Press needle for the Prevention of Aspiration Pneumonia in Elderly People: Study Protocol for a Randomized Double-Blind Placebo-Controlled trial.

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Study protocol

Keywords: Press needle, aspiration pneumonia, elderly people, randomized double-blind placebo-controlled trial

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Abstract

Background:

Pneumonia is the fifth most common cause of death among the Japanese, with 97% of deaths occurring among elderly people aged 65 years or older. The incidence ratio of aspiration pneumonia is high for elderly people. Therefore, prophylaxis is important in geriatric medicine. In our previous studies, we reported that stimulation to the acupoints at ST36 and KI3 of the lower limbs with press needle improved the swallowing function of patients with dysphagia. The improvement of swallowing function may prevent aspiration pneumonia. The aim of this study is to investigate the protective efficacy of using press needle stimulation in the lower limbs for aspiration pneumonia.

Methods/design:

This is a multi-center, randomized double-blind placebo-controlled trial. A total of 140 patients with cerebrovascular disorder with a history of aspiration pneumonia will be recruited from six centers and randomly assigned to either the real press needle group or the sham press needle group in a 1:1 ratio. The press needle will be replaced twice a week. Treatment will be administered bilaterally at acupoints ST36 and KI3. The primary outcome is the frequency of onset of aspiration pneumonia. The secondary outcome is improvement of the latent time of swallowing reflex (LTSR). The investigation period is of 12-month. The primary outcome will be evaluated throughout the period, and secondary outcomes will be assessed at baseline, 1st month, 6th month, and at the end of the investigation period.

Discussion:

This study will evaluate the effects of press needle on prevention of aspiration pneumonia and improvement of swallowing function of patients. The results of this study will help support the prophylaxis of aspiration pneumonia.

Trial registration:

UMIN000023123, registered on July 12th, 2016; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000026460

Introduction

Background and rationale {6a}

In Japan, pneumonia is the fifth most common cause of death. Moreover, 97% of deaths due to pneumonia occur among elderly people aged 65 years or older. In addition, the ratio of aspiration pneumonia among age-specific pneumonia increases with aging [1]. Among patients with pneumonia aged 70 years or older, approximately 70% of cases are considered to be that of aspiration pneumonia [2]. In particular, people with cerebrovascular disorders are easily affected by aspiration pneumonia [3–4]. In

other words, aspiration pneumonitis is an important disease associated with vital prognoses in elderly people. Aspiration pneumonia is caused by an influx of saliva and other fluids, especially at night. The decrease in swallowing reflex is deeply related to the onset of aspiration pneumonia [5]. Furthermore, physiological changes with aging contribute to this decrease [6]. The causes include: (1) a decrease in masticatory force due to missing teeth, (2) poor alimentary bolus formation with decreased capacity of saliva secretion, (3) delay in swallowing reflex creation with a decrease in the pharynx perception, (4) prolongation of the larynx elevation distance at the swallowing reflex with the larynx low degree, and (5) aprosexia with the decrease in cognitive function [7–8]. In addition, a history of cerebrovascular disorder results in a decrease in substance P, an important trigger of swallowing reflex and reduces swallowing function [9].

The strategies for preventing aspiration pneumonia include: (1) improvement of the swallowing function with rehabilitation, (2) pharmacotherapy, (3) mouth care, (4) prevention of gastroesophageal reflux, (5) maintenance of consciousness, (6) maintenance of nutritional status, and (7) vaccination against pneumococcus [10]. However, the number of patients with aspiration pneumonia has increased [1]. Therefore, a novel therapy that improves swallowing function and prevents aspiration pneumonia is required.

We previously reported improvements in the swallowing function of elderly people with cerebrovascular disorders using acupuncture stimulation [11–13]. However, the protective efficacy of acupuncture stimulation for aspiration pneumonia has not yet been reported.

Objectives {7}

The aim of this study is to investigate the protective efficacy of acupuncture stimulation using press needle for aspiration pneumonia in patients with cerebrovascular disorder.

Trial design {8}

Randomized double-blind placebo-controlled trial

Methods: Participants, Interventions, And Outcomes

Study setting {9}

Potential participants with cerebrovascular disease with a history of aspiration pneumonia will be recruited from the National Hospital Organization Yonezawa Hospital, Minamisanriu Hospital, Kesennuma City Motoyoshi Hospital, Saka General Hospital, Sendai Tomizawa Hospital, and Ikeno Clinic.

When a patient matches the eligibility criteria, the physician will contact the administrator.

If the participants are interested in our study, they will be informed about the purpose and content of research as well as the benefits and drawbacks of participation in detail.

After screening, the participants meeting the inclusion criteria will be enrolled.

The study flow is shown in the SPIRIT Figure (Fig. 1).

Participants will undergo treatment for a period of 12-month.

Eligibility criteria {10}

Inclusion criteria

All eligible participants should meet the following criteria:

(1) Patients with cerebrovascular disease with a history of aspiration pneumonia

(2) Patients in the lifetime (maintenance stage or chronic stage) of rehabilitation for cerebrovascular disease

(3) Patients in, out of, or receiving home care at a joint research facility

Exclusion criteria

Participants with any one of the following will be excluded:

(1) Patients with serious diseases, such as chronic respiratory diseases, malignancies, and chronic ischemic diseases, that can result in pneumonia

(2) Patients with metal allergies

(3) Patients with severe skin disorders

(4) Patients who do not develop a swallowing reflex at the time of the initial latent time of swallowing reflex (LTSR) measurement.

(5) Patients with three or more severe aspiration pneumonia episodes in the past three months.

Who will take informed consent? {26a}

The study administrator or a physician at the collaborating hospital will explain the procedure to the patient or family and obtain their informed consent.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

The aim of this study is to investigate the protective efficacy of press needle stimulation for aspiration pneumonia in patients with cerebrovascular disorder.

Press needle stimulation has been found to significantly improve swallowing function in patients with cerebrovascular disorder compared to placebo press needle stimulation [11]. Therefore, a placebo press needle was chosen as placebo control in our trial.

Intervention description {11a}

Participants will receive press needle stimulation at two acupuncture points ST36 (Zusanli) and KI3 (Taixi) [14] on the lower limbs for 12-month. According to traditional Chinese medicine, stimulation of these two acupuncture points is beneficial in the age-related decline in swallowing function. Press needle is a therapeutic device in which an acupuncture needle is safely secured to a circular surgical tape. Pionex Zero (Seirin Corporation, Shizuoka, Japan) non-invasive press needles will be used in this study (Fig. 2). The irritation area in contact with the skin is not a needle but a protrusion, which is designed not to penetrate the skin. While the previous study used an invasive device [11], the present study used a safer one, taking into account the observation period of 12-month. The safety and quality of Pionex Zero are controlled by the Japanese Ministry of Health, Labour and Welfare (Notification Number: 22B1X00006000004). As the sham press needle used for the control group, the protruding part of the Pionex Zero is removed. The authenticity of this Sham device has been confirmed [15]. The press needles and sham press needles will be replaced twice a week in the intervention group and control group, respectively.

Criteria for discontinuing or modifying allocated interventions {11b}

In cases of skin abnormality in the area of application of the press needles, physicians will be consulted and the intervention paused for a period of time. Subsequently, physicians will be consulted about the possibility of resuming treatment. The intervention will also be discontinued if other diseases develop during the period and require treatment.

Strategies to improve adherence to interventions {11c}

Frequent bedside visits and health assessments will be an important part of monitoring adherence.

Relevant concomitant care permitted or prohibited during the trial {11d}

Usual treatments for cerebrovascular disease, its sequelae, and aspiration pneumonia are acceptable. High-dose steroids and immunosuppressive therapy are unacceptable.

Provisions for post-trial care {30}

Treatment with press needle shall be allowed to continue after the observation period depending on the participant's will. This will also apply to participants assigned to the control group. The costs will be borne by the participant.

Outcomes {12}

Primary outcome

The primary outcomes will help determine whether aspiration pneumonia is prevented and if press needle stimulation is effective. The primary outcome is the number of cases of aspiration pneumonia during this period. Diagnosis of aspiration pneumonia will be performed by the attending physician based on the Japanese Respiratory Society Guidelines for the Management of Hospital-Acquired Pneumonia in Adults. The total number of diagnoses will be calculated at the end of the study.

Secondary outcomes

Secondary outcomes will help determine whether seal acupuncture improves swallowing function and general conditions. The secondary outcomes are LTSR, fever frequency, Barthel index (BI), body mass index (BMI), general blood test analysis, and the Mini-Mental State Examination (MMSE). The LTSR measures the time between the insertion of an 8 Fr tube into the nasal cavity to the uvula of the palate and the initiation of swallowing after the injection of 1 mL of distilled water. A total of three measurements are taken, and the mean value is calculated. Fever is defined as the body temperature of 37.5°C or more. The number of days of fever during the study period will be counted.

Participant timeline {13}

Enrolment

Participants who meet the eligibility criteria and are determined to participate will be enrolled after consultation with their physician.

Assessments

LTSR, BI, BMI, blood test parameters, and MMSE will be measured before starting the intervention. LTSR will be measured one month after the start of the intervention. At the end of the study period, all assessments will be measured. Measurements are allowed 15 days before and after the scheduled date.

Sample size {14}

The calculation of the sample size is based on previous studies. The incidence of aspiration pneumonia in previous studies was 0.091 (4/44) for the intervention group and 0.292 (14/48) in the control group [16]. The sample size was calculated with a two-tailed significance level of 5% and a power of 80%, resulting in a total of 118 participants, 59 in each group. To account for 20 dropout participants, the

calculation 118 + 20 = 138 suggests that 138 patients should be recruited. We rounded this value to a total of 140 patients.

Recruitment {15}

Potential participants with cerebrovascular disease with a history of aspiration pneumonia will be recruited from the National Hospital Organization Yonezawa Hospital, Minamisanriu Hospital, Kesennuma City Motoyoshi Hospital, Saka General Hospital, Sendai Tomizawa Hospital, and Ikeno Clinic. The physician will contact the administrator when a patient matches the eligibility criteria. If the participants are interested in our study, they will be told of the purpose and content of research as well as the benefits and drawbacks of participating in detail. After screening, the participants who met the inclusion criteria will be enrolled. The study flow is shown in the SPIRIT Figure (Fig. 1). Participants will undergo a 12-month treatment period.

Assignment of interventions: allocation

Sequence generation {16a}

After obtaining written informed consent from the participants and baseline screening. Random numbers of 001–140 will be automatically generated by the SPSS software (whole random numbers). The participants will be randomly assigned to the intervention group or control group at a ratio of 1:1. An overview of the case distribution of each center, specific measurements, and time points of data collection can be found in the SPIRIT Figure (Fig. 3).

Concealment mechanism {16b}

The random allocation sequence will be stored and concealed from the treating physicians, statisticians, and outcome assessors to prevent detection bias.

Implementation {16c}

The designated statisticians will generate the allocation sequence, and different investigators designated by the project leader will enroll or assign participants.

Assignment of interventions: Blinding

Who will be blinded {17a}

Information including the number of cases of aspiration pneumonia, LTSR, fever frequency, BI, BMI, general blood sampling, and the MMSE will be assessed by independent assessors who are blinded to the assignment and treatment. The principal investigators, statisticians, and outcome assessors will be blinded to the treatment assignments until the database is locked.

Procedure for unblinding if needed {17b}

Unblinding the investigators will be permissible only in specific situations, such as when knowledge of the actual treatment is highly necessary for the appropriate management of participants (e.g., serious adverse events).

Data collection and management

Plans for assessment and collection of outcomes {18a}

An overview of specific measurements and time points for data collection can be found in the SPIRIT Figure (Fig. 3). After meeting the participant, all data will be recorded in detail in the case report form (CRF) of the medical record. At each assessment, an investigator from the institution will be responsible for examining each patient. Information on the baseline number of cases of pneumonia in the past three months, medical history, and previous medications will be collected only during the initial interview.

Plans to promote participant retention and complete follow-up {18b}

Communication will be frequent with the attending physician at each center to facilitate participant retention.

Data management {19}

A third person (data manager) will independently check and judge the input data. The principle investigators from each of the trial sites will confirm whether all CRFs have been timely completed and ensure that the withdrawal of participants and all adverse events are documented in the CRFs. All original data and relevant records will be properly classified and stored at each study center under confidential conditions for 3 years.

Confidentiality {27}

Participants' personal information will be kept confidential in the same way as their medical records in the hospital before, during, and after the trial.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statisticians will independently undertake statistical analysis. Parametric data will be presented as mean ± standard deviation (SD), while non-parametric data as median and 95% confidence interval (95% CI). Two-tailed t-tests and chi-square tests will be used to compare the demographic and clinical characteristics of the two groups at baseline. MMSE, BI, and total caloric intake at baseline and endpoint

will be compared between the two groups using repeated measures analysis of variance (ANOVA). Febrile days of the two groups will be compared using the two-tailed t-test. The probabilities of being pneumonia-free and survival from pneumonia-related death will be estimated using the Kaplan-Meier product-limit method. Pneumonia-free and survival rates will be calculated from the date of random assignment to the date of pneumonia onset, date of death, or cutoff date for patients alive at the time of closure of the dataset. A Cox proportional hazards regression model will be used to examine the relationships between modifiable factors and incidence of pneumonia or pneumonia-related mortality. Relative risks (RRs) and 95% confidence intervals (CIs) will be calculated to assess response rate. Number needed to treat pneumonia will be calculated from two-by-two tables. Plausible predictors (age, sex, ease of diagnosis, duration of illness, activities of daily living ability, cognitive function, and treatment assignment) will be included in the original model. Backward stepwise regression will be performed, and $P > 0.2$ will be used for variable removal. Statistical analysis will be performed using SPSS 21.0 software (IBM, Armonk, USA). All statistical tests will be two-sided tests, and the statistical significance threshold will be set at 5%.

Interim analyses {21b}

No interim analysis is planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

No additional analysis is planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

If missing values are encountered, multiple imputation will be used to obtain the final data. The primary analysis will use intention to treat (ITT) to assess whether a clinical intervention using a press needle has an impact on the incidence of aspiration pneumonia in the intervention and control groups.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Not planned in this study.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The principal investigator will ask the chief audit officer to conduct an audit for the purpose of improving the scientific and ethical quality of the research.

The investigators will prepare a written audit plan and, based on this, visit the institution to check the approval documents by the head of the institution, review the explanatory and consent documents, and check the contents of the CRFs against the medical records.

The results of the audit will be submitted to the principal investigator, principal investigator of the institution, and head of the institution.

Composition of the data monitoring committee, its role and reporting structure {21a}

The principal investigator will ask the data controller and monitoring personnel to monitor the study to ensure that the study is being conducted safely and in accordance with the research protocol with accurate data collection.

The principal investigator will prepare a monitoring plan, and the data controller and monitoring staff will conduct the monitoring in accordance with the monitoring plan.

The data controller and the monitoring personnel will submit a monitoring report to the principal investigator.

Adverse event reporting and harms {22}

Adverse events such as signs and symptoms and other discomfort, will be observed and recorded in detail during the study. The attending physician will take appropriate action in the event of a serious adverse event/failure and report it to the principal investigator of the institution. The principal investigator will review information regarding (1) the type of the adverse event, (2) the severity classification, (3) the severity and the reason for the determination of severity, (4) predictability, (5) the causal relationship with the intervention, (6) the history of the event, and (7) the identification of the participant. The severity classification will be determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0: http://www.jcog.jp/doctor/tool/CTCAEv4J_20150310.pdf).

Frequency and plans for auditing trial conduct {23}

The study will be audited every six months from the first participant’s enrollment date..

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

If there are changes to the eligibility criteria, outcomes, and analyses, a new version of the protocol will be submitted to the Tohoku University Hospital Ethics Committee for approval.

Dissemination plans {31a}

Research results will be presented in the form of papers and conference reports.

Discussion

Aspiration pneumonia is primarily caused by the subclinical aspiration of nasal, laryngeal, and periodontal secretions that go unnoticed mainly at night. One of the mechanisms by which this aspiration

occurs is through the decreased swallowing and coughing reflex. The proper functioning of these reflexes requires that substance P synthesized in the cervical ganglion, the sensory branch of the vagus and glossopharyngeal nerves, is maintained constant in the peripheral nerves of the pharynx and endotracheal tissue. Substance P is also enhanced by dopamine, which is synthesized in the substantia nigra and striatum. When the deep cortex, including the substantia nigra and striatum, is impaired due to cerebrovascular disease, which is the subject of this study, the ability to synthesize dopamine is also impaired, leading to a decrease in swallowing function [9]. Acupuncture stimulation of the neck improves swallowing function and the expression of 5-HT_{1A} in the arcuate nucleus [17]. Studies directly investigating the mechanism of dopamine synthesis in the nigrostriatal striatum as described above are lacking. However, use of acupuncture for treatment of cerebrovascular disease [18] has shown improvement in cerebral blood flow in aged rats and reduction of infarct volume [19]. Studies using rats with Parkinson's disease, which is a different disease with similar striatum nigra involvement, have shown that acupuncture prevents cell death in the nigra and striatum [20]. The addition of acupuncture to the treatment of patients with Parkinson's disease has been reported to significantly increase blood dopamine [21]. From these reports, it can be inferred that acupuncture stimulation may promote dopamine synthesis in the substantia nigra striata as a probable mechanism for improvement of swallowing function.

In this study, the stimulation will be delivered to the lower limb. The study is based on previous studies showing that stimulation of the lower limbs of patients with cerebrovascular disease improved swallowing function [11]. However, stimulation sites other than the lower limbs have been reported to improve swallowing dysfunction [17]. In the present study, the lower limb was chosen as the site of stimulus because of the possibility of continuing stimulation during the 12-month observation period.

The press needles used in the real stimulation group and the placebo press needles used in the control group are identical in appearance when attached to the skin. Furthermore, there is no difference between the two devices in terms of the sensation felt by the participants. Thus, it is difficult for participants to distinguish between the two devices [15].

The same investigator will be responsible for the examination of each patient at different time periods.

All indicators will be assessed by independent assessors.

The principal investigators, statisticians, and outcome assessors will be blinded to the treatment assignments until the database is locked.

In conclusion, the purpose of this study is to test the therapeutic efficacy and safety of acupuncture stimulation for the prevention of aspiration pneumonia in patients with cerebrovascular disease.

The results of this study will provide evidence-based data, thus, opening a new avenue, for the use of acupuncture stimulation for aspiration pneumonia prophylaxis in patients with cerebrovascular disease.

Trial Status

The version of the protocol used in this study is the 4th edition (publication date: November 11, 2020). This study is currently preparing to begin recruitment. Recruitment of participants is scheduled to begin on June 1, 2021, and will end on March 31, 2025.

Abbreviations

LTSR
latent time of swallowing reflex
ST36
stomach meridian 36
KI3
kidney meridian 3
BI
Barthel Index
BMI
body mass index
MMSE
Mini-Mental State Examination
CRF
case report form
SD
standard deviation
95% CI
95% confidence interval
ANOVA
analysis of variance
RRs
relative risks
CI
confidence intervals
ITT
intention to treat

Declarations

Ethics approval and consent to participate {24}

The Research Ethical Committee of Tohoku University approved this trial protocol (2019-2-19). No individual clinical data are presented in this manuscript.

Consent for publication {32}

Not applicable

Availability of data and materials {29}

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests {28}

The authors declare that they have no competing interests.

Funding {4}

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Authors' contributions {31b}

SK conceived and designed the protocol and accepted the overall responsibility for this study. SK, AK, ST, RA, MO, and TI drafted the manuscript. AK and TN are involved in participant recruitment and acquisition of data. SK, RA, ST, and TI contributed to the study design and drafting of the manuscript. All authors critically revised and commented on the intellectual content of this manuscript. All authors reviewed the draft of this paper and have read and approved the final paper.

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Figures

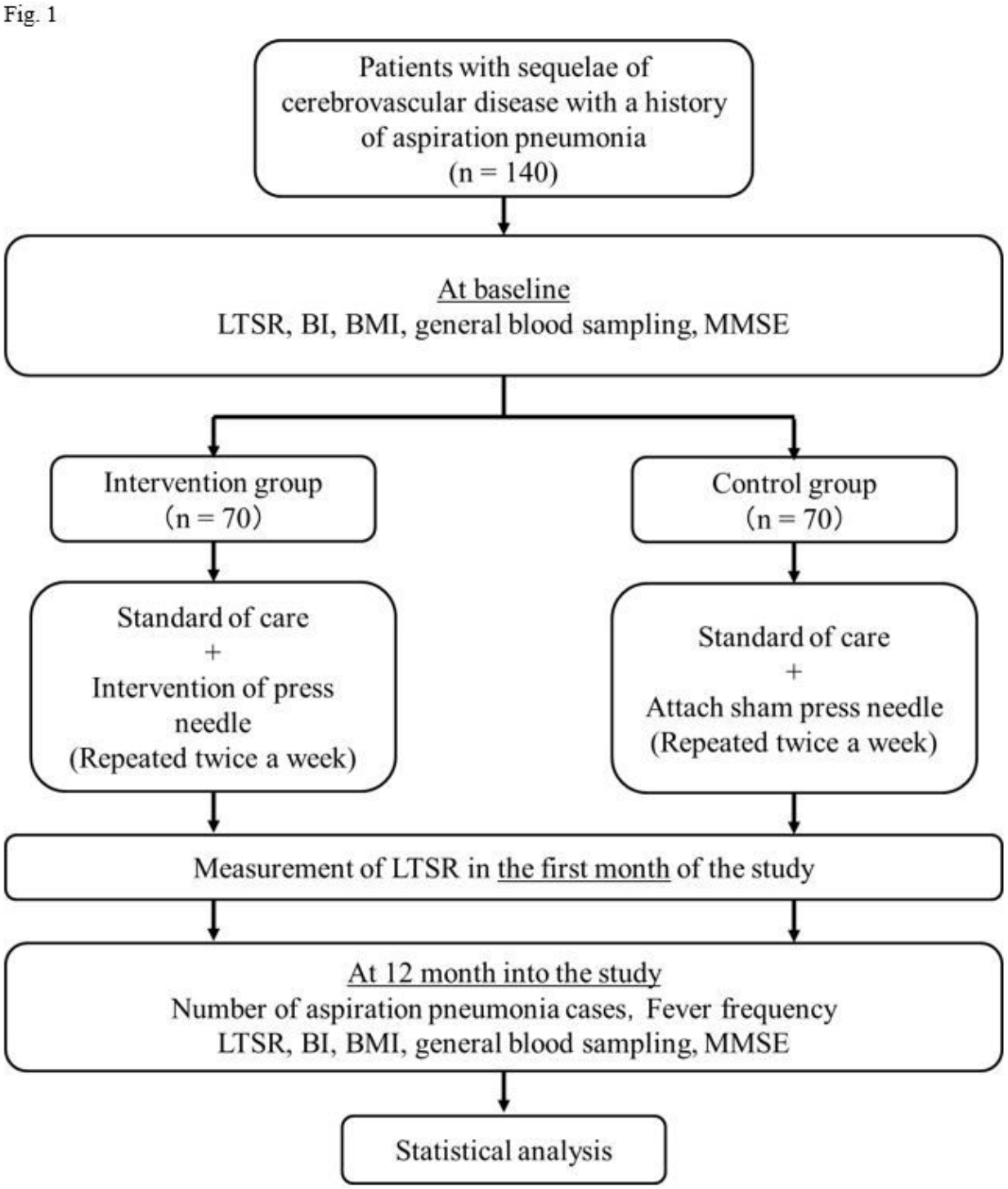

Figure 1

Flow chart of the clinical trial. LTSR: latent time of swallowing reflex; BI: Barthel Index; BMI: Body mass index; MMSE: Mini-Mental State Examination.

Fig. 2.1

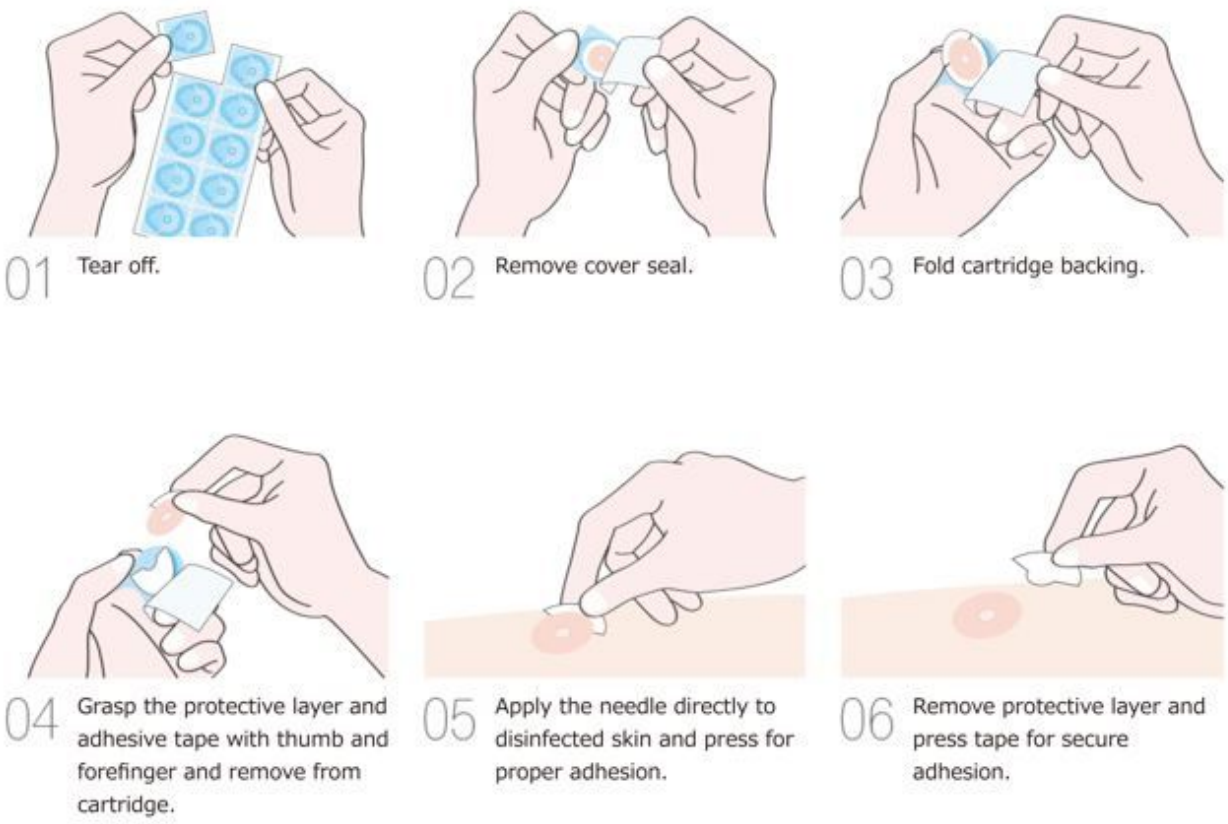

Fig. 2.2

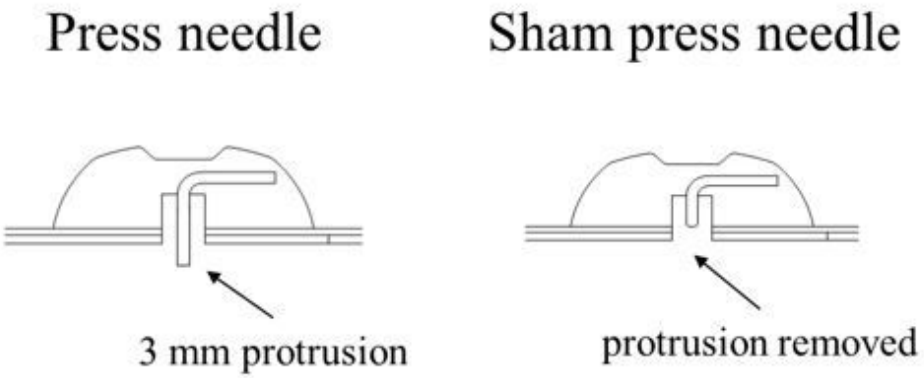

Figure 2

Fig. 2.1 How to apply Pionex Zero (https://www.pyonex.info/products.html),). The press needle used in this study is a Pionex Zero (Seirin Corporation, Shizuoka, Japan. https://www.youtube.com/watch?v=1thnSQjZU8o (Accessed on 6 Oct 2020)). The patented plastic case and sheath allow the practitioner to insert the needle without touching the needle tip or the surface of the Micropore™ adhesive tape.

Fig.2.2 Images of the press needle and sham press needle used in this study. The press needle has a non-sharp protrusion of 3 mm. The sham press needle the protrusion is removed.

Fig. 3

	Baseline	observation period				
Timepoint (month)		1	3	6	9	12
Enrolment:						
Eligibility screen	✔					
Informed consent	✔					
Medical history	✔					
Randomization	✔					
Intervention:						
Intervention group		←	—	—	—	→
Control group		←	—	—	—	→
Assessment: Primary outcome:						
Incidence of aspiration pneumonia		←	- -	- -	- -	→
Secondary outcomes:						
Fever frequency		←	- -	- -	- -	→
LTSR	✔	✔				✔
BI	✔					✔
BMI	✔					✔
MMSE	✔					✔
General blood sampling	✔					✔

Figure 3

Measurement items and data collection plan. The number of occurrences of aspiration pneumonia and frequency of fever during the 12-month observation period will be determined. LTSR: latent time of swallowing reflex; BI: Barthel Index; BMI: Body mass index; MMSE: Mini-Mental State Examination.