PHAryngeal electrical STimulation for early decannulation in TRACheotomised stroke patients with neurogenic dysphagia (PHAST-TRAC): a prospective randomised single-blinded trial

Rainer Dziewas, MD[1], Rebecca Stellato, MSc[2], Ingeborg van der Tweel, PhD[2], Ernst Walther, MD[3], Cornelius J. Werner, MD[4], Tobias Braun, MD[5], Giuseppe Citerio, MD[6], Mitja Jandl, MD[7], Michael Friedrichs, MD[8], Katja Nötzel, MD[9], Milan R. Vosko, MD[10], Satish Mistry, PhD[11], Shaheen Hamdy, PhD[12], Susan McGowan, MSc[13], Tobias Warnecke, MD[1], Paul Zwittag, MD[14], Philip M Bath, FMedSci[15], on behalf of the PHAST-TRAC Investigators

1 Department of Neurology, University Hospital Münster, Münster, Germany (Prof. Rainer Dziewas, MD, Prof. Tobias Warnecke, MD)

2 Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands (Rebecca Stellato, MSc, Prof. Ingeborg van der Tweel, PhD)

3 Zentrum für Neurologie und Neurorehabilitation, Schön Klinik Hamburg Eilbek, Hamburg, Germany (Ernst Walther, MD)

4 Section “Interdisciplinary Geriatrics”, Department of Neurology, University Hospital RWTH Aachen University, Aachen, Germany (Cornelius J. Werner, MD)

5 Neurologische Klinik, Universitätsklinikum Gießen und Marburg GmbH, Gießen, Germany (Tobias Braun, MD)

6 School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; Neurointensive Care, San Gerardo Hospital, ASST-Monza, Italy (Prof. Giuseppe Citerio, MD)

7 Isar-Amper-Klinikum, Klinikum München Ost, Haar, Germany (Mitja Jandl, MD)

8 Median Klinik Berlin Kladow, Berlin, Germany (Michael Friedrichs, MD)

9 Neurologie, Vivantes Klinikum Neukölln, Berlin, Germany (Katja Nötzel, MD)

10 Klinik für Neurologie 2, Kepler Universitäts Klinikum, Linz, Austria (Milan R. Vosko, MD)

11 Department for Clinical Research, Phagenesis Limited, Manchester, United Kingdom (Satish Mistry, PhD)

12 Centre for Gastrointestinal Sciences, Faculty of Biology, Medicine and Health, University of Manchester and the Manchester Academic Health Sciences Centre (MAHSC), United Kingdom (Prof. Shaheen Hamdy, PhD)

13 National Hospital for Neurology & Neurosurgery, Therapy & Rehabilitation Services London, United Kingdom (Susan McGowan, MSc)

14 Klinik für Hals-, Nasen- und Ohrenheilkunde, Kepler Universitäts Klinikum, Linz, Austria (Prof. Paul Zwittag, MD)

15 Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham NG5 1PB, United Kingdom (Prof. Philip M Bath, FMedSci)

ABSTRACT

Background

Dysphagia after stroke is common, especially in severely affected, tracheotomised patients. In a pilot trial, pharyngeal electrical stimulation (PES) improved swallowing function in this group of patients. The PHAryngeal electrical STimulation for early decannulation in TRACheotomised stroke patients with neurogenic dysphagia trial (PHAST-TRAC) was designed to replicate and extend this single-centre experience.

Methods

Patients with recent stroke who required tracheotomy were randomised to receive three days of PES or sham. All patients had the stimulation catheter inserted; sham treatment was applied by connecting the base station to a simulator box instead of the catheter. Randomisation was done via a computerised interactive system with randomisation (stratified by site) in blocks of 4 patients per site. Patients and investigators applying PES were not masked. The primary-endpoint was assessed blinded to treatment assignment by a separate investigator at each site. The primary outcome was readiness for decannulation 24-72 hours post-treatment, assessed using fiberoptic endoscopic evaluation of swallowing and based on a standardised protocol including absence of massive saliva, presence of spontaneous swallows and laryngeal sensation. We planned a sequential statistical analysis of superiority for the primary endpoint. Interim analyses were to be performed after primary outcome data were available for 50 patients (futility), 70 patients, and every additional 10 patients thereafter up to 140. Analysis was by intention-to-treat. The trial was registered as ISRCTN18137204.

Findings

From 29th May 2015 to 5th July 2017, 69 patients (PES 35, sham 34) from 9 sites (7 acute care hospitals, 2 rehabilitation facilities) in Germany, Austria and Italy were included: PES group mean age 61.7 (SD 13.0) years, 8 (23%) patients with haemorrhagic stroke, median time onset to randomisation 28.0 [IQR 20, 49] days; sham group age 66.8 (10.3) years, 12 (35%) patients with haemorrhagic stroke, onset to randomisation 28.0 [18, 40] days). The Independent Data & Safety Monitoring Board recommended to stop the trial early for efficacy after 70 patients had been recruited and primary endpoint data of 69 patients were available. This decision was approved by the steering committee. PES was associated with more patients being ready for decannulation as compared to sham: 17 (49%) vs. 3 (9%), odds ratio (OR) 7.00 (2.41-19.88), p=0.00082). No patient required recannulation within 48 hours or during their documented follow-up period up to 30 days or hospital discharge. Adverse

events (AEs) were reported in 24 patients (69%) of the PES group and 24 patients (71%) of the sham group. The number of patients with at least one serious adverse event (SAE) did not differ between the groups: 10 (29%) vs. 8 (23%), OR 1.3 (0.44-3.83), p=0.7851). 7 patients (20%) from the PES group and 3 patients (9%) from the sham group died during the study period. None of the patient deaths or SAEs reported were judged to be PES-treatment- or investigational device-related.

Interpretation

PES increased the proportion of patients with stroke and subsequent tracheotomy who were ready for decannulation in this study population, many of whom received PES within a month of their stroke. Future trials should confirm whether PES is beneficial in tracheostomised patients who receive stimulation similarly early after stroke and explore its effects in other cohorts.

Funding

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for manuscripts pubished in English from inception until the 16th May 2018 with the terms “stroke” and “dysphagia” in combination with “treatment”, “stimulation”, “therapy”, “rehabilitation”, “tracheotomy”, “tracheostomy” or “decannulation”. Reference lists from identified reviews and trial publications were also checked for additional trials. We identified 4 randomised-controlled trials (RCT) and one meta-analysis where pharyngeal electrical stimulation (PES) was delivered in non-ventilated stroke patients with heterogeneous results. However, there was one single-centre pilot RCT recruiting specifically tracheotomised stroke patients, which had previously been conducted by the leading study site of the PHAST-TRAC trial. These patients could not be decannulated after successful weaning from the respirator because of severe and persistent post stroke dysphagia (PSD). PES was significantly associated with improvement of airway protection and remission of dysphagia.

Overall, PSD remains one of the most debilitating complications for stroke victims in both the hospital and community healthcare settings conferring a significant comorbidity with a 6-times increased risk of aspiration pneumonia and a 3-times increased mortality. This is brought all the more into focus as there remains little or no hope of life changing treatments for these patients and specifically the Cochrane Database for Therapies in Dysphagia after Stroke, reported little evidence for any treatments being effective in this disorder.

Added value of this study

In the present study, PHAryngeal electrical STimulation for early decannulation in TRACheotomised stroke patients with neurogenic dysphagia (PHAST-TRAC), a multicentre randomised sham-controlled trial of severely dysphagic, tracheotomised stroke patients, PES allowed investigators to designate 17 of 35 (49%) patients as ready for decannulation in comparison with 3 of 34 (9%) in the control group (primary endpoint). A prespecified subgroup-analysis revealed that response to PES-treatment related to a shorter time from stroke onset to randomisation, and shorter period on mechanical ventilation. With regards to secondary outcomes, following both the randomised and open-label phases of the study, 37 of 65 (57%) patients who received PES were ready for decannulation. Patients responding to PES (ready for decannulation) were discharged from hospital significantly earlier than non-responders (not ready for decannulation). In 4 of 15 (27%) patients, not responding to a treatment cycle of PES (10 minutes per day for three consecutive days), a second treatment cycle proved to be effective. A summary post-hoc meta-analysis of results from PHAST-TRAC and the previous pilot-trial in the same population and with the same outcome

measure showed that treatment effects were similar and that PES was associated with a >10-times chance of decannulation as compared to sham.

Implications of all the available evidence

This study provides evidence that PES is effective in promoting earlier decannulation in tracheotomised stroke patients with PSD. The size of the difference between active and control groups could constitute a significant change to current approaches in the ability for clinicians to treat these patients, where at present there is no recognised treatment option available. However, due to the small sample size and differences in treatment effects in subgroups, further trials are needed to corroborate these encouraging findings.

INTRODUCTION

Post-stroke dysphagia (PSD) is a common complication of acute stroke affecting up to 80% of patients, and 11-50% even at 6 months.[1-3] PSD interferes with oral feeding and is associated with dehydration, malnutrition, aspiration pneumonia, prolonged hospital stay, poor long-term outcome and increased mortality.[4-6] Around 1-2% of all stroke patients, and 25% of stroke patients treated on the intensive care unit (ICU), require a tracheotomy[7-10] due to severe dysphagia with prolonged insufficient airway protection, or the need for long-term ventilation.[11,12] Despite the clinical benefits provided by tracheotomy during the acute stage of the illness,[12] the continuing presence of the cannula once the patient has been successfully weaned from the respirator has negative consequences for timely rehabilitation, patient comfort, days of hospitalisation[10], hospital re-admission-rates,[13] and the financial costs of care.[13,14] Further, the presence of a tracheotomy tube at discharge from the ICU is predictive of poorer outcome, in part because of cannula-related complications.[15,16] In stroke patients, severe dysphagia with related insufficient airway protection is often the main reason why decannulation cannot be performed even three months post stroke.[12,17]

Currently, treatment options for accelerating decannulation are very limited.[1] Pharyngeal electrical stimulation (PES) is a novel technique shown to enhance reorganisation of the swallow-related motor-cortex, facilitate activation of cortico-bulbar pathways, and increases salivary substance P levels, a swallow-related neurotransmitter.[18-20] Studies using PES to treat PSD in unselected stroke patients showed heterogeneous results.[21-23] However, in a single-centre, randomised controlled pilot study recruiting 30 tracheotomised acute stroke patients, dysphagia improved enabling decannulation in 15/20 (75%) patients of the treatment group, whereas only 2/10 (20%) of control patients showed spontaneous remission of PSD sufficient enough to allow for subsequent removal of the tracheal cannula.[24] The PHAryngeal electrical STimulation for early decannulation in TRACheotomised stroke patients with neurogenic dysphagia trial (PHAST-TRAC) was designed to replicate, validate, and extend this single-centre experience to a larger phase III design.[25]

METHODS

Study Design and Participants

PHAST-TRAC was an international, prospective, randomised-controlled, single-blind trial with sequential design and analysis using a triangular test.[26] The study included a second part where non-responding patients in either randomised group were given open-label treatment. The study protocol was approved by all relevant national competent authorities (Bundesinstitut für Arzneimittel und Medizinprodukte of Germany, Agentur für Gesundheit und Ernährungssicherheit GmbH of Austria, Ministero della Salute of Italy) and local ethics committees for the participating sites, and all patients or their legal representative provided written informed consent. Patients were enrolled across 9 centres (7 acute care hospitals, 2 rehabilitation facilities) in Germany, Austria and Italy. Details on the study protocol have been published previously.[25] The study was sponsored by Phagenesis Ltd., Manchester, UK. A steering committee was responsible for the design, conduct, and reporting of the study. Interim-analyses were reviewed by an Independent Data and Safety Monitoring Board (IDSMB) after randomisation of 50 and 70 patients, respectively. Pre-specified stopping rules are given below (statistical analysis). The trial was registered as ISRCTN18137204 (http://www.isrctn.com). The study protocol and the statistical analysis plan is available at: http://www.phagenesis.com/wp-content/uploads/2018/04/PHAST-TRAC_Studyprotocol_AnalysisPlan.pdf. The authors will share a subset of anonymised individual patient data with the international VISTA Rehabilitation Collaboration (http://www.vista.gla.ac.uk).

Patient Population

Patients were eligible for study participation if they were over 18 years of age, had presented with a supratentorial stroke (haemorrhagic or ischemic), were mechanically ventilated for at least 48 hours post-stroke, were successfully weaned from mechanical ventilation but remained tracheotomised, had been free of sedation for at least 3 days at the time of first decannulation screening, scored ≥-1 points on the Richmond Agitation and Sedation Scale (RASS),[27] and could not be decannulated due to severe dysphagia. After signing the informed consent form, patients' readiness for decannulation was assessed twice over 24-72 hours and a minimum 10 days after the stroke using fiberoptic endoscopic evaluation of swallowing (FEES). The presence of massive pooling of saliva, limited spontaneous swallows (<1/minute), and/or no sensation elicited by endoscope contact with the laryngeal vestibule (for details of the algorithm see Figure S1 in the Supplementary Appendix) meant that patients were not ready for decannulation.[28] Key exclusion criteria were infratentorial stroke, pre-existing dysphagia, pre-existing disease that typically causes dysphagia (for

example Parkinson's disease, motor neuron disorders), participation in any other study potentially influencing the outcome of PES, presence of a cardiac pacemaker or an implantable defibrillator, nasal deformity or previous oesophageal surgery or any other circumstance where placement of a standard nasogastric tube would be deemed unsafe, need for high levels of oxygen supply (>2 l/min), required emergency treatment, or had less than three months life expectancy (for a complete list of in- and exclusion criteria see Table S1 in the Supplementary Appendix).

Randomisation and masking

Patients were randomised to PES or sham 1:1 via a computerised interactive wireless randomisation system (IWRS) that applied randomisation stratified by study site in blocks of 4 patients per centre. At each trial site, the randomisation procedure was obtained from the IWRS by a dedicated group of investigators responsible only for treatment application. All other investigators and healthcare workers not involved in treatment were blinded. Conversely, treating investigators were not involved in any outcome assessment or any other study-related activities such as patient recruitment or dysphagia assessment prior to or after randomisation. As with many device studies, blinding patients could not be guaranteed because they could, in principle, feel whether PES was applied or not. In all other aspects, PES and sham condition were kept as similar as possible. PES or sham stimulation had to be commenced within 24 hours of randomisation.

Procedures

For the study intervention (PES), a commercial device (Phagenyx®, Phagenesis Ltd, Manchester UK), which comprises a nasogastric feeding catheter housing stimulation ring-electrodes, and a computerised base station that delivers stimulation in the range 1-50 mA at 5Hz was used. In all patients the stimulation catheter was placed prior to randomisation. The catheter was inserted via the nose to an aboral depth related to the patient's height so that the pair of treatment ring electrodes located on the outer surface of the catheter were adjacent to the pharynx. A coloured zone on the outer catheter surface and visible at the nares also aided correct placement and easy confirmation of correct electrode depth. Duration of catheter insertion procedure (minutes), ease of catheter insertion (rated on a scale of 1-very difficult to 7-very easy), and electrode depth from nostrils (cm) were captured.

In all patients, (active) PES or sham stimulation was given on three consecutive days for 10 minutes. The current intensity (mA) at which PES-treatment was delivered was individually adjusted and optimised at every session by the healthcare worker interacting the with the

base station's touchscreen in response to patient responses. This treatment optimisation procedure involved increasing the current intensity incrementally from 1 mA to detect the perceptual threshold (PT – patient first aware of stimulation) and then maximum tolerated threshold (MTT – patient no longer wants current increased further) intensity levels three times each respectively. Thereafter, the optimal treatment intensity was automatically calculated by the base station using the average values of three trials according to the formula PT + 0.75 x (MTT - PT).[21]

In the sham group, the optimisation procedure was imitated as closely as possible to mitigate any bias or effect of time spent interacting with the patient during (real) PES but no current was applied. To this end, in sham patients, the base station was connected to a small patient simulator box instead of the stimulation catheter placed in the patient. The patient simulator box allowed the treating investigator to interact with the base station as if the stimulation catheter were connected and a real stimulation was about to be delivered. Moreover, in both treatment groups (PES and sham), the connecting ends of the stimulation catheter, base station and patient simulator were hidden inside a disposable "blinding pouch" to further reduce the risk of bias or unblinding (Figure S2 in the Supplementary Appendix illustrates the setup for the PES and sham treatments). Following the treatment optimisation procedure, the treating investigator then delivered 10 minutes of PES or sham stimulation.

Following randomised treatment, the primary outcome was assessed at 24-72 hours after the last stimulation. All patients who had not responded (i.e. showing persistent dysphagia requiring the tracheal cannula to be left *in situ* with the tracheal cuff inflated), irrespective of treatment assignment, were offered open-label treatment with PES. 24-72 hours after the last open-label PES-treatment, outcome was again assessed using the same FEES-based decannulation algorithm.

Outcomes

The primary endpoint of the study was readiness for decannulation after 3 days of PES-treatment, assessed as described above using the FEES-based algorithm.[28] Readiness for decannulation could be clinically followed by either immediate removal of the tracheal tube or cuff deflation (planned analysis). The primary-endpoint assessment was performed blinded to treatment assignment by a separate investigator at each site. Investigators from all sites being responsible for outcome assessment were trained in using this algorithm. In addition, to ensure that the decannulation procedure was correctly applied at the study sites, all FEES-videos of the primary endpoint assessment were anonymised and adjudicated by an independent FEES-Review-Board (SMG, TW, PZ) not involved in any other study-related

activity. Results of the board's rating were used in post-hoc analyses and not communicated with the sites during the conduct of the trial.

Secondary endpoints were treatment effect in delayed and retreated patients, necessity of recannulations (at day 2 and during follow-up of 30 days or until discharge, whichever is first), PES treatment parameters, dysphagia scores (dysphagia severity rating scale (DSRS); functional oral intake scale (FOIS), Table S2 and S3 in the Supplementary Appendix), severity of stroke (modified Rankin Scale and National Institutes of Health Stroke Scale scores) (at day 2, during follow-up of 30 days or until discharge, whichever was first), length of stay on different levels of care, Speech and Language Therapy (SLT) management plan, number and type of adverse events (AEs), including adverse device events (ADEs).[22,29]

For post-hoc analysis, the binary FEES-score (primary endpoint ratings from the local investigators and independent FEES review board) was transformed in to an ordered categorical outcome ranging from 0 (none of the three items present) to 3 (all three items present).

Statistical analysis

Group sequential monitoring of cumulative data was performed using a triangular test.[26] The maximum number of patients, where the upper and lower decision boundaries met, was set at 140 with the aim of being able to detect an absolute difference between the groups of 25% assuming that the control rate would be 20%, overall type I error of 0.05, and power 0.80 (the 90th percentile of the required sample size was estimated to be 126 patients). Interim analyses were to be performed after primary outcome data were available for 50 (futility) and then at 70 and for every additional 10 patients thereafter up to 140. Decision rules allowed.[25]

1. Stopping the trial for futility, i.e. where the difference between treatment groups was very unlikely to equal or exceed 25%, at 50 patients;

2. Stopping the trial for superiority of PES treatment, i.e. readiness for decannulation is more common with PES and equals or exceeds an absolute difference between groups of 25%, at 70, 80, 90, 100, 110, 120, 130 and 140 patients.

Patients who did not reach a primary outcome were considered not ready for decannulation. For sensitivity purposes, the heterogeneity of the treatment effect on the primary outcome was assessed in pre-specified subgroups (age, sex, stroke type, time from onset to randomisation, duration of mechanical ventilation, baseline stroke severity, and stimulation intensity) by adding an interaction term and using exact inference for logistic regression (LogXact11,Cytel Inc., Cambridge, USA).[30]

Other outcomes were analysed using Fisher's exact test for binary data, Mann-Whitney-U test for ordinal data, and Student's t test (pooled) for continuous data. Regressions were performed using binary logistic regression, Cox regression and multiple linear regression. Kaplan-Meier analysis was used on length of stay data. Data are shown as number (%), median (interquartile range, IQR), mean (standard deviation, SD) and either mean difference (MD), hazard ratio (HR), odds ratio (OR) with 95%-confidence-intervals (CI). The nominal level of significance for all analyses, including interaction testing, was $p<0.05$. No adjustment was made for multiplicity of testing for secondary analyses, and all analyses were by intention to treat. Statistical analyses were performed by the University of Utrecht (RS and IvdT) (sequential analysis of the primary endpoint using PEST 4.4)[31] and Cytel Inc. (all other analyses using R-project software, version R-3.4.1).[32]

Role of the funding source

The study was sponsored and funded by Phagenesis Ltd. (Manchester, UK). A scientific design committee (RD, IvdT, SM, SH and PB) was responsible for the design of the study. A steering committee (PMB (chair) and RD) was responsible for the conduct and reporting of the study and interpretation of the results. The study was managed by a Clinical Research Organisation (FAKKEL, Belgium, for further details see Supplementary Appendix) that also verified the accuracy of all collected data. The sponsor was involved in the design of the study; compensated sites for data collection, the Clinical Research Organisation (FAKKEL) for study management and source data verification, University Medical Centre Utrecht (The Netherlands) and Cytel Inc. (Cambridge, USA) for data analysis and contributed to the data interpretation and the writing of the manuscript. Interim-analyses were reviewed by an Independent Data and Safety Monitoring Board (IDSMB) without involvement of the sponsor or the steering committee after 50 and 70 patients had been recruited. The steering committee and all other authors had full access to all data. The corresponding author had final responsibility for the decision to submit for publication.

RESULTS

The study was conducted between 29th May 2015 and 5th July 2017. Figure 1 shows the CONSORT diagram with the flow of patients through the randomised and open-label parts of the study. The stimulation catheter could not be placed in one patient and therefore 69 of the 70 successfully screened patients underwent randomisation. A total of 35 patients were assigned to receive early PES and 34 to receive sham stimulation during the blinded study phase. Sequential analysis after 50 patients demonstrated no futility. After 70 patients had

been recruited, sequential analysis indicated superiority in favour of PES treatment (Figure S3 in the Supplementary Appendix) such that the IDSMB recommended that the trial should stop. The one patient in whom the stimulation catheter could not be placed and who was not randomised was initially adjudicated as a treatment failure and only later when this mistake was detected, was removed from the intention to treat population. The steering committee reviewed the same data and IDSMB advice to stop and agreed with the decision (see table S4 in the Supplementary Appendix).

25 (36%) patients were women and the mean age was 64 (SD 12) years. 49 (71%) patients had an ischemic stroke, and 20 (29%) an intracerebral haemorrhage. The mean NIHSS was 17.5 (SD 4.6), and patients were randomised at a median of 28 [IQR 19, 41] days after ictus and following 15 [IQR 9, 22] days of mechanical ventilation (Table 1).

17 of 35 patients (49%) in the PES group and 3 of 34 patients (9%) in the sham group were judged to be ready for decannulation after the blinded first part of the study (OR 7.00, 95% CI 2.41-19.88, p=0.00082; Table 2). In predefined subgroups, significant treatment-by-subgroup interactions were present, these favouring treatment in patients treated earlier after stroke, or with a shorter duration of mechanical ventilation (Figure 2). Following the decision to decannulate, 14 of 17 patients in the PES group were decannulated and the cuff was permanently deflated in 3 (Table 2). No patients who had decannulation performed required re-cannulation over the next 48 hours, or during their documented follow-up period up to hospital discharge. The decannulation assessment occurred mainly 24-48 hrs after the third day of treatment/sham (N=21 in sham, 24 in treatment arm); the remaining were assessed in the time window 48-72 hrs (N=13 in sham,10 in treatment arm).

15 of the 35 patients (43%) from the early treatment group received a second (retreat) cycle of PES during the unblinded study phase, with one patient (3%) withdrawing; subsequently, four of the 15 retreated patients (27%) were judged to be ready for decannulation. 30 patients from the sham group received a first (delayed) cycle of PES during the unblinded second part of the study; with a further one (3%) withdrawn due to identification of a bleeding gastric ulcer precluding catheter insertion. 16 (53%) of these patients were judged to be ready for decannulation after three days of PES (Table 2, subheading “open label (Part 2) of the study”). Taking account of both the randomised and open-label components of the study, and following at least one course of PES, a total of 57% (37 of 65) patients became ready for decannulation 24-72 hrs after PES. Clinical dysphagia scores (DSRS, FOIS) did not differ between the treatment groups (Table 2),

During the randomised part of the study, mean PES stimulation intensity and threshold were 33.6 mA (SD 8.3) and 15.2 mA (SD 9.3) respectively (Table S5 in the Supplementary Appendix).

The average time needed for the initial catheter-insertion was 8.7 min (median 6.4, range 2-30 min), and 70% (44/63) of users judged this procedure to be very easy (score of 6 or 7 on the rating score; Figure S4 in the Supplementary Appendix). The stimulation catheter could not be inserted in two patients (one prior to randomisation, one prior to the second treatment phase).

While at baseline and directly after study intervention the majority of patients needed to be treated on the intensive or intermediate care unit, during follow-up, level of care decreased in most of the patients, without any difference between PES- and sham-group (Table 2).

During the follow-up period, only 20 SLT reports from 9 patients and 2 centres were obtained. These reports documented a gradual improvement over time in 5 patients, while in 4 patients no oral intake was possible. Since these data did not add information to the documented dysphagia scores they have not been analysed or presented in detail.

Seven patients in the PES-group, three patients in the sham-group and one patient prior to randomisation died during the study (Table 3). Seven of these occurred >30 days after randomisation. None of the deaths having been judged to be PES-treatment or investigational device- (base station and catheter) related by the IDSMB. The number of patients with at least one serious adverse event (SAE) did not differ between the treatment groups (PES=10 (29%) vs. sham=8 (23%), OR 1.3 (0.44-3.83) p=0.7851). No SAEs occurred during the second treatment phase of 15 patients who had also received PES during the first part of the trial (retreat patients); no serious adverse PES-treatment or investigational device-related events (SADEs) were observed in the entire study (Table 3). A total of 12 non-serious device-related adverse events (ADEs) were observed in eight different patients (Table 3). Most notably, in three patients, technical problems with the stimulation device occurred that were later resolved. Additionally, in one patient the stimulation catheter could not be placed and another one did not tolerate 10 minutes of PES. Finally, one patient experienced discomfort during stimulation and removed his stimulation catheter prematurely (for further details with regards to SAEs, device-related AEs and AEs please refer to tables S6, S7a, S7b and S8 respectively in the Supplementary Appendix).

Post-hoc, treatment responders (patients deemed ready for decannulation) and non-responders (patients deemed not ready for decannulation) were compared for different outcomes. As shown in Table S9 (Supplementary Appendix), there was a significant difference in dysphagia scores between these groups favouring treatment-responders both at discharge and 90-day-follow-up. Similarly, treatment responders were discharged significantly earlier than treatment non-responders (median LOS after PES was 14 days [95% CI 12-15] in responders vs. 36 days [95% CI 16-102] in non-responders, p=0.0006) (Figure S5). Finally, when analysing stimulation intensities, patients who responded to PES

had lower PES-threshold levels (12.1 vs. 18.5 mA) and a trend to both lower PES-tolerance levels (37.0 vs. 42.3 mA) as well as to lower PES-stimulation-intensities (31.2 vs. 36.0 mA) than those who did not respond (Table S10 in the Supplementary Appendix).

To address the issue of blinding at the study sites, a first post-hoc analysis was conducted that re-analysed study outcome based on the findings of the independent FEES-Review-Board. Here, PES was also associated with an increased proportion of patients who were ready for decannulation (10 (29%) in the PES group vs. 2 (6%) in the sham group (OR 6.40, 95%-CI 1.28-31.88; p=0.0234; Table S11 in the Supplementary Appendix), although the treatment effect was smaller.

A second post-hoc analysis was run to evaluate in more detail differences in swallowing function between the PES and sham group and to account for differences in patient recruitment (both in numbers and clinical characteristics) across study sites. As is shown in Figure S6 (Supplementary Appendix), PES was associated with a shift to fewer FEES markers of dysphagia (median difference -1.0, 95% CI -2.0, 0.0, p=0180), while the proportion of patients with worst scores were similar between groups (10 patients (29%) in the PES and 9 (31%) in the sham group). As shown in Table S12 (Supplementary Appendix), patients from the study site with highest recruitment differed from other sites with less severe stroke (NIHSS 16.3 (SD 3.9) vs. 19.3 (SD 5.1), p=0.0017) and shorter times for onset to randomisation (median 23.50 [IQR 18.75-28.25] vs. median 53 [IQR 30-66], p<0.0001) and time on ventilator (mean 10.9 (SD 4.7) vs. mean 33.2 (SD 23.4)), p<0.0001). A multiple variable model predicting response, and comprising PES, age, onset-to-randomisation (OTR), duration of ventilation, NIHSS, and recruitment site (Münster) found that only PES and OTR were significantly related to outcome (PES, p=0.0066; OTR, p=0.0361 (Table S13 in the Supplementary Appendix).

Meta-analysis

An electronic search for similar trials was performed in PubMed, with the terms “stroke” and “dysphagia” in combination with “treatment”, “stimulation”, “therapy”, “rehabilitation”, “tracheotomy”, “tracheostomy” or “decannulation” from inception to May 16th 2018. Only trials that used PES in tracheotomised stroke patients were selected. A post-hoc summary meta-analysis of results from the randomised part of PHAST-TRAC and the only other related trial conducted by the leading study site in the same population and using the same outcome measure[24] showed that treatment effects were similar between these two trials and that PES was associated with a >10 fold chance of decannulation as compared to sham (Figure S7 in the Supplementary Appendix).

DISCUSSION

In this multicentre randomised sham-controlled trial of severely dysphagic tracheotomised stroke patients, PES allowed investigators to rate 49% (17/35) patients as ready for decannulation in comparison with 9% (3/34) in the control group. Response to treatment appeared to be related to a shorter time from stroke onset to randomisation, and shorter period on mechanical ventilation. Following both the randomised and open-label parts, more than 55% (37/65) of patients who received PES were ready for decannulation and patients responding to PES were discharged from hospital significantly earlier than non-responders.

The effect size of PES in this study was in keeping with that of an earlier single-centre pilot trial,[24] as summarised in the meta-analysis. Similarly, the low rate of spontaneous recovery in the control group is compatible with the "Decannulation and Functional Outcome After Tracheostomy in Patients with Severe Stroke" (DECAST) cohort study, where only 26% (14/53) of tracheotomised stroke patients could be decannulated within 3 months of stroke.[17]

The relationship between treatment efficacy and short times to treatment is presumably related to the development of critical illness dysphagia due to critical illness polyneuropathy and myopathy in patients with prolonged ICU treatment and mechanical ventilation.[33,34] Apart from stroke-related impairment of the central swallowing network, polyneuropathy and myopathy will damage swallowing related cranial nerves and muscles, respectively. Further, PES is critically dependent on intact laryngeal and pharyngeal sensory afferent pathways, so that severe polyneuropathy may interfere with its known effect on brain plasticity. Although the present study did not include neurophysiological evaluations, the higher sensory thresholds observed in patients who were not deemed ready for decannulation as compared to successfully treated ones, supports the notion of impaired sensory feedback as an important reason for treatment failure.

Another key finding of this trial was that a second cycle of PES proved to be effective in approximately 25% (4/15) of patients still requiring a tracheal cannula after having received PES. This result is in line with a recent open-label cohort study[35] and suggests that patients who do not respond to one cycle (three days) of treatment should be treated with a second.

Apart from confirming the present results, future trials should therefore particularly focus on the substantially more difficult to treat group of tracheotomised stroke patients with longer times from stroke-onset (>>28 days) and longer times of preceding mechanical ventilation (>>15 days). These trials should allow for the possibility of repetitive PES and, ideally, determine potential biomarkers of treatment success.

The positive results of the present study are clearly different from that of the STEPS trial, where PES, applied according to the same treatment paradigm, did not improve swallowing safety (primary endpoint) or clinical dysphagia scores (secondary endpoints) in a cohort of

126 non-ventilated stroke patients.[21] Although, based on the data available, no firm conclusions with regards to the reasons for these discrepant findings can be drawn, some key differences between both trials might help in providing some tentative explanations. First, STEPS recruited less severely affected stroke patients (mean NIH of below 10, as compared to 17.5 in PHAST-TRAC) and many were on a partial oral diet at study inclusion. Second, in STEPS the median OTR time was 11 days as compared to 28 days in PHAST-TRAC, which suggests that spontaneous recovery of PSD might have been more prevalent in STEPS than in PHAST-TRAC. Last, stimulation intensities were different with a mean of 14.5 mA in STEPS compared to 33.6 mA in PHAST-TRAC, which suggests that PES may have been given at a more effective dose in PHAST-TRAC.

The strength of this phase III trial is its multicentre sham-controlled design in a well-defined group of stroke patients and consistent results across the blind and open-label parts of the study. However, some limitations are apparent. First, the trial, whilst being the largest study of PES in this cohort of patients, was still small, reflecting the adaptive design which led to a reduction in sample size. Nevertheless, the findings have robust confidence intervals and are consistent both internally and externally. Second, PES was delivered in a single-blind fashion with the person providing PES being unblinded. Since both treatment and endpoint assessments were done locally at the sites, this might have introduced a bias, although endpoint assessors were blinded for patients' randomisation. To address this concern prospectively, an independent review board blinded to recruitment site and treatment assignment, re-evaluated videos from the primary outcome FEES examination, and their results are compatible with the findings of investigators. Third, the primary outcome was assessed a few days after the end of treatment after which open-label treatment was offered to all patients who did not reach the primary outcome, irrespective of their treatment group. As a result, the effect of randomised treatment on long term outcomes was not possible. Nevertheless, 20 patients benefitted from this additional opportunity for active treatment. Fourth, the mean age of the sham group was numerically higher than that of the treatment group which might have had a negative impact of the recovery rate in the first group. However, since the subgroup analysis did not show an interaction of age and PES, this baseline difference may not have impacted on the result. Last, the majority of patients were recruited from one site and their experience and treatment delivery approach may underpin the primary outcome result. Therefore, a replication of findings, preferentially in a larger trial, would seem desirable. However, early recruitment after stroke rather than the recruiting site appeared to predict response in multiple variable modelling.

In conclusion, in severely dysphagic, tracheotomised stroke patients, PES was safe and superior to sham in improving airway protection and swallowing function and led to higher rates of decannulation.

Future trials should confirm these results and explore the effect of PES in other cohorts of tracheotomised patients.

Contributors

RD, IvdT, SM, SH, and PMB contributed to the conception and design of the study. RD, EW, CJW, TB, GC, MJ, MF, KN, MRV, enrolled patients in the study and contributed to data collection and verification. SMG, TW, and PZ performed the independent FEES video reviews. RS and IvdT analysed the primary endpoint data; RD, SH and PMB interpreted the data. RD, SH and SM reviewed adverse events and handled the data for IDSMB-review. RS and IvdT were non-voting members of the IDSMB and were advisors to the Scientific Committee. RD performed a literature search for the meta-analysis. RD, SM, SH and PMB prepared figures and tables and drafted the manuscript, which was critically revised for important intellectual content by RS, IvdT, EW, CJW, TB, GC, MJ, MF, KN, MRV, SMG, TW, and PZ. All authors approved the final version of the manuscript.

Conflicts of Interest

RD reports reimbursement of travel expenses that occurred during the study conduct and his role as principal investigator from Phagenesis Ltd.; RD reports travel reimbursement for scientific committee meetings; RD reports that the University Hospital Münster received payment per patient for study conduct; RD reports that the University Hospital Münster received payment per patient within the PHADER-registry; RD received honoraria for serving as a consultant for Nestlé HealthScience; RD worked as non-payed advisor for the company Phagenesis Ltd; RS and IvdT report that Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht received payment for the execution of the sequential analysis and for the participation in the IDSMB reviews as part of the PHAST TRAC study from Phagenesis Ltd.; EW reports reimbursement of travel expenses that occurred for training during the study conduct; EW reports that Schön Klinik Hamburg Eilbek received payment per patient for study conduct and received payments per patient for the PHADER registry; CJW reports reimbursement of travel expenses that occurred for training during the study conduct; CJW reports that RWTH Aachen University received payment per patient for study conduct; TB reports reimbursement of travel expenses that occurred for training during the study conduct; TB reports that University Hospital Giessen received payment per patient for study conduct; GC reports that University Hospital Bicocca received payment per patient for study conduct; MJ reports reimbursement of travel expenses that occurred for training during the study conduct; MJ reports that Isar-Amper Klinikum received payment per patient

for study conduct; KN reports reimbursement of travel expenses that occurred for training during the study conduct; KN reports that Hospital Vivantes Neukölln received payment per patient for study conduct; MRV reports reimbursement of travel expenses that occurred prior and during the study conduct; MRV reports that Kepler University Hospital received payment per patient for study conduct and received payments per patient for the PHADER registry; MF reports reimbursement of travel expenses that occurred during the study conduct; MF reports that Median Klinik Berlin-Kladow received payment per patient for study conduct; SM reports fees from Phagenesis Ltd. he receives as employee of that company; SH reports to own stocks and shares from Phagenesis Ltd., to receive fees for acting as chief scientific officer of Phagenesis Ltd., to receive lecture fees from Nestle Healthscience; SMG reports reimbursement of travel expenses from Phagenesis Ltd. that occurred for training and review meetings during the study conduct; she reports fees from Phagenesis Ltd. for working in the FEES review board; TW reports reimbursement of travel expenses from Phagenesis for review meetings; he reports that the University Hospital Münster received fees for his work within the FEES review board; PZ reports reimbursement of travel expenses from Phagenesis Ltd. that occurred for training and review meetings during the study conduct; he reports fees from Phagenesis Ltd. for working in the FEES review board; PMB reports personal fees and travel reimbursement from Phagenesis for his role as chair of the scientific committee of PHAST-TRAC, grants from British Heart Foundation, grants from NIHR Health Technology Appraisal, share-holding from Platelet Solutions Ltd, personal fees and share-holding from Diamedica, personal fees for working as a consultant from Nestle, Athersys and Covidien, and personal fees from ReNeuron for chairing a data monitoring committee; PMB reports that University Hospital Nottingham received payment per patient for study conduct and received payments per patient for the PHADER registry; PMB received honorarium and reimbursement of travel expenses from Phagenesis Ltd for his role as Co-Chief Investigator of the PhEED trial.

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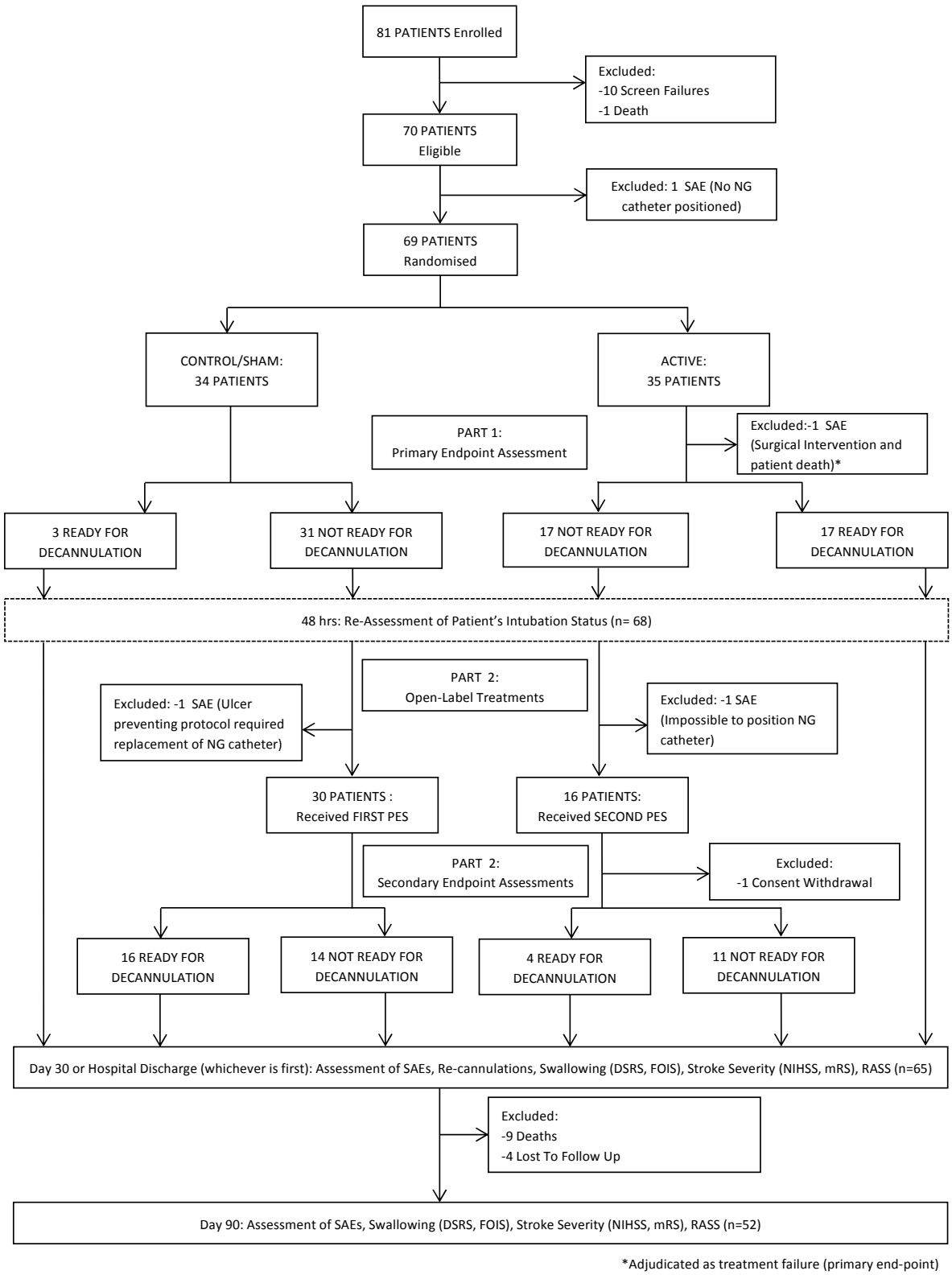
Figure 1. CONSORT flow diagram



NG=Nasogastric, SAE = Serious Adverse Event, DSRS = Dysphagia Severity Rating Scale, FOIS = Functional Oral Intake Scale, RASS = Richmond Agitation and Sedation Scale, NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale

Table 1. Baseline characteristics of 69 randomised patients.

	All	PES	Sham
Patients	69	35	34
Age (years)	64.2 (11.9)	61.7 (13.0)	66.8 (10.3)
Sex, female (%)	25 (36)	11 (31)	14 (41)
mRS premorbid >0 (%)	3 (4.6)	1 (3.0)	2 (6.2)
mRS>4 (%)	67 (99)	34 (100)	33 (97)
Medical history (%)			
Hypertension	49 (71)	23 (66)	26 (77)
Hyperlipidaemia	4 (6)	1 (3)	3 (9)
Diabetes	8 (12)	3 (9)	5 (15)
Atrial fibrillation	5 (7)	3(9)	2 (6)
Previous stroke/TIA	10 (15)	7 (20%)	3 (9)
Smoking	8 (12)	5 (14)	3 (9)
OTR (days)	28.0 [19, 41] (11-120)	28.0 [20, 49] (11-120)	28.0 [18, 40] (11-95)
Ventilation (days, range)	15.0 [9, 22] (3-131)	15.0 [9, 24] (5, 131)	13.5 [9, 22] (3, 60)
Feeding status, PEG (%)	9 (21)	5 (23)	4 (18)
NIHSS (/24)	17.5 (4.6)	17.6 (5.0)	17.5 (4.3)
Ischaemic Stroke (%)	49 (71)	27 (77)	22 (65)
Haemorrhagic Stroke (%)	20 (29)	8 (23)	12 (35)
Lesion side, right (%)	33 (48)	17 (49)	16 (47)
DSRS (/12)	12 (0)	12 (0)	12 (0)
FOIS (/7)	1 (0)	1 (0)	1 (0)

Number of patients enrolled (randomised) per site: Münster 40 (40), Hamburg 14 (8), Aachen 8 (6), Monza 6 (5), Munich 4 (4), Berlin Median 3 (2), Berlin Vivantes 2 (2), Linz 2 (2), Giessen 2 (0).

DSRS: dysphagia severity rating scale; FOIS: functional oral intake scale; ICH: intracerebral haemorrhage; IS: ischemic stroke; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; OTR: Onset-to-randomisation time (days); PES: pharyngeal electrical stimulation.

Data are number (%), median [interquartile range] (with range), or mean (standard deviation). There were no significant differences between the treatment groups.

Table 2. Primary and related outcomes in the randomised and open label parts of the trial with sensitivity analyses.

	N	PES	Sham	OR/MD (95% CI)	p
Primary Outcome					
Randomised Part 1 of the study					
Patients	69	35	34		
”Ready for decannulation” after PES/Sham) **(%)** **(Primary outcome)**		17 (49)	3 (9)	7.00 (2.41-19.88)	0.00082
Removal of the tracheal tube (%)*		14 (82)	1 (33)	9.33 (0.62-139.57)	0.1404
Deflation of the tube-cuff (%)*		3 (18)	1 (33)	0.43 (0.03-6.41)	0.5088
Secondary Outcomes					
Open Label (Part 2) of the study					
Patients	45	15	30		
”Ready for decannulation” after open label treatment)** **(%)**	20 (44)	4 (27)	16 (53)	0.32 (0.08-1.23)	0.1185
Removal of the tracheal tube (%)*	17 (38)	3 (20)	14 (47)	0.29 (0.07-1.22)	0.1097
Deflation of the tube-cuff (%)*	3 (7)	1 (7)	2 (7)	1.00 (0.08-12.00)	1.0000
Re-cannulation within 48 hrs (%)		0 (0)	0 (0)	-	-
Re-cannulation within 30 days or hospital discharge (whichever is first) (%)		0 (0)	0 (0)	-	-
DSRS					
Day 2	60	30, 10.6 (2.4)	30, 10.4 (2.7)	0.27 (-1.05, 1.59)	0.6873
Day 30 or Hospital Discharge (whichever is first)	50	25, 8.0 (4.6)	25, 8.9 (3.3)	-0.88 (-3.17, 1.41)	0.4437
Day 90	53	27, 4.6 (5.3)	26, 5.7 (5.1)	-1.10 (-3.97, 1.77)	0.4449
FOIS					
Day 2	61	31, 1.7 (1.2)	30, 1.9 (1.4)	-0.191 (-0.878, 0.495)	0.5789
Day 30 or Hospital Discharge (whichever is first)	50	25, 3.0 (2.4)	25, 2.5 (1.7)	0.560 (-0.61, 1.73)	0.3407

Day 90	53	27, 4.6 (2.6)	26, 3.9 (2.5)	0.745 (-0.660, 2.150)	0.2922
NIHSS					
Baseline	68	34, 17.6 (5.0)	34, 17.5 (4.3)	0.118 (-2.129, 2.364)	0.9170
Day 2	47	24, 15.6 (4.5)	23, 15.7 (6.4)	-0.027 (-3.287, 3.233)	0.9867
Day 30 or Hospital Discharge (whichever is first)	48	24, 14.0 (5.0)	24, 13.8 (5.9)	0.292 (-2.865, 3.448)	0.8533
Day 90	16	8, 10.1 (9.2)	8, 16.9 (8.6)	-6.750 (-16.281, 2.781)	0.1510
mRS					
Baseline	68	34, 5.0 (0.0)	34, 5.0 (0.2)	0.029 (-0.029, 0.088)	0.3210
Day 2	61	31, 4.6 (1.3)	30, 4.6 (1.3)	0.078 (-0.570, 0.727)	0.8094
Day 30 or Hospital Discharge (whichever is first)	54	28, 4.8 (0.5)	26, 4.7 (0.5)	0.091 (-0.163, 0.345)	0.4769
Day 90	51	26, 4.1 (0.8)	25, 4.3 (1.0)	-0.203 (-0.730, 0.324)	0.4421
Level of care					
Baseline					
Patients	65	32	33		
Intensive Care Unit		8 (25)	7 (21)	1.24 (0.39-3.93)	0.7746
Intermediate Care Unit		21 (66)	23 (70)	0.83 (0.29-2.35)	0.7944
Normal ward		3 (10)	3 (10)	1.03 (0.19-5.55)	1.0000
Day 2					
Patients	50	25	25		

Intensive Care Unit		3 (12)	1 (4)	3.27 (0.32-33.84)	0.6092
Intermediate Care Unit		15 (60)	16 (64)	0.84 (0.27-2.65)	1.0000
Normal ward		7 (28)	8 (32)	0.83 (0.25-2.78)	1.0000
Day 10					
Patients	24	13	11		
Intensive Care Unit		2 (15)	1 (9)	1.82 (0.14-23.25)	1.0000
Intermediate Care Unit		4 (31)	5 (46)	0.53 (0.10-2.84)	0.6752
Normal ward		7 (54)	5 (46)	1.40 (0.28-7.02)	1.0000
Day 30					
Patients	14	7	7		
Intensive Care Unit		0 (0)	0 (0)	-	-
Intermediate Care Unit		2 (29)	1 (14)	2.40 (0.16-34.93)	1.0000
Normal ward		5 (71)	6 (86)	0.42 (0.03-6.06)	1.0000

DSRS: dysphagia severity rating scale; FOIS: functional oral intake scale; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; PES: pharyngeal electrical stimulation.

Data are number odds ratio (OR) (95% confidence interval); comparison using triangular test for primary outcome as specified in trial protocol, and Fisher's exact test otherwise. Data for DSRS. FOIS, NIHSS, mRS are N, Mean (SD); comparison using two-sample t-test. Day 2 is 48 hrs after final PES treatment.

* statistical comparison within the subgroup of patients reaching the primary endpoint.

** This is data related only to the open label part of the study where all non-responders were given PES.

† One patient in the PES group had a *non-treatment-related* adverse event occurring prior to third day of PES which required transfer to another hospital for surgery; as a result, FEES assessment was not possible. Conservatively, he was assigned to no decannulation.

Table 3. Adverse events (AEs) and serious adverse events (SAEs)

	PES	Sham	Non-randomised**
SAEs:			
Prior randomisation*	1 (1)	1 (1)	3 (2)
0-1 month after randomisation	3 (3)	4 (4)	
1-3 months after randomisation	8 (7)	4 (1)	
TOTAL study	12 (10)	9 (8)	3 (2)
Most commonly observed SAEs (≥3 events)			
Pneumonia	2 (2)	1 (1)	
Cardiac Arrest	2 (2)	1 (1)	
Sepsis	3 (3)	4 (4)	
Hydrocephalus	2 (2)	0 (0)	1 (1)
AE (non-serious)	55 (21)	50 (21)	0 (0)
Most commonly observed AEs (≥3 events)			
Diarrhoea	2 (2)	4 (4)	
Vomiting	6 (4)	6 (2)	
Pneumonia	3 (3)	6 (5)	
Urinary Tract Infection	8 (7)	3 (3)	
Infection (Other)	6 (6)	4 (3)	
Musculoskeletal Pain	3 (2)	0 (0)	
Hypoxia	2 (2)	1 (1)	
Thrombophlebitis	2 (2)	1 (1)	
Adverse Device-related Events (ADEs)	8 (5)	4 (3)	0 (0)
Most commonly observed ADEs (≥3 events)			
Medical Device Complication	6 (5)	3 (2)	0 (0)
Serious ADEs (SADEs)	0 (0)	0 (0)	0 (0)

Figures are shown as number of events (number of patients). None of the patient deaths or SAEs reported were judged to be intervention- (PES-treatment) or investigational device (Phagenyx® base station and catheter)-related by the Independent Data and Safety Monitoring Board.

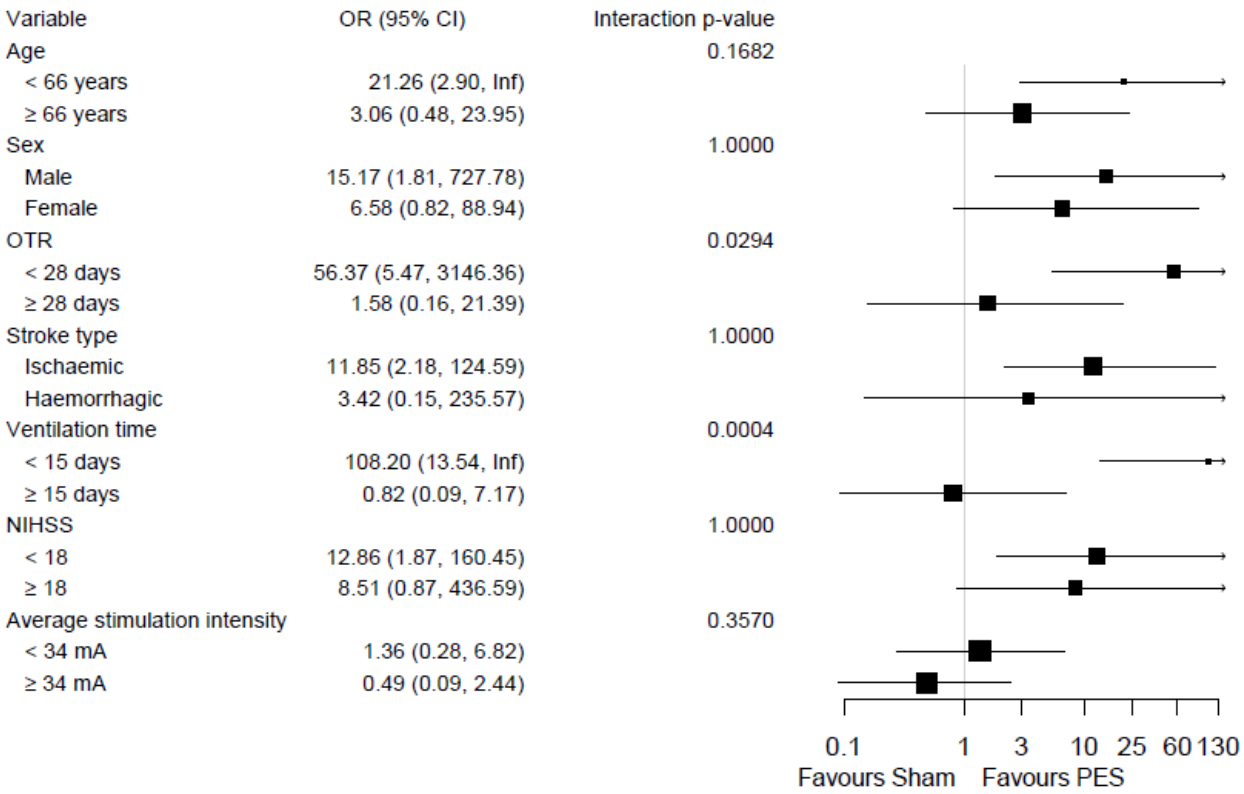
*Prior randomisation is defined as period from date of informed consent to date of randomisation.

**Non-randomised is defined as patients who were never ultimately randomised.

ADEs, also referred to as device deficiencies, are defined as an inadequacy of the medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labelling.

See Supplementary Appendix Tables S5 (SAEs), S6a and S6b (ADEs) and S7 (AEs) for further details.

Figure 2. Forest plot of treatment by subgroup interactions.



Data for variables are presented dichotomised using the median of each variable except for Average Stimulation Intensity where the mean was used. Only OTR and Ventilation time were significantly related to treatment success. Age: patient age in years, OTR: Onset-to-randomisation time (days), NIHSS: National Institute of Health Stroke Scale.