To evaluate the activity and the efficacy of traditional swallowing therapy (TST) plus neuromuscular electrostimulation (NMES) vs TST plus sham-NMES in Multiple Sclerosis patients with dysphagia

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Abstract

Dysphagia is a disabling, life-threatening symptom that can cause death in Multiple Sclerosis people (pwMS) through aspiration pneumonia. Speech therapists use behavioural therapies (compensatory and rehabilitative) to alleviate such swallowing problems, with limited benefit. Compensatory strategies such as postural changes and changes in food consistency, have been found to be partially effective, especially in patients with mild dysphagia and may be ineffective in patients with more severe dysphagia. The rehabilitative strategies include “no swallow exercises” which aim to strengthen isolated muscles used in swallowing (such as tongue strengthening) and “swallowing exercises” that aim at strengthening all the muscles used in swallowing while executing a hard, effortful, or prolonged swallow. To date, no randomized clinical trials have shown that rehabilitative strategies are effective. Neuromuscular electrical stimulation (NMES), often referred to as electrical stimulation, was introduced as a novel therapy for dysphagia in the late 2001 (Fred)The principles of NMES in the limb rehabilitation literature are well established. However published protocols applying NMES to swallowing function have shown mixed results in people with stroke and only one study was published on MS people. This will be a double blinded, randomized clinical trial (patients and research staff blinded) with two arms: standard speech therapy plus Active NMES vs speech therapy with Sham NMES. The aim of this study is to determine whether NMES added benefit to a therapy program comprised of standard swallowing exercises in dysphagic pwMS.

Introduction

Recent studies has shown that dysphagia in MS is more frequent than previously believed, the real prevalence ranging from 33 to 43%. (Solaro et al 2013) Dysphagia is a disabling, life-threatening symptom that can cause death in MS people through aspiration pneumonia. Dysphagia has also been reported in about 17% of patients with low disability (EDSS score lower than 2.5) (Abraham, et al 1997). These figures, which are based on

clinical evaluations, are undoubtedly higher when the symptom is evaluated by means of instrumental investigations (Tassorelli, et al 2008). According to the De Pauw study (De Paw, et al2002), permanent dysphagia emerges in mildly impaired patients (EDSS 2-3), and becomes increasingly common as disability worsens, reaching a prevalence of 65% in the most severely disabled subjects (EDSS 8-9). Thus, diagnosis in the early stages may play an important role in limiting the consequences of this dysfunction. However, as patients themselves sometimes underestimate this symptom, diagnosis must be supported, as recently described in the literature, by functional tests and instrumental evaluations. A specific questionnaire (DYMUS: Dysphagia in Multiple Sclerosis) was published and validated for the assessment of dysphagia in MS. Its good internal consistency and the feasibility of administration has made it a reliable means to detect dysphagia in MS. In particular it consents to distinguish dysphagia to solids from dysphagia to liquids (Bergamaschi, et al.).2008). However, a more detailed and objective evaluation is needed to investigate specific deficits and to plan appropriate rehabilitation; the Fiberoptic Endoscopy Evaluation of Swallowing (FEES) may be used for this purpose. In the 20 years since these initial reports, the FEES has become a validated technique for the evaluation of pharyngeal swallowing (Leder, et al 2008). The swallowing disturbances in MS are characterised by impairment of the oral and pharyngeal phases. Abraham et al. found impairment of the upper oesophageal sphincter in 100% of a small MS population (Abraham et al.1997). Calcagno et al., using a mixed clinical and instrumental examination, subdivided their population into three groups according to the severity of dysphagia: severe, moderate and slight. Severe dysphagia group showed impairment of both oral and pharyngeal phases of swallowing, moderate dysphagia group showed motor impairment of the tongue, lips, velum or larynx, while the mild dysphagia group showed deficiency either of the velum or of the glottic closure. In the same paper, Calcagno et al. found that the compensatory strategies resolved dysphagia in about 94% of the cases (46 pts. Out of 49) (Calcagno et al., 2009). These strategies help to redirect and improve the food flow, avoiding aspiration and reducing the risk of pneumonia, but patients remain dysphagic and always need to perform compensatory strategies. (De Angelis et al 2008; Inagaki et al 2009,) As far as we know, this is the only study evaluating the rehabilitative approach, but it was not a control study. The role of food was highlighted in a recent paper showing that the main effect of food hardness is a delay in oral ejection time, which strongly delays total swallowing time, whereas pharyngeal bolus transit is dependent on its viscosity (Taniguchi et al 2008,). Recently, a pilot study (Frost, et al 2018) has shown as NMES could probably improve voice quality in MS patients: in fact, dysarthria has been proven to affect quality of life in MS patients (Piacentini, 2014).

NMES is a form of muscle stimulation with short electrical pulses that is frequently used in physiotherapy to strengthen healthy muscles and has been well described for several decades. NMES is used with a variety of different parameters for different types of treatment, since muscle contraction depends on different electrical parameters. An increase in frequency will result in an increased tension of the stimulated muscle, whereas increased intensity spreads current over a larger area, stimulating more motor units. Lastly, increasing the current duration causes more motor unit activation. NMES can be used for either muscle strengthening, retardation of atrophy or muscle re-education, and different stimulation parameters have to be chosen for each of these three

applications of NMES. The use of NMES in dysphagia treatment is relatively new; the first study was published in 2001 (Freed, 2001). Although Logemann reported that the therapeutic effects of NMES still lacks convincing supporting evidence, (Logemann, et al 2007), several studies have been carried out (Heijnen et al 2012, Kim et al 2017, Li et al 2015, Langmore et al 2016, Shaw et al 2007). Research using NMES, including randomized controlled trials, has demonstrated functionally improved swallowing with subjects moving from modified diets to more normal diet and fluids when NMES is used in conjunction with traditional therapy, but not when used in isolation (Chen, et al 2016). Moreover, recent UK guidelines from the National Institute of Clinical Excellence (NICE) recognized the positive results from these trials and promoted a further research to support the routine clinical use (NICE, 2014). NMES has been used in a wide range of patients, suffering from diverse pathologies: from head and neck cancer, to post-stroke dysphagia, obtaining different results (Chen 2016; Frost, 2018). Although it has been hypothesized, that neuromuscular electrical stimulation might enhance muscle strength in weak and disused oro-pharyngeal muscles, its clinical effectiveness remains unclear. Regardless the mechanism of action, clinical results showed that NMES enhances laryngeal elevation (Park et al 2009), reduces upper esophageal sphincter pressure (Heck et al 2012) and it enhances tongue base retraction during swallowing in health volunteers (Jungheim et al 2017). As reported by Oh (Oh et al 2007) and Hamdy (Hamdy et al 2000), the improvement of the swallowing function in stroke, after electrical stimulation is correlated with cortical reorganization, suggesting that multiple sessions of NEMS of the neck muscles could improve swallowing function also trough the recruitment of new cortical areas.

NMES has poor been used in treating dysphagia in MS patients (Alali, 2016). A pilot study performed with pharyngeal electrical stimulation for dysphagia associated with MS showed an improvement in penetration and aspiration scale, suggesting a potential benefit for the treatment of this symptom (Restivo et al 2013)

However, this type of treatment can be performed only in specialized centers and it is probably more invasive than NMES. In 2009, Bogaardt (Bogaardt et al 2009) conducted a Class IV trial with a sample of 25 patients with MS. The primary focus of the study was to examine the effects of NMES on pooling of saliva or liquid in the valleculae and pyriform sinuses. Six of the 25 patients had significant reduction in pooling of saliva in the pyriform sinuses, and 23 participants reported through a questionnaire that their swallowing had improved (Bogaardt, et al 2009). As far as we know, this is the unique paper focusing on the therapeutic effects of NMES in MS patients. Our research group recently published about the use of NMES in people with stroke and dysphagia. The methodology resulted safe with a good effectiveness in add on with traditional speech therapy. In fact, combined treatment seem to reduce the risk of penetration and aspiration in stroke dysphagic people. (Simonelli et al 2019).

The aim of the study is to determine whether NMES added benefit to a therapy program comprised of standard swallowing exercises in dysphagic pwMS

Materials and methods

The research plan will be implemented within a multi-center collaboration. Each of the 8 centers will recruit 17 inpatient and outpatient with a diagnosis of MS, according to revised McDonald criteria (Thompson et al 2018), with dysphagia. Each patient will be evaluated with a general and neurological evaluation scored according to the Expanded Disability Status Scale (EDSS) of Kurtzke and its functional systems.
Inclusion criteria will be:
1) Sex (both);
2) Age (older than 18)
3) Diagnosis: definite MS (Thompson et al 2018)
4) Stability: recruited subjects must be in a stable phase of the disease, without relapses which induce worsening > 1 point in the EDSS and with an EDSS <=8
5) ASHA<6 and DYMUS >2
6) Novelty: subjects should not have been trained with dysphagia program in the last 6 month
7) Mini-Mental State Examination: > 24;

Exclusion criteria will be:
1) dysphagia related to other diseases
2) presence of tracheal cannula
3) local or general contraindications to the use of equipment for electrical muscle stimulation of the neck
4) malignancies or acute inflammation in the anterior region of the neck.
5) lack of collaboration due to mental impairment

Baseline characteristics:
At T0, a clinical and instrumental examination will be suggested, concerning:
- the cognitive profile (Brief International Cognitive Assessment for MS); (Benedict et al 2012)
- the presence and severity of fatigue scored with Modified Fatigue Impact Scale; (Tellez et al 2005)
- the presence and severity of depression (Beck depression Inventory); (Solaro et al 2016)
- the motor performance with Timed 25 Foot walk Test ,Timed Up and Go, and 9 hole Peg Test (Gijbels et al 2012, Kragt et al 2006, Sebastião et al 2016,);
- the body mass index (kg/m2) and blood parameters (in particular proteins and albumin) will be examined in all of the patients, in order to define their nutritional state;
- Mini Nutritional Assessment (Vellas et al , 2006). To verify the appropriate food calories intake
- the voice quality: (Frost, 2018). In order to carry out the speech analysis, the software PRAAT (a system for doing phonetics) was developed by Paul Boersma & David Weenink at the Phonetic Sciences department at the University of Amsterdam) will be adopted.
As far as the dysphagia concerned, its presence and severity will be assessed using:
- ASHA score, (American Speech –Language Hearing Association, 1998) performed by a speech therapist; ASHA suggests that patients should be divided in groups from level 1

(individuals cannot swallow anything safely by mouth) to level 7 (individual's ability to eat independently is not limited by swallowing function. Swallowing is safe and efficient for all food consistencies. Compensatory strategies are effectively used when needed).

A non instrumental evaluation will be used, due to its feasibility, by an examiner unaware of the research protocol. The assessment takes into consideration anamnesis regarding the swallowing problem, evaluation of the anatomy and functionality, of sensitivity and the reflexes, of the swallowing apparatus. Finally, the oral feeding test is performed, which evaluates the oral and pharyngeal phases of swallowing.
- FEES, performed by a phoniatrician in a blinded way in order to verify: 1) rest status, with reports of possible secretions or food presence, particularly in the lower pharyngeal tract; 2) preliminary report on: a) glottis enclosure ability (phonation) b) coordination between breathing and vocalization, c) ability and sensitivity of the cough reflex. 3) "dry" swallowing, with observation of the pushing-back movement of the tongue, the time for swallowing voluntary activation(pharyngeal phase), the research of larynx elevation and epiglottis basculatory movement; 4) proposal of food coloured with green of varying consistencies to test the swallowing act with determined quantities: a) liquid: a spoonful, i.e. 10 ml, repeated three times; b) semisolid (gelatine consistency): a spoonful, i.e. 10 ml, repeated three times; c) solid: half a cracker, repeated with three bits. During each swallowing act, the observer will have to examine the same functions described above in point n. 3, and his/her attention will focus on premature falls of the bolus towards the pharynx, with or without penetration and/or aspiration; the word "premature" indicates that it is contemporary to the oral phase and is to be used to indicate the alimentary falls before the pharyngeal phase of swallowing; penetration and/or aspiration during the pharyngeal phase of swallowing; laryngeal
penetration, defined as passage of material into the laryngeal vestibule above the vocal folds and aspiration, defined as passage of material under the level of
the true vocal folds; reports of the permanence of food and/or secretion in the lower tract of the pharynx after the pharyngeal phase of swallowing (pharyngeal residue
or pooling) and evidence of penetration and/or aspiration of this residual component; the occurrence, or absence, of the cough reflex as a consequence of penetration and/or aspiration.

According to the FEES examination will be scored the severity of dysphagia through the Dysphagia Outcome and Severity Scale (DOSS Score) (O'Neil et al 1999). We'll also use the Penetration and Aspiration Scale (Rosembek et al, 1996) and the Pooling scale, able to evaluate the excess residue in the pharynx and larynx. (Farneti et al 2014). The FEES will be record by video.
- the DYMUS questionnaire (Bergamaschi et al., 2008)
- the Swal-QOL. This is a 44-items questionnaire is a highly valid instrument for evaluating and has a very reliable shorten reproducibility (Ginocchio D et al 2016). Its 11 subscales represents the different aspects of quality of life. The minimum and maximum score per subscale ranges from 0 to 100, indicating extremely impaired quality of life versus no impairment experienced by the individual;

- Visual Analogue Scale (VAS) for dysphagia: self-assessment of dysphagia severity will be rated from 0 (none) to 10 (worst imaginable) scale. Respondents will be classified as having no dysphagia (score 0), mild dysphagia (scores 1-4), moderate dysphagia (scores 5-6) and severe dysphagia (scores 7-10);
- the meal time.
-CGI (Clinical Global Impression Scale) scale for evaluating clinical changes after treatment (Busner et al 2007)

Two Speech Language Pathologists (SLPs) trained in dysphagia management will be involved: one, as evaluating speech therapist, will be blind on the NMES treatment and the other one as a treating speech therapist.
As far as the dysphagia concerned, patients will be considered dysphagic according to ASHA (score<6) and DYMUS (score >2).
The NICE guidelines (NICE 2014) identified from the literature a number of possible adverse events for NMES, which they classified under Safety section.
Those deemed likely were burning sensation, skin irritation or soreness beneath the electrodes and coughing or expectoration, neck or jaw pain and increasing severity of dysphagia. Incidences of these events were recorded during the NMES therapy. The therapists who delivered the NMES therapy were also asked to record any other adverse reactions. In addition, therapists were asked to record whether the adverse reaction was resolved by repositioning the electrodes.
Finally, the speech and language therapists were asked to note whether there was any change in the quality of the voice as a result of the NMES, as previous research has shown (Frost, 2018).
The training will consist of 16 sessions. After 8 (T1) every patient will be examined using: ASHA scale; VAS for dysphagia and meal time. After 16 (T2) sessions, every patient will be examined with both clinical and instrumental examinations; after 12 weeks (T3) from the end of treatment every patient will undergo clinical evaluations. At T3 the CGI will also be submitted to the pwSM caregivers

Rehabilitation treatment
According to the presence of dysphagia, scored as previously described by ASHA and DYMUS scales, were estimate that, we can enrol 17 pwMS for each center.. The candidates will be randomly allocated (according to 2 blocked randomization lists, generated electronically by www.random.org) in two groups numbered consecutively and equal numbers will be allocated to the intervention group “standard rehabilitative treatment plus neuromuscular electrostimulation” (SRT-NMES), odd numbers to the control group “standard rehabilitative treatment plus Sham (SRT-S). Randomization will be done by single center.
Both SRT-NMES and SRT-S groups will be received 16 sessions of traditional dysphagia therapy according to their degree of dysphagia, contemporary associated with Sham or NMES, according to our previous experiences, two 30-min treatment a day, separated by a rest period of at least 45 minutes for four consecutive days per week, within a period of 4 weeks.
During the study period, steroids will not be permitted.

Patients who will experience relapses during the study period will be considered as drop-out.

Traditional dysphagia therapy

The training will be performed by expert speech therapists. Traditional dysphagia therapy (TDT) involved orofacial, lingual, and laryngeal motor exercises, including progressive resistance training, combination of lingual strengthening exercises, laryngeal adduction-elevation exercises, effortful swallow manoeuvre, Mendelsohn manoeuvre (Mendelsohn et al 1987), Masako manoeuvre (Fujiu et al 1996) and Shaker exercises (Shaker et al 1997). Compensatory swallowing strategies included various modifications of head, neck, and body postures and adjustment of food/liquid temperature, viscosity, and volume. It may be necessary to whisk food completely or partially, often adding a thickening liquid in drinks to allow an adequate water intake for nutritional support.
(Gonzales-Fernandez et al 2008). The choice of specific positioning strategies and swallowing manoeuvres or exercises was based on the FEES findings and the clinical swallowing examination. The rehabilitative treatment will be administered in the 8 centers taking part to the study .

Neuromuscular electrostimulation (NMES)

In the present study, VitalStim equipment will be used (VitalStim Therapy; Chattanooga Group, Chattanooga,TN, USA). Therapists received additional training and information on NMES by an experienced laryngologist certified to use surface electrical stimulation. The training was given according to the manual of the manufacturer, the VitalStim certification course (http://www.vitalstim.com).

Skin preparation and electrode placement will be in accordance with the manufacturer's instructions.
Channel 1 is horizontally immediately above thyroid notch. Channel 2 is parallel, below notch.
Having applied the electrodes, the amplitude of each channel of the stimulator will be increased and the subject will identify when they will be able just feel it. The amplitude will be then further increased until the subject will feel a 'grabbing sensation' which corresponded to muscular contraction. This will be the amplitude used for the therapy. This process will be repeated for the second channel of the stimulator. The typical electrical stimulus is at 80 Hz and at 300 microsec, and it will be adapted to avoid annoying stimulus to the patients.
During therapy, both channels will be active. In "sham" group the same electrodes will be positioned.
To maintain the double-blind study, the electrodes in the "sham" group will be placed in the same positions as the active treatment, with a current between 3 and 5 mA (average of 3.5 mA) until the patient begins to feel a slight tingling, current unable to perform muscle contraction. (Park J. S. et Al).

During electrical stimulation, traditional swallowing therapy will be carried out, by a trained speech therapist.
Before the study starting, the team of the 8 Centres, reached a consensus for the administration of clinical scales and how to score the FEES findings.

Briefly:

Subjects:
136 clinically definite MS subjects, both outpatients and inpatients (see inclusion and exclusion criteria below). Each patient will be informed on overall requirements of the study, and his/her written consent will be obtained
Primary Outcome:
The first aim of this study is to determine whether NMES adds benefit to a speech therapy traditional program. Performance between the groups will be compared at completion of treatment, after adjustment for baseline differences.
The mean difference at ASHA score between SRT-S vs SRT-NMES will represent the primary outcome.
Secondary outcome will be the differences obtained at To-T2 and T0-T3 in the two groups in DYMUS scale,FESS/DOSS score, the MNA, the Swallowing Quality of life questionnaire, Penetration and Aspiration Score, the Visual Analogue Scale and the Pooling score.
Hypothesizing a response to treatment in the 30% of the SHAM group and in 60% of active NMSE a sample size of 56 subjects for each group provides a power of 0.9 and a significance level of 5%. (h = 0.6128748, n =55.94774, sig.level = 0.05, power = 0.9, alternative = two.sided)
We estimate we could have a dropout of approximately 10-15%. In this light we decided to enrol 136 pwMS (17 for each center) Baseline characteristics and comparability of the two treatment groups will be assessed by the two samples t-test for continuous variables and by chi-square or Fisher's exact test for categorical variables. To address the first aim of the study, will be used analysis of covariance comparing changes in study outcomes from baseline to T2 adjusting for differences in baseline measures of swallow performance, diet and quality of life across the two treatment arms. To evaluate the differences intra-group, we will performed longitudinal analyses using general linear models for repeated measures of outcome data collected at baseline to T2 .

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