Pharyngeal electrical stimulation in amyotrophic lateral sclerosis: a pilot study

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Abstract

Background: Patients with amyotrophic lateral sclerosis (ALS) suffer from dysphagia that increases the risk for aspiration, pneumonia and weight loss. Pharyngeal electrical stimulation (PES) is a therapeutic technique that applies electric stimuli to the patient's pharynx in order to improve swallowing based on the principle of cortical plasticity and reorganization. Previous studies have demonstrated positive effects in patients with various neurological diseases.

Objective: This study was initiated to investigate the effect of PES on swallowing function in patients with ALS.

Methods: In all, 20 ALS patients with severe dysphagia [characterized by a Penetration Aspiration Scale (PAS) of at least 4 in thin liquid] were randomized to receive either PES for 10 min at 3 consecutive days in addition to Standard Logopaedic Therapy (SLT) or SLT alone. Swallowing function was evaluated by Fiberoptic Endoscopic Evaluation of Swallowing (FEES) at five timepoints: at baseline, 1 day, 4 days, 3 weeks and 3 months after treatment. Primary endpoint was the severity of penetrations or aspirations as classified by PAS. Secondary endpoints were adverse events, dysphagia-related quality of life, Swallowing Quality of Life (SWAL-QOL), Dysphagia Severity Rating Scale (DSRS), residues, leaking, ALS Functional Rating Scale Revised (ALSFRS-R), and the performance in Clinical Evaluation of Swallowing (CES). The trial is registered under the name of 'Pharyngeal Electrical Stimulation in Amyotrophic Lateral Sclerosis' with ClinialTrials.gov, number NCT03481348 (https://clinicaltrials.gov/ct2/show/NCT03481348).

Results: Both groups combined showed a significant improvement ($p = 0.003$) of median Total-PAS from 3.6 [interquartile range (IQR) = 2.9–5.0] at baseline to 2.3 (IQR = 1.8–4.0) 1 day after treatment. During subsequent study visits, PAS increased again but remained below baseline. PES and control group did not differ significantly 1 day after intervention ($p = 0.32$). Similar effects were found in the majority of secondary endpoints.

Interpretation: The findings suggest that PES may not provide an additional positive effect on swallowing function in ALS. SLT seems to yield at least short-term positive effects on swallowing function and swallowing-specific life quality in ALS.

Registration: ClinialTrials.gov: NCT03481348

Keywords: amyotrophic lateral sclerosis, Fiberoptic Endoscopic Evaluation of Swallowing, logopaedic therapy, pharyngeal electrical stimulation

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Introduction

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease characterized by the loss of upper motor neurons (UMNs) in the motor cortex as well as lower motor neurons (LMNs) in the brainstem and spinal cord that leads to death within 3 years.[1]

During the course of the disease, the majority of patients develop bulbar symptoms including dysphagia[2] which carries the risk of aspiration pneumonia. In addition, ALS is commonly associated with rapid weight loss due to an increased energy expenditure.[3] Weight loss and malnutrition are aggravated by dysphagia.[4] Multiple studies have

shown that weight loss is an independent negative prognostic factor.[5–9]

Dysphagia is characterized by tongue atrophy, weakness of jaw muscles, inadequate bolus transport, reduced contraction of the pharynx and excursion of the hyoid due to degeneration of the cranial nerves V, VII, IX, X and XII.[10] Degeneration of the UMN causes prolonged contractions of the pharynx and therefore leads to an inadequate bolus transport.[11] These alterations cause penetrations, aspirations, predeglutitive leaking as well as oral and pharyngeal residues.[10,12,13]

Previous studies have shown evidence for compensating mechanisms in patients with dysphagia after brain damage: Hamdy *et al.*[14] found that the ipsilateral cortical representation of the pharynx is reduced in dysphagic patients shortly after stroke using magnetic stimulation. However, after several months, the pharyngeal representation was enlarged in the contralateral, undamaged hemisphere. Teismann *et al.*[15] used magnetoencephalography to study the involvement of both hemispheres in the various phases of swallowing in healthy individuals. They found that the left sensorimotor cortex was mainly activated during the oral phase of swallowing. However, activation of the right sensorimotor cortex was associated with the late, pharyngeal phase of swallowing, regardless of handedness. The same method was used to study the cortical activation in patients with ALS.[16] Overall, activation was decreased compared with healthy participants. Interestingly, the right pharynx–associated cortex showed a higher level of activation compared with the left side, which was even more pronounced in patients with severe dysphagia. This observation indicates cortical plasticity with regard to the lateralization of swallowing function in patients with ALS. Consistently, positron emission tomography (PET) studies in ALS patients with UMN involvement demonstrated cortical hypometabolism throughout the whole brain, far beyond primary motor regions, suggesting that such neurons are in a state of non-functioning and potentially amenable to neuronal plasticity.[17]

Pharyngeal electrical stimulation (PES) refers to a therapy that applies electric stimuli to the patient's pharynx via a transnasal inserted catheter. As opposed to other stimulation techniques as, for example, transcranial direct current stimulation (tDCS), the application of PES in ALS does not primarily aim at modifying cortical excitability but rather inducing cortical plasticity based on the application of repetitive electrical stimuli.[18,19] By this mechanism, the cortical representation of swallowing shall be shifted to other regions that are less affected by neurodegeneration. Another potential mechanism of PES involves the restoration of sensory feedback as indicated by increasing levels of substance P.[20]

Multiple studies demonstrated potential positive effects of PES on swallowing performance in patients with multiple sclerosis (MS) and after stroke.[21–23] Patients with MS showed significant improvements in the Penetration Aspiration Scale (PAS) after PES compared with patients receiving sham stimulation.[21] Further studies examined the effect of PES on successful decannulation in tracheotomized stroke patients. As assessed by Fiberoptic Endoscopic Evaluation of Swallowing (FEES), significantly more patients in the PES group were considered to be ready for decannulation after treatment compared with patients receiving sham stimulation.[22,23]

These findings suggest that PES may improve dysphagia of different etiologies. Considering the evidence for compensational mechanisms in ALS by means of cortical plasticity[16] and since ALS features an asymmetrical pattern of initial manifestation and spreading,[24] we hypothesized that a shift of the swallowing function to cortex regions featuring a lower degree of neurodegeneration by applying PES was possible.

Thus, the aim of this pilot trial was to examine the effect of PES on swallowing performance and the risk of aspiration in patients with ALS.

Methods

Study design and participants

This study is a prospective, randomized, parallel-group, controlled trial investigating the effect of PES on swallowing function in patients with ALS. The study was conducted at the Department of Neurology, Ulm University, in accordance with the Declaration of Helsinki, International Conference on Harmonization Guideline for Good Clinical Practice and the applicable local regulations. The Independent Ethics Committee of Ulm University, Germany, approved the study protocol (approval number 169/17). The trial is registered with ClinialTrials.gov (number NCT03481348). All participants provided written informed consent.

Patients with possible, probable or definitive ALS according to the revised version of the El Escorial World Federation of Neurology criteria[25] were eligible for study participation. Patients with atypical phenotypes such as primary lateral sclerosis (PLS), progressive muscular atrophy (PMA) and progressive bulbar palsy (PBP) were not included. In addition, a combined UMN/LMN bulbar involvement with moderate to severe dysphagia – defined as a PAS[26] value of at least 4 in thin liquid as assessed by FEES at baseline – was required. Exclusion criteria were tracheostomy, severe psychiatric disorders or dementia, implanted pacemaker or cardiac defibrillator and severe cardiopulmonary diseases.

Randomization

At baseline, eligible patients were enrolled in the study and received the next consecutive randomization number. The randomization list was generated by the Institute of Epidemiology and Medical Biometry, University of Ulm, Germany, by use of a validated system, which involves a pseudorandom number generator to ensure that the resulting treatment sequence will be both reproducible and nonpredictable.

Each eligible patient was randomly assigned (1:1) to one of the two study groups and received the next consecutive randomization number. The trial was not blinded and included an open control group.

Procedures

Patients were allocated to two groups. Patients of the PES group underwent PES in addition to Standard Logopaedic Therapy (SLT), whereas patients of control group received only SLT. PES and SLT were both performed on 3 consecutive days by two formally trained speech and language therapists and a formally trained medical student.

For PES, a commercial device from Phagenesis® Ltd, Manchester, UK (Phagenyx®), was used, which includes a transnasal catheter with stimulation electrodes that were positioned in the pharynx. PES treatments consisted of three applications on 3 consecutive days for 10 min each. Electrical stimuli were applied with a frequency of 5 Hz and a duration of 200 µs for each stimulus. Intensity ranged from 1 to 50 mA and was individually determined based on the level of perceptual threshold (PT) and maximum tolerated threshold (MTT) that were measured before each application. Subsequently, the applied treatment intensity was automatically calculated by the stimulation device based on the formula $((MTT - PT) \times 0{,}75) + PT$. It had been previously shown that this way PES induced the greatest effect on corticobulbar excitability.[27]

SLT was executed over 3 days for 45 min each day by the same speech and language therapist for both groups. To date, no generally accepted standard protocol for logopaedic therapy in ALS has been established. Therefore, logopaedic therapy largely relies on local expertise. In our centre, logopaedic therapy is based on three main procedures (for detailed description, see Supplementary Material).[28]

Restitutional procedures aim at training the sensorimotor perception and the economic use of the remaining functions through passive manual treatment, tactile and thermal stimulation and moderate movement exercises of the orofacial and pharyngeal–laryngeal tract. To that end, Orofacial Regulation Therapy according to Castillo Morales[29] and Facio-oral Tract Therapy according to Kay Coombes[30] combined with voice, respiratory and manual training were used.

Compensatory procedures include changes in posture (e.g. chin tuck[31]) or specific swallowing techniques (e.g. supraglottic swallowing[32]) as recommended by the guidelines for neurogenic dysphagia by the Deutsche Gesellschaft für Neurologie (German Society for Neurology, DGN).[33]

Adaptive procedures include an adaption of patients' eating and drinking habits like the optimal placement of the bolus on the tongue or special aids for eating and drinking (e.g. cup with a recess for the nose).

Swallowing function was evaluated by FEES using endoscopes with 2.5 mm (Karl Storz SE & Co. KG, Tuttlingen, Germany) and 2.9 mm diameter (RS1®, Orlvision GmbH, Lahnau, Germany), recorded with the software rp Szene® (Rehder/Partner Medizintechnik GmbH, Hamburg, Germany) and evaluated by an experienced and FEES-certified speech therapist. The following consistencies were evaluated: porridge (apple puree), fluid (water), nectar-like (banana nectar), soft (bread without crust) and solid-mixed (apple).

Bolus volume was gradually increased. Materials were dyed with blue or green colour to highlight penetrations or aspirations that were classified by PAS (see Supplementary Material). If any risk for aspiration was detected, the subsequent, larger bolus volumes were not tested.

Outcomes

The primary endpoint was the extent of penetrations or aspirations as classified by PAS[26] in a validated German translation.[34] Higher values signify larger extents of penetrations/aspirations. Physiological swallowing corresponds to a value of 1, values between 2 and 5 indicate penetrations (i.e. food components penetrating the larynx above the level of vocal folds) of increasing extents, whereas values between 6 and 8 signify aspirations below the level of vocal folds. If one consistency could not be tested or the bolus volume could not be increased due to risk of aspiration, a PAS value of 8 was assigned.

Secondary endpoints were swallowing-specific quality of life (Swallowing Quality of Life, SWAL-QOL[35,36]), recommendations for food and compensational mechanisms (Dysphagia Severity Rating Scale, DSRS[37]) and classification of residues and leaking. Residues are parts of the bolus that remain in the pharynx after swallowing and put the patient at risk of aspiration,[13] while leaking describes that solid or fluid food enter the pharynx before triggering swallowing reflex. The cranial nerves for swallowing function were evaluated by Clinical Evaluation of Swallowing (CES[38]) including oral and sensorimotor functions, for example, tongue mobility, strength of jaw muscles, velum elevation, cough and gag reflex.

In addition, the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R[39]) as the standard clinical ALS scale measuring the extent of functional impairment was used in a validated German version.[40]

Outcome parameters were collected at five timepoints: at baseline, 1 day, 4 days, 3 weeks and 3 months after treatment (see Supplementary Material).

Statistical analysis

This trial was an exploratory pilot study. The sample size was determined by practicability, that is the ability to recruit the desired number of patients in a monocentric setting within a reasonable time frame (24 months). All randomized patients were analyzed.

To assess the effect of PES on swallowing function (PAS; primary endpoint), the Mann–Whitney *U* test was used. To estimate the treatment effect, we calculated the median difference between both groups including a two-sided 95% confidence interval.

Group comparisons for continuous variables were performed using the Mann–Whitney *U* test.

Changes of continuous variables to baseline were analyzed using the Wilcoxon signed-rank test. Tolerability was analyzed descriptively by listing adverse events and serious adverse events.

Progression rate was calculated based on the following formula:

[48 – (ALSFRS-R at baseline)]/months between onset and baseline

All statistical tests were performed at a two-sided level of alpha of 0.05 and interpreted as exploratory. An adjustment for multiple testing was not done. GraphPad Prism version 8 (GraphPad Software, San Diego, California, USA) was used for statistical analysis.

Role of the funding source

This study is an investigator-initiated trial of Ulm University, with institutional support from Phagenesis® Ltd, Manchester, UK, who provided the catheters and the stimulation device for this study free of cost.

Results

Trial profile

Between March 2018 and April 2020, 20 patients were enrolled and randomly assigned to receive either PES + SLT ($n = 10$) or SLT alone ($n = 10$). The trial was conducted as per the study protocol.

In the PES group, all treatments except one were completed. One patient's general condition worsened during treatment so that the therapy had to be terminated after 1 day. However, this incident

was due to pneumonia and dislocation of the gastric tube and therefore was not associated with PES. Over the entire duration of the study, there were 6/10 dropouts in the PES group compared with only 1/10 dropout in the control group. Dropouts in both groups were mainly caused by the patients' request to not perform subsequent study visits at the hospital due to further disease progression and severe disability. Two patients in the PES group died during the study due to disease progression.

Median treatment stimulation level was 12.7 mA [interquartile range (IQR) = 7.2–18.7].

Apart from age at baseline [PES group: 76.0 years (IQR = 66.3–79.0) *versus* control group: 57.5 years (IQR = 50.3–69.3)], there were no significant differences with regard to demographic and clinical characteristics at baseline (sex, onset: spinal *versus* bulbar, disease duration, PAS, ALSFRS-R; Table 1).

Table 1. Baseline characteristics.

	PES	Control
Age (years)	76.0 (66.3–79.0)	57.5 (50.3–69.3)
Sex		
Male	5 (50%)	3 (30%)
Female	5 (50%)	7 (70%)
Onset		
Spinal	2 (20%)	2 (20%)
Bulbar	8 (80%)	8 (80%)
Disease duration (months)	14.0 (6.5–17.5)	10.0 (8.0–19.5)
PAS	4.1 (3.1–5.7)	3.5 (2.7–4.1)
ALSFRS-R	31.5 (26.3–37.0)	36.0 (29.8–44.0)
Progression rate	1.2 (0.67–2.7)	0.95 (0.44–1.7)
SWAL-QOL	125 (119–149)	151 (132–185)
PEG		
At baseline	1 (10%)	1 (10%)
During the study	4 (40%)	4 (40%)
NIV	7 (70%)	5 (50%)
Dyspnoea during daily activities	3 (30%)	1 (10%)
Dropouts	6 (60%)	1 (10%)
Patients per visit		
BL	10	10
d1	9	10
d4	9	8
w3	7	10
m3	4	9

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; BL, baseline; d1, 1 day after treatment; d4, 4 days after treatment; IQR, interquartile range; m3, 3 months after treatment; NIV, noninvasive ventilation; PAS, Penetration Aspiration Scale; PEG, percutaneous endoscopic gastrostomy; PES, pharyngeal electrical stimulation; SWAL-QOL, Swallowing Quality of Life; w3, 3 weeks after treatment.
Data are median (IQR) or *n* (%).

Primary endpoint (PAS)

Both groups combined, a significant improvement ($p = 0.003$) of the median Total-PAS was found from 3.6 (IQR = 2.9–5.0) at baseline to 2.3 (IQR = 1.8–4.0) 1 day after treatment (d1). At the follow-up visits after 4 days (d4), 3 weeks (w3) and 3 months (m3), PAS worsened again but was still significantly better at d4 ($p = 0.03$) and w3 ($p = 0.01$) compared with baseline (Figure 1).

In all, 82.4% of all patients showed an improved Total-PAS after treatment (d1) in comparison with baseline. The proportion of these patients decreased during the study to 68.8%, 66.7% and 53.8% at d4 to m3.

When analyzing each food consistency individually, improvement of PAS was most prominent in fluids (Table 2).

The change of median Total-PAS between each visit and baseline did not differ between both groups (Figure 2, Table 3).

The improvement of swallowing function in a PES patient is depicted in Figure 3.

Secondary endpoints

Similar to the primary endpoint, improvements in the total cohort but no significant differences between both study groups were found for most secondary endpoints (Table 3). Overall, we detected significant improvements of residues, DSRS score and SWAL-QOL at various timepoints during follow-up, which were generally most pronounced

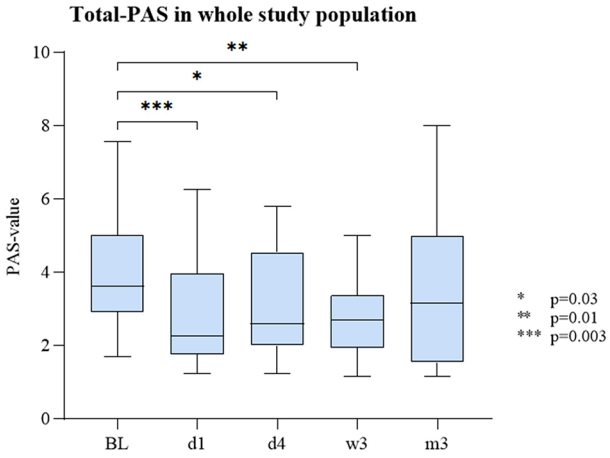

Figure 1. Total-PAS in whole study population.
BL, baseline; d1, 1 day after treatment; d4, 4 days after treatment; m3, 3 months after treatment; PAS, Penetration Aspiration Scale; w3, 3 weeks after treatment.

1 day and 4 days after treatment and tended to diminish over the following weeks thereafter.

When analyzing SWAL-QOL subscores, 70.6% of all patients showed improvements of mental state directly after the intervention (d1) (23.5% showed worse values), and 47.1% of patients had less dysphagia-related burden (29.4% worsened). Accordingly, 64.7% of patients stated to have less dysphagia-specific symptoms (35.3% stated to have more). In all, 52.9% of all patients showed improved values with regard to appetite and pleasure of eating (23.5% showed worse values). Also, 47.1% stated that they had less difficulties to select appropriate food (29.4% stated to have more difficulties), 47.1% had less fear of complications when eating (41.2% stated more fear) and 47.1% needed less time for food intake (23.5% needed more time). Regarding social participation, 35.3% of the total cohort displayed improved values at d1 compared with baseline (23.5% showed worse values).

CES showed slight improvement compared with baseline [12.0 (IQR = 10.0–13.8)]. After treatment, the score was 11.0 (IQR = 10.0–13.0, $p = 0.30$) at d1, 11.5 (IQR = 9.8–14.0, $p = 0.64$) at d4 and 11.0 (IQR = 10.5–13.0, $p = 0.75$) at w3. At m3, value was equal to baseline [12.0 (IQR = 10.3–15.8, $p = 0.18$)].

In all cohorts, ALSFRS-R remained relatively stable over the course of the study. Regarding the bulbar subscore, the change was 0.0 (−0.75 to 0.75) in the PES and 0.0 (−1.0 to 0.0) in the control group at m3, which was not significantly different ($p = 0.33$).

Adverse events

One patient reported an uncomfortable feeling in the pharynx while using noninvasive ventilation after PES. Another patient reported a mild burning pain in the nasopharynx after PES. In this patient, during FEES 1 day after treatment, an erythema was detected that diminished 4 days later (Figure 4). Both events were considered minor and did not require PES treatments to be cancelled. In the control group, no adverse events were recorded.

Discussion

Dysphagia is a burdensome symptom in ALS, which puts patients at risk of aspirations and pneumonia.[2] Furthermore, dysphagia-associated weight loss is known to be an independent, negative prognostic factor for disease progression.[7] Therefore, treatment of dysphagia plays an essential role in ALS. However, therapy options are currently limited to logopaedic therapy. Previous studies in other neurological indications had shown a positive effect of PES on dysphagia[21–23,41,42] based on the principal of cortical plasticity which suggested a potential for positive effects in ALS as well. Therefore, we explored the effect of PES on swallowing performance in a small randomized controlled pilot study in 20 patients with ALS. Patients in the PES group received PES over 3 consecutive days. In addition, patients in both groups received extensive logopaedic therapy.

This is the first study investigating the effect of PES in ALS. Strengths of this study are the randomized controlled study design, the long postinterventional observation period and the objective primary outcome parameters by means of PAS values evaluated by FEES. Main limitations are the small sample size, the rather short duration of the intervention and the open label design (no placebo/sham stimulation). Also, age of onset as a known prognostic factor was unevenly distributed between groups and may have negatively affected the outcome of the PES group compared with the younger controls.

The Total-PAS as the primary outcome parameter improved in both study groups (PES and control group) as measured directly after the completed treatment (=3 sessions of PES + SLT

Table 2. Primary and secondary endpoints in total cohort..

		BL	d1	d4	w3	m3
Primary endpoint (PAS)	Total	3.6 (2.9–5.0)	2.3 (1.8–4.0) **$p = 0.003$**	2.6 (2.0–4.6) **$p = 0.03$**	2.7 (1.9-3.4) **$p = 0.01$**	3.2 (1.5-5.0) $p = 0.52$
	Fluid	3.8 (2.6–6.1)	2.4 (1.3–3.5) **$p < 0.001$**	2.8 (1.1–3.7) **$p = 0.03$**	2.4 (1.1-2.9) **$p = 0.02$**	3.0 (1.6-4.5) $p = 0.22$
	Nectar-like	4.9 (2.8-6.3)	2.0 (1.0-4.6) **$p = 0.03$**	2.8 (1.3-4.3) **$p = 0.03$**	3.1 (1.6-4.0) $p = 0.06$	3.0 (1.6-7.0) $p = 0.60$
	Porridge	2.0 (1.5-2.4)	2.0 (1.4-2.0) $p = 0.67$	2.0 (1.5-4.6) $p = 0.29$	2.0 (1.6-2.5) $p = 0.42$	2.0 (1.0–3.3) $p = 0.16$
	Soft	2.0 (1.0-8.0)	1.5 (1.0-8.0) $p = 0.72$	1.0 (1.0–8.0) $p = 0.19$	2.0 (1.0-8.0) $p = 0.78$	1.0 (1.0-8.0) $p = 0.57$
	Solid-mixed	8.0 (1.3–8.0)	8.0 (1.8–8.0) $p = 0.80$	5.5 (1.3–8.0) $p = 0.38$	8.0 (2.0–8.0) $p = 0.88$	8.0 (1.0–8.0) $p = 0.91$
	Pill	1.0 (1.0–1.0)	1.0 (1.0–1.5) $p > 0.99$	1.0 (1.0–8.0) $p > 0.99$	1.0 (1.0–1.0) $p = 0.50$	1.0 (1.0–8.0) $p > 0.99$
Secondary endpoints	ALSFRS-R	34.0 (27.5–39.5)	Not analyzed	33.0 (30.3–40.8) $p = 0.98$	34.0 (26.3–40.5) **$p = 0.04$**	33.0 (29.0–40.5) $p = 0.14$
	SWAL-QOL	137.0 (124.5–157.5)	150.0 (129.5–162.0) $p = 0.18$	146.0 (111.0–179.0) $p = 0.64$	146.0 (111.0–164.3) $p = 0.68$	154.0 (128.0–171.0) $p = 0.72$
	DSRS	4.0 (4.0–5.0)	3.0 (3.0–4.0) **$p < 0.0001$**	3.0 (3.0–4.0) **$p = 0.002$**	3.0 (3.0–5.0) $p = 0.09$	4.0 (3.0–5.0) $p = 0.23$
	Leaking	0.4 (0.3–0.7)	0.4 (0.1–0.6) $p = 0.34$	0.4 (0.2–0.5) $p = 0.72$	0.3 (0.1–0.4) $p = 0.10$	0.2 (0.2–0.4) $p = 0.66$
	Residues	0.8 (0.5–1.3)	0.7 (0.2–1.0) $p = 0.05$	0.5 (0.2–1.0) **$p = 0.04$**	0.7 (0.3–1.1) **$p = 0.03$**	0.4 (0.2–0.8) $p = 0.06$
	CES	12.0 (10.0–13.8)	11.0 (10.0–13.0) $p = 0.30$	11.5 (9.8–14.0) $p = 0.64$	11.0 (10.5–13.0) $p = 0.75$	12.0 (10.3–15.8) $p = 0.18$
	Recommendation	3.0 (2.0–4.0)	2.0 (2.0–4.0) $p = 0.22$	2.0 (2.0–4.0) $p = 0.63$	3.0 (2.0–4.0) $p = 0.86$	3.0 (2.0–4.0) $p = 0.65$

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; BL, baseline; CES, Clinical Evaluation of Swallowing; d1, 1 day after treatment; d4, 4 days after treatment; DSRS, Dysphagia Severity Rating Scale; IQR, interquartile range; m3, 3 months after treatment; PAS, Penetration Aspiration Scale; SWAL-QOL, Swallowing Quality of Life; w3, 3 weeks after treatment. Bold values signify significant *p*-values. Data are median (IQR).

or SLT alone) which was most prominent in fluids. During the further course of the study, the Total-PAS worsened again but still remained above baseline. Accordingly, recommendation of food intake and DSRS improved suggesting that patients were able to cope with more demanding food consistencies, and compensatory mechanisms were less needed.

As there were no significant differences between both groups, the observed improvements are likely to be attributed to the extensive logopaedic therapy. It seems that PES yields no additional positive effects, although the number of participants in our study was too low in order to draw any definite conclusions.

The mechanism of PES is based on the assumption of cortical reorganization after brain damage by compensatory enlargement of the pharyngeal representation in the unaffected hemisphere,[27] which had been hypothesized to constitute a

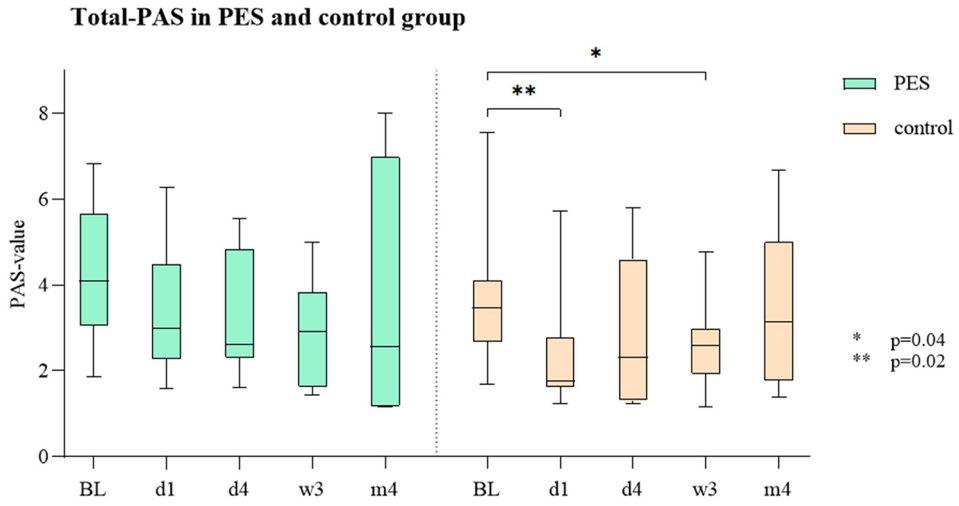

Figure 2. Total-PAS in PES and control group.
BL, baseline; d1, 1 day after treatment; d4, 4 days after treatment; m3, 3 months after treatment; PAS, Penetration Aspiration Scale; PES, pharyngeal electrical stimulation; w3, 3 weeks after treatment.

possible compensatory mechanism in ALS as well.[16] However, as opposed to stroke, neurodegeneration in ALS is a pathologic process that does not only affect a localized area but spreads over the whole nervous system.[43,44]

Brettschneider *et al.*[43] defined four stages of spreading, whereby, besides the motor cortex and the α-motor neurons in the anterior horn, the bulbar neurons in the brainstem are affected already in the first stage. Therefore, the lack of effect of PES in ALS might possibly be explained by the lack of compensatory capacity of the bulbar neurons. Accordingly, it seems that PES exclusively causes lateralization at cortical level but not in the brainstem since brainstem reflexes remain unaffected after PES.[18,27] The lack of lateralization in the brainstem could possibly be explained by the smaller number of neurons compared with the cortex. As both UMNs in the cortex and LMNs in the brainstem are affected in ALS, cortical reorganization alone may not have a sufficient impact on swallowing function. Also, atrophy of bulbar muscles may constitute a further limitation of PES in ALS. Furthermore, since patients with moderate to severe dysphagia were included in this study, it seems possible that their disease was too far advanced in order to provide sufficient capacities for cortical reorganization or that compensation mechanisms were already exhausted. Thus, it cannot be excluded that PES might be effective in earlier patients with less severe dysphagia.

The tDCS is another stimulation method based on delivering constant, low direct currents via electrodes to specific brain regions. One study found tDCS to be effective in MS patients with dysphagia and brainstem involvement[45] while most studies indicated that tDCS was likely ineffective in ALS.[46–48] Although tDCS is primarily aiming at modulating excitability of neurons as opposed to PES that primarily relies on the principle of cortical reorganization, these results demonstrate that stimulation procedures might be less effective in neurodegenerative diseases due to their underlying pathomechanisms.

Moreover, previous studies showed that PES probably mainly affects the pharyngeal phase of swallowing.[18,19] As dysphagia in ALS is additionally caused by an impaired oral phase at an early stage,[49] PES may not cause an sufficient improvement of swallowing function. Also, respiratory insufficiency must be considered as an additional complicating factor at least in a subgroup of patients which might aggravate dysphagia.

Apart from pathophysiological aspects, protocol parameters with regard to PES application such as number of treatment sessions, overall treatment duration and stimulation levels must be considered as these significantly vary between studies.[23,42,50] For example, in the MS study, 5 days of PES (as opposed to 3 days in this study) were applied,[45] and another study in stroke indicated that some patients might benefit from

Table 3. Treatment effects in PES and control group.

			d1	d4	w3	m3
Primary endpoint (PAS)	Total	PES Control PES *versus* Control	−0.8 (−1.5 to −0.3) −1.8 (−2.2 to −0.2) $p=0.32$	−0.2 (−1.9 to 0.5) −1.5 (−1.8 to −1.2) $p=0.74$	−1.1 (−2.0 to 0.5) −1.4 (−1.7 to 0.5) $p=0.69$	−0.02 (−2.0 to 2.2) −0.7 (−1.0 to 0.5) $p=0.71$
	Fluid	PES Control PES *versus* Control	−0.5 (−2.0 to 0.4) −2.5 (−3.3 to −1.0) $p=0.08$	0.0 (−1.8 to 0.3) −2.0 (−2.5 to −1.5) $p=0.24$	−0.5 (−4.7 to 0.8) −2.4 (−4.4 to −0.5) $p=0.74$	0.6 (−1.0 to 1.3) −1.5 (−2.8 to 0.5) $p=0.19$
	Nectar-like	PES Control PES *versus* Control	−0.1 (−3.2 to 0.7) −2.3 (−4.8 to −0.2) $p=0.37$	−1.8 (−4.0 to −0.5) −1.9 (−2.8 to −0.5) $p=0.75$	−1.8 (−2.5 to −0.3) −1.5 (−4.2 to 1.0) $p=0.9$	0.9 (−1.3 to 3.0) −0.8 (−3.4 to 1.0) $p=0.56$
	Porridge	PES Control PES *versus* Control	0.0 (−0.5 to −0.3) 0.0 (−0.3 to 0.0) $p=0.96$	0.0 (−0.5 to 1.0) 0.0 (0.0 to 1.0) $p=0.65$	0.0 (−0.8 to 0.6) 0.5 (−0.5 to 1.0) $p=0.54$	−0.3 (−0.9 to 2.3) 0.0 (0.0 to 1.0) $p=0.41$
	Soft	PES Control PES *versus* Control	0.0 (0.0 to 0.0) 0.0 (−0.5 to 1.5) $p=0.88$	0.0 (−1.5 to 0.0) 0.0 (−1.0 to 0.0) $p=0.86$	0.0 (−3.3 to 1.8) 0.0 (0.0 to 1.0) $p=0.27$	−2.0 (−7.0 to 7.0) 0.0 (−0.5 to 7.0) $p=0.46$
	Solid–mixed	PES Control PES *versus* Control	0.0 (0.0 to 0.5) 0.0 (−3.5 to 0.0) $p=0.08$	0.0 (0.0 to 1.5) 0.0 (−6.0 to 0.0) $p=0.15$	0.0 (0.0 to 0.0) 0.0 (−1.0 to 1.3) $p>0.99$	0.5 (−5.3 to 5.5) 0.0 (−0.5 to 2.5) $p=0.75$
	Pill	PES Control PES *versus* Control	0.0 (0.0 to 0.0) 0.0 (0.0 to 0.0) $p>0.99$	0.0 (−0.5 to 0.0) 0.0 (0.0 to 0.0) $p=0.26$	0.0 (−1.8 to 0.0) 0.0 (0.0 to 0.0) $p>0.99$	0.0 (−5.3 to 5.3) 0.0 (0.0 to 0.0) $p>0.99$
Secondary Endpoints	ALSFRS-R	PES Control PES *versus* Control	Not analyzed	0.0 (−3.0 to 2.0) 0.0 (−1.0 to 2.0) $p=0.37$	−1.5 (−6.8 to 1.5) −1.0 (−4.0 to 0.0) $p>0.99$	−0.5 (−1.0 to 1.5) −1.0 (−7.5 to 0.5) $p=0.54$
	SWAL-QOL	PES Control PES *versus* Control	9.5 (−3.8 to 24.0) −2.0 (−11.0 to 13.0) $p=0.29$	0.5 (−17.0 to 16.0) 3.0 (−17.0 to 21.0) $p=0.52$	−6.0 (−12.0 to 8.5) 0.0 (−17.0 to 11.0) $p=0.93$	4.0 (4.0 to 9.0) −4.0 (−36.0 to 3.3) $p=0.07$
	DSRS	PES Control PES *versus* Control	−1.0 (−2.0 to −0.3) −1.0 (−1.0 to −1.0) $p=0.90$	−1.0 (−1.0 to 0.0) −1.0 (−2.0 to −1.0) $p=0.09$	−0.5 (−2.0 to 0.3) 0.0 (−1.0 to 0.0) $p=0.79$	−2.0 (−2.0 to 1.0) 0.0 (−1.0 to 0.5) $p=0.46$
	Leaking	PES Control PES *versus* Control	−0.2 (−0.32 to 0.06) 0.0 (−0.16 to 0.21) $p=0.08$	−0.1 (−0.18 to −0.03) 0.06 (−0.19 to 0.42) $p=0.12$	−0.09 (−0.31 to 0.09) −0.21 (−0.25 to 0.14) $p=0.73$	−0.05 (−0.4 to 0.21) −0.02 (−0.45 to 0.16) $p=0.95$
	Residues	PES Control PES *versus* Control	0.0 (−0.57 to 0.03) −0.24 (−0.66 to 0.07) $p=0.95$	−0.15 (−0.37 to 0.19) −0.32 (−0.55 to −0.25) $p=0.09$	−0.34 (−1.1 to 0.17) −0.2 (−0.41 to 0.0) $p=0.58$	0.0 (−0.12 to 0.11) −0.51 (−0.67 to 0.01) $p=0.28$
	CES	PES Control PES *versus* Control	0.0 (−2.0 to 1.5) −1.5 (−2.0 to 0.2) $p=0.73$	1.0 (−3.0 to 4.0) 0.0 (−4.0 to 1.0) $p=0.10$	1.0 (−1.5 to 3.0) −1.0 (−1.8 to 0.8) $p=0.19$	0.5 (−1.0 to 3.5) 1.5 (0.0 to 4.0) $p=0.57$
	Recommendation	PES Control PES *versus* Control	0.0 (−1.0 to 0.0) −1.0 (−1.0 to 0.0) $p=0.65$	0.0 (−1.0 to 0.5) 0.0 (−1.0 to 0.0) $p=0.85$	0.0 (−1.0 to 0.3) 0.0 (−1.0 to 1.3) $p=0.91$	0.5 (−0.8 to 1.0) 0.0 (−1.0 to 2.0) $p=0.88$

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; CES, Clinical Evaluation of Swallowing; d1, 1 day after treatment; d4, 4 days after treatment; DSRS, Dysphagia Severity Rating Scale; IQR, interquartile range; m3, 3 months after treatment; PAS, Penetration Aspiration Scale; PES, pharyngeal electrical stimulation; SWAL-QOL, Swallowing Quality of Life; w3, 3 weeks after treatment.
Data are median (IQR).

a second treatment cycle.[23] As ALS is a neurodegenerative disease featuring continuous deterioration of swallowing and considering the limitations with regard to cortical plasticity as explained above, the long-term application of PES at certain time intervals might be necessary in order to achieve a noticeable therapeutic effect. Furthermore, interestingly, stimulation levels in this study as determined based on the individual perceptual and MTTs of each patient were lower compared with previous studies in other indications.[23,42] For ALS patients, there is

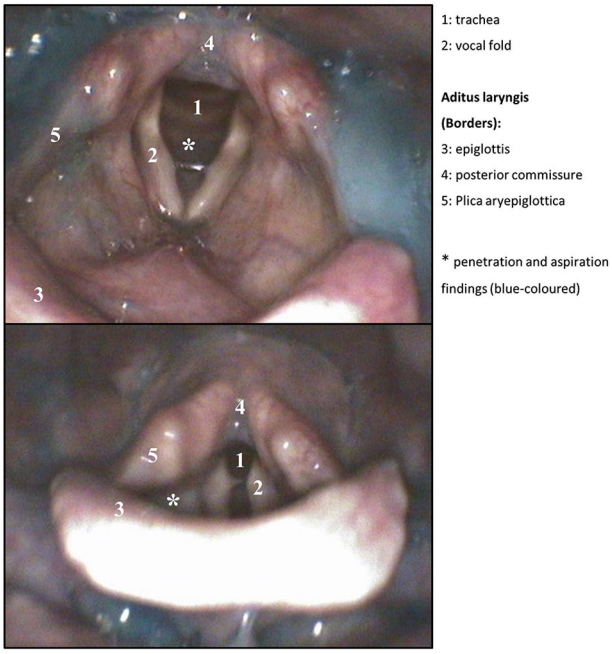

Figure 3. Swallowing function (blue-coloured water) before (BL) and after treatment (d1). The figure shows the penetration and aspiration findings evaluated by FEES in a patient receiving PES before and 1 day after completed treatment (=3 sessions of PES) during a swallowing test with a teaspoon of blue-coloured water. Above: silent aspiration (*) in the trachea (1) without ejection from the airway (PAS = 8) at baseline. Below: penetration of water (*) into the airways but remaining above the vocal folds (2) (PAS = 3) 1 day after completed treatment (=3 sessions of PES).
BL, baseline; d1, 1 day after treatment; FEES, Fiberoptic Endoscopic Evaluation of Swallowing; PAS, Penetration Aspiration Scale.

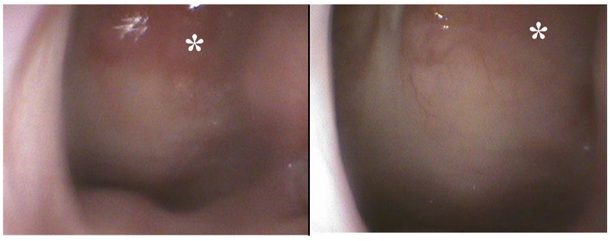

Figure 4. Erythema at the pharyngeal wall after PES. The figure shows an erythema after PES in FEES 1 day after treatment that diminished 5 days after treatment. Left: erythema (*) 1 day after intervention. Right: diminishing erythema 5 days after intervention.
FEES, Fiberoptic Endoscopic Evaluation of Swallowing; PES, pharyngeal electrical stimulation.

evidence for a disinhibition of the somatosensory cortex,[51,52] which could possibly explain a lower tolerability threshold for sensory inputs. As generally lower stimulation levels were used in this study compared with other indications, it is possible that therapeutically effective stimulation levels were not achieved.

Overall, PES was well tolerated as no serious adverse events and only two mild adverse events occurred. Therefore, as reported previously for other indications,[21–23] we confirm that PES is a well-tolerated, low-risk procedure. On the other hand, the high share of dropouts in the intervention group (60%) suggests that patients did not notice any beneficial effects which were large enough to overcome the significant burden of multiple on-site visits in a state of severe disability. However, the higher median age of patients in the PES group compared with the control group has also to be considered in this context.

On the other hand, of note, our results suggest positive effects of SLT on swallowing function of ALS patients. Evaluating individual PAS values, it is remarkable that about half of the patients were able to cope with larger bolus volumes of fluid and nectar-like consistencies after treatment. Moreover, residues as a risk factor for aspirations[13] were reduced. Also, many patients reported positive effects on dysphagia-related burden in the SWAL-QOL subscores, although this result has to be interpreted carefully due to the subjective nature of the SWAL-QOL and the fact that patients were likely sensitized with regard to dysphagia-related symptoms due to their participation in the study. Due to the underlying pathology of neurodegeneration, the positive effect of the SLT is likely based on successful implementation of compensational mechanisms rather than regeneration of damaged structures. As swallowing-specific quality of life improved after treatment in both study groups, the results of this study highlight the importance of SLT as a symptomatic therapy in ALS. This observation is in accordance with previous studies that showed that severity of dysphagia is directly related with life quality.[53–56] However, since this study was not placebo-controlled, a placebo effect cannot be ruled out completely.

In conclusion, a positive effect of PES in ALS could not be demonstrated, although PES emerged as a safe and relatively easy-to-use therapy. Further studies would be useful to explore whether modified treatment schemes might constitute an effective therapy for ALS.

Importantly, our results further suggest that SLT according to the protocol applied in this study might yield at least short-term positive effects on swallowing performance. Currently, there are no standardized recommendations for SLT in ALS

patients with dysphagia. Our results highlight the importance of further exploring the effect of specific SLT protocols on swallowing function in ALS by means of randomized controlled trials.

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Christine Herrmann: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Writing – original draft; Writing – review & editing.

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Ethical approval and consent to participate

The study was approved by the Independent Ethics Committee of Ulm University, Germany (approval number 169/17). All study patients provided written informed consent.

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Supplemental material

Supplemental material for this article is available online.

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