hoehn and yahr stage transition times. Movement disorders. 25(6): 710-716.
26. Fahn S (1987) Unified parkinson's disease rating scale. Recent development in Parkinson's disease.
27. Lawton MBrody E (1969) Instrumental activities of daily living scale (iadl). The Gerontologist. 9: 179-186.
28. Brown RG, Maccarthy B, Jahanshahi MMarsden CD (1989) Accuracy of self-reported disability in patients with parkinsonism. Archives of Neurology. 46(9): 955-959.
29. Cohen JTManor Y (2011) Swallowing disturbance questionnaire for detecting dysphagia. The Laryngoscope. 121(7): 1383-1387.
30. Farahat M, Malki KH, Mesallam TA, Bukhari MAlharethy S (2014) Development of the arabic version of dysphagia handicap index (dhi). Dysphagia. 29(4): 459-467.
31. Silbergleit AK, Schultz L, Jacobson BH, Beardsley TJohnson AF (2012) The dysphagia handicap index: Development and validation. Dysphagia. 27(1): 46-52.
32. Sallum RaA, Duarte AFCecconello I (2012) Analytic review of dysphagia scales. ABCD. Arquivos Brasileiros de Cirurgia Digestiva (São Paulo). 25(4): 279-282.
33. Kendall KA, Mckenzie S, Leonard RJ, Gonçalves MIWalker A (2014) Timing of events in normal swallowing: A videofluoroscopic study. Dysphagia. 15(2): 74-83.
34. Rosenbek JC, Robbins JA, Roecker EB, Coyle JLWood JL (1996) A penetration-aspiration scale. Dysphagia. 11(2): 93-8.
35. Monte FS, Da Silva-Júnior FP, Braga-Neto P, Nobre E Souza MÂSales De Bruin VM (2005) Swallowing abnormalities and dyskinesia in parkinson's disease. Movement disorders. 20(4): 457-462.

36. Khedr EMAbo-Elfetoh N (2010) Therapeutic role of rtms on recovery of dysphagia in patients with lateral medullary syndrome and brainstem infarction. Journal of Neurology, Neurosurgery & Psychiatry. 81(5): 495-499.
37. Khedr EM, Abo-Elfetoh NRothwell JC (2009) Treatment of post-stroke dysphagia with repetitive transcranial magnetic stimulation. Acta Neurologica Scandinavica. 119(3): 155-161.
38. Khedr EM, Rothwell JC, Ahmed MA, Shawky OAFarouk M (2007) Modulation of motor cortical excitability following rapid-rate transcranial magnetic stimulation. Clinical neurophysiology. 118(1): 140-145.
39. Khedr EM, Rothwell JC, Shawky OA, Ahmed MAHamdy A (2006) Effect of daily repetitive transcranial magnetic stimulation on motor performance in parkinson's disease. Mov Disord. 21(12): 2201-5.
40. Lomarev MP, Kanchana S, Bara-Jimenez W, Iyer M, Wassermann EM, et al. (2006) Placebo-controlled study of rtms for the treatment of parkinson's disease. Movement disorders. 21(3): 325-331.
41. Martin RE (2009) Neuroplasticity and swallowing. Dysphagia. 24(2): 218-229.
42. Michou EHamdy S (2009) Cortical input in control of swallowing. Current Opinion in Otolaryngology & Head and Neck Surgery. 17(3): 166-171.
43. Sörös P, Inamoto YMartin RE (2009) Functional brain imaging of swallowing: An activation likelihood estimation meta-analysis. Human Brain Mapping. 30(8): 2426-2439.
44. Babaei A, Siwiec RM, Kern M, Douglas Ward B, Li SJ, et al. (2013) Intrinsic functional connectivity of the brain swallowing network during subliminal esophageal acid stimulation. Neurogastroenterology & Motility. 25(12): 992-e779.
45. Babaei A, Ward BD, Siwiec RM, Ahmad S, Kern M, et al. (2013) Functional connectivity of the cortical swallowing network in humans. NeuroImage. 76: 33-44.
46. Lowell SY, Reynolds RC, Chen G, Horwitz BLudlow CL (2012) Functional connectivity and laterality of the motor and sensory components in the volitional swallowing network. Experimental Brain Research. 219(1): 85-96.
47. Ciucci MR, Barkmeier-Kraemer JMSherman SJ (2008) Subthalamic nucleus deep brain stimulation improves deglutition in parkinson's disease. Movement disorders. 23(5): 676-683.
48. Rommel N, Borgers C, Van Beckevoort D, Goeleven A, Dejaeger E, et al. (2015) Bolus residue scale: An easy-to-use and reliable videofluoroscopic analysis tool to score bolus residue in patients with dysphagia. International journal of otolaryngology. 2015.

Table 1: Demographic, clinical and staging data at baseline assessment

Variable	Real rTMS Group (19 patients. Mean ± SD	Sham rTMS Group (11 patients). Mean ± SD	P value Mann-Whitney test
Patients Age (years)	60.7 ± 8.8	57.4 ± 10.0	0.16
Age at Onset (years)	55.1 ± 10.4	53.9 ± 10.7	0.18
Duration of Illness (years)	5.7 ± 3.9	6.5 ± 3.7	0.36
Total Score of UPDRS III	61.9 ± 13.2	64.6 ± 19.9	0.84
Hoehn and Yahr	3.1 ± 1.1	3.5 ± 1.0	0.18
IADL	16.4 ± 4.5	15.5 ± 5.0	0.34
self-assessment	18.7 ± 2.4	18.3 ± 3.4	0.74
Total score of Arabic Dysphagia Handicap Index	36.0 ± 14.9	33.4 ± 15.0	0.63
Swallowing disturbance questionnaire	17.4 ± 6.1	16.2 ± 5.8	0.50

UPDRS III; Unified Parkinson's Disease Rating Scale part III; IADL; Instrumental activity of Daily Living

Table 2a: Effect of 10 sessions of high frequency rTMS on different clinical rating scales (UPDRS III, IDAL and self-Assessment) among studied groups

	Pre-sessions	Post 10 sessions	Post 1 month	Post 2 month	Post 3month	P value Two Way ANOVA Time X Group
(UPDR III)						
Real	61.9 ± 13.2	39.7 ± 14.5	43.7 ± 14.4	45.4 ± 13.4	45.8 ± 13.1	P= 0.0001, df= 2.18(59), F= 20.3
Sham	64.6 ± 19.9	61.0 ± 17.5	62.3 ± 18.8	62.9 ± 18.3	64.2 ± 18.2	
Hoehn and Yahr						
Real	3.1 ± 1.1	2.6 ± 0.79	2.7 ± 0.80	2.8 ± 0.96	2.8 ± 0.98	P= 0.21, df= 1.0(27), F=1.6
Sham	3.5 ± 1.0	3.5 ± 0.97	3.5 ± 0.97	3.6 ± 0.97	3.6 ± 0.97	
(IDAL)						
Real	16.4 ± 4.5	19.3 ± 5.5	18.6 ± 5.2	18.5 ± 5.3	18.9 ± 4.9	P= 0.066, df= 1.4(38), F=3.2
Sham	15.0 ± 5.0	15.5 ± 4.8	15.0 ± 4.8	15.1 ± 4.7	15.2 ± 4.6	
Self-Assessment scale						
Real	18.7 ± 2.4	13.6 ± 2.4	14.0 ± 2.0	14.3 ± 2.5	14.5 ± 2.5	P= 0.0001, df= 2.9 (76), F= 17.9
Sham	18.8 ± 3.6	17.9 ± 3.2	18.4 ± 3,6	18.2 ± 3.1	18.0 ± 3.3	

UPDRS III; Unified Parkinson's Disease Rating Scale part III; IADL; Instrumental activity of Daily Living

Table 2b: Effect of 10 sessions of high frequency rTMS on A – Dysphagia Handicap Index among studied groups

	Pre-sessions	Post 10 sessions	Post 1 month	Post 2 months	Post 3 months	P value Two Way ANOV Time X Group
A – Dysphagia Handicap Index (functional)						
Real	14.5 ± 5.5	8.9** ± 4.1	9.4* ± 4.3	9.8* ± 5.0	9.9* ± 5.2	P= 0.0001, df= 2.4 (63), F
Sham	14.6 ± 6.8	14.7 ± 6.9	14.0 ± 6.4	15.6 ± 7.1	15.1 ± 6.8	10.7
A – Dysphagia Handicap Index (DHI physical)						
Real	15.7 ± 7.0	8.8* ± 5.7	8.7* ± 6.2	9.2* ± 6.2	9.2* ± 6.2	P= 0.0001, df= 1.6 (42), F
Sham	14.6 ± 7.4	14.0 ± 7.1	14.4 ± 6.8	14.4 ± 7.3	14.6 ± 7.2	16.7
A – Dysphagia Handicap Index (emotional)						
Real	5.8 ± 4.0	3.7 ± 2.8	3.5 ± 2.7	3.4 ± 2.7	3.4 ± 2.7	P= 0.02, df= 1.6 (32), F= 5.5
Sham	4.9 ± 2.1	4.2 ± 2.4	4.7 ± 2.2	4.7 ± 2.2	4.7 ± 2.2	
A – Dysphagia Handicap Index (total)						
Real	36.0 ± 15.0	21.5*± 10.9	21.6*±11.6	22.3*± 12.4	22.6* ± 12.4	P= 0.0001, df= 1.5 (38), F
Sham	33.5 ± 15.1	32.6 ± 15.0	32.9 ± 14.1	34.4 ± 14.7	34.4± 15.1	15.6
A – Dysphagia Handicap Index (impression)						
Real	5.0 ± 1.2	2.8 ± 1.0	3.1 ± 1.1	3.0 ± 1.0	3.1 ± 1.1	**P= 0.0001, df= 1.4 (36), F**
Sham	4.2 ± 1.7	3.8 ± 1.7	3.7 ± 1.7	3.9 ± 1.8	4.0 ± 1.9	**14.6**

Table 3: Videofluroscopy details of each items Pre and post sessions in studied groups

	Pre session (H2-H1)	post sessions (H2-H1)	P value Paired t-test	Pre session PTT	Post-session PTT	P value Paired t-test	Pre session PAscore	Post session PAscore	P value Paired t-test	Pre session residue	Post session residue	P value Paired t-test
FLUID												
Real group (9 cases)	1.0±0.7	0.6±0.3	P=0.04	1.6±0.7	1.1±0.3	P=0.03	1.9±0.8	1.4±0.7	P=0.1	0.9±0.6	0.7±0.7	P=0.16
Sham group (6 cases)	0.8±0.7	0.8± 0.6	P = 0.9	1.4± 0.9	1.2±0.7	P= 0.3	1.5±0.5	1.3±0.5	P= 0.3	1.2±0.7	1.2±0.7`	P= 0.9
Two ways ANOVA Time X Groups	Df=1(13), F= 0.3, P= 0.10			Df=1(13), F= 1.5, P= 0.2			Df=1(13), F= 0.7, P= 0.4			Df=1(13), F= 1.5, P= 0.2		
SEMISOLID												
Real group (9 cases)	1.1±0.9	0.6±0.3	P=0.2	1.5±0.8	1.2±0.6	P=0.3	1.4±0.7	1.2±0.7	P=0.2	0.9±0.6	0.7±0.7	P=0.16
Sham group(6 cases)	1.1±0.9	0.9± 0.6	P = 0.3	1.6± 0.7	1.4±0.7	P= 0.2	1.3±0.5	1.2±0.5	P= 0.4	1.3±0.8	1.2±0.4`	P= 0.9
two ways ANOVA (Time X Group)	Df=1(13) F=0.4, P = 0.5			Df=1(13) F=0.01, P = 0.93			Df=1(13), F=0.6, P = 0.8			Df=1(13), F=0.03, P = 0.8		
SOLID												
Real group (9 cases)	0.7±0.6	0.5±0.4	P=0.009	1.4±0.6	1.1±0.5	P=0.01	1.4±0.7	1.2±0.7	P=0.4	1.1±0.6	0.9±0.6	P=0.16
Sham group(6 cases)	0.8±0.7	0.9± 0.7	P = 0.19	1.4± 0.7	1.5±0.7	P= 0.6	1.2±0.4	1.1±0.0	P= 0.4	1.3±0.8	1.3±0.5	P= 1.0
Two ways ANOVA Time X Groups	Df=1(13), F=10.3, P = 0.007			Df=1(13), F=5.3, P = 0.03			Df=1(13), F=0.8, P = 0.7			Df=1(13), F=0.65, P = 0.4		

PTT; The pharyngeal transit time; H1; the time of the first superior-anterior movement of the hyoid bone, H2 the time when the hyoid bone reaches the maximum elevation, PA score; penetration-aspiration scale, Residue; post-swallow residueH2-H1

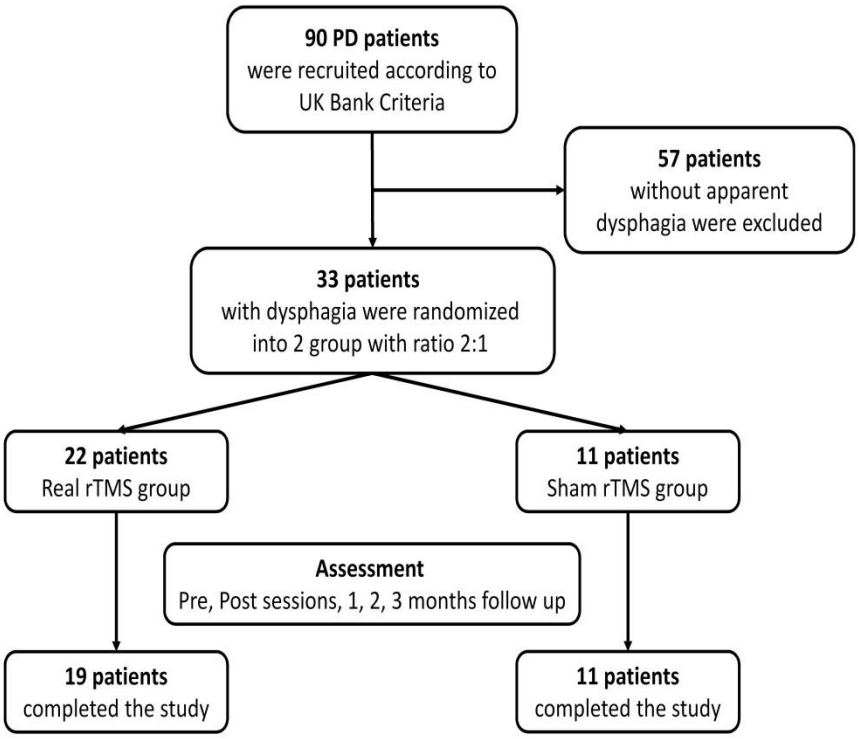

Figure 1 flow chart

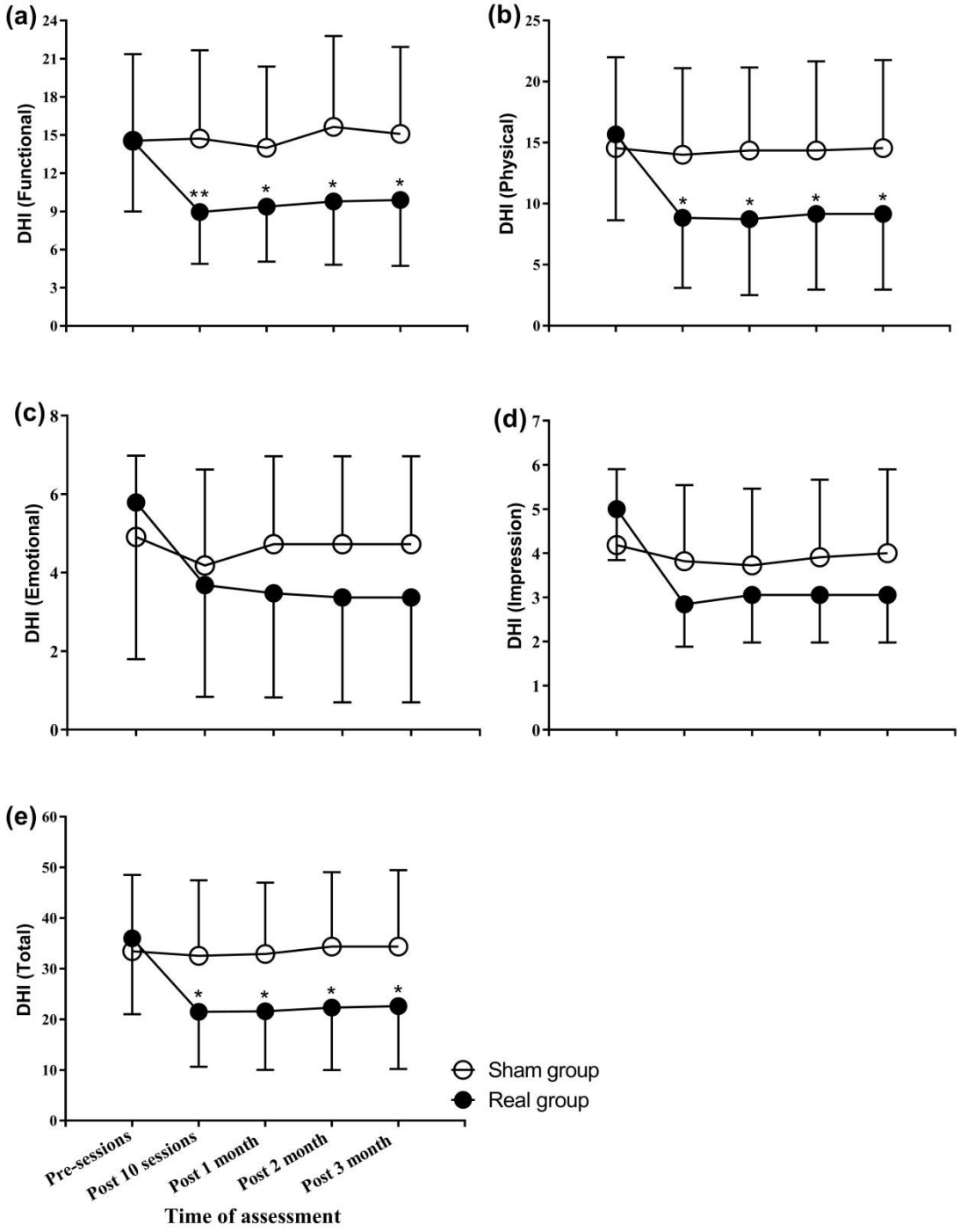

Figure 2: Show changes in Arabic Dysphagia Handicap Index among the studied group. A significant effect of time (pre, post treatment and one, two and three months later) on all sub items (functional, physical, and emotional) as well as the total score of the Arabic-Dysphagia Handicap index in the real group while no such changes were observed in the sham group. A significant interaction effect (time Xgroup) for A- DHI subitems and total scores

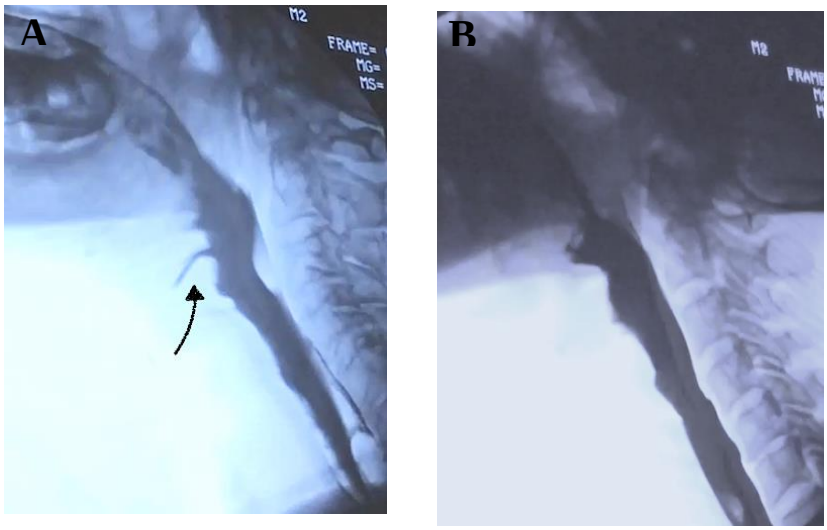

Figure 3a: Lateral fluoroscopic views in a PD patient with dysphagia. A) Before rTMS sessions, there is a penetration, scored as (3) on the penetration-aspiration scale, with fluid bolus entering the airway (arrow). B) Notable improvement is shown after rTMS sessions, with no evidence of penetration. Sore (1) on the penetration-aspiration scale.

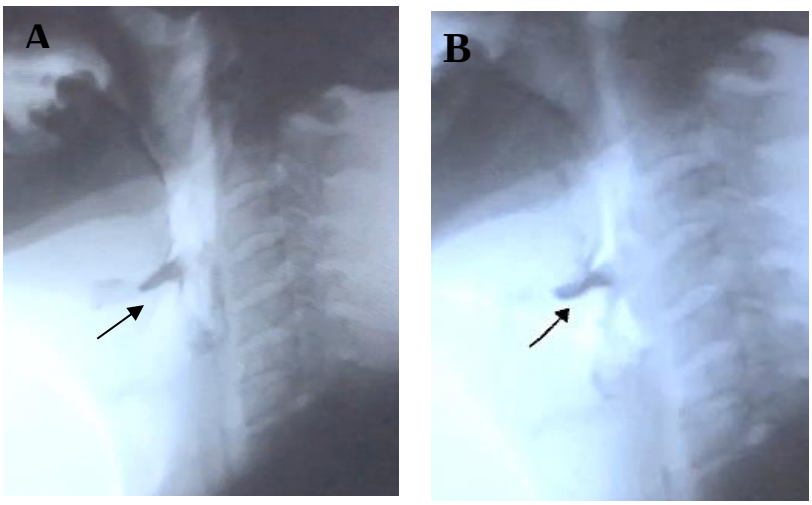

Figure 3b: Lateral fluoroscopic views in a PD patient with dysphagia. A) Before rTMS sessions, residual barium is filling the vallecula (arrow). B) No notable clearance of the barium after rTMS