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Clinical Study (No. HZ（2019）146)

Study on Bronchoscopy for the Treatment of Post-Stroke Dysphagia and Stroke-Associated Pneumonia

Product Name: Olympus BF-P180 Fiber Bronchoscope

State Food and Drug Administration (Imported) Medical Device No. 2007, No. 3221928

Study Type: Interventional Study

Study Center: Zunyi First People's Hospital

Date: September 01, 2019

This study will adhere to this clinical study protocol.

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Study Protocol

I. Study Background

Stroke-associated pneumonia (Stroke-Associated Pneumonia ,SAP) is one of the most common respiratory complications of acute stroke, occurring in approximately 4% to 9% of patients after stroke[1-4]. The incidence of SAP is higher in patients with acute ischemic stroke treated in neurological intensive care units and those requiring nasogastric tube feeding (21% and 44%, respectively)[5,6]. Compared to patients without pneumonia, those with SAP have higher mortality rates and poorer long-term outcomes[2,3]. Pneumonia is the most common cause of fever within 48 hours after acute stroke and the most frequent complication within 2-4 weeks after supratentorial ischemic infarction[1,7,8]. Furthermore, retrospective data indicate that pneumonia and respiratory diseases are the most common reasons for hospitalization among stroke survivors during the first five years after ischemic stroke[9]. Independent risk factors for in-hospital pneumonia include age greater than 65 years, dysarthria or absence of speech due to aphasia, severe post-stroke disability, cognitive impairment, and dysphagia[10]. In an early prospective study of 124 acute stroke patients treated in the intensive care unit, risk factors were mechanical ventilation, abnormal chest X-ray on admission, and dysphagia[5]. Aspiration pneumonia after stroke is often due to stroke-related dysphagia

(i.e., impaired motor and sensory mechanisms of swallowing) or decreased level of consciousness leading to impaired cough reflex and glottic closure. Moreover, prophylactic antibiotic use in acute stroke patients does not reduce the incidence of post-stroke pneumonia or improve outcomes[12,13].

Dysphagia is a common symptom in terminal illnesses. In the last weeks to months of life, declining swallowing function diminishes the desire and ability to eat. Difficulty swallowing solids and liquids is one of the most common symptoms in the final days of life[13,14]. Swallowing disorders affect quality of life (e.g., social interaction, communication) and lead to impaired nutrition and hydration. Dysphagia is also a major predisposing condition for aspiration and can lead to pneumonia, and in some cases, even choking or death. Considering the central role of food and nutrition in social interaction and the general concern about nutrition for health, swallowing disorders can also cause frustration and distress for family caregivers and healthcare staff. Additionally, for many patients with terminal illnesses, the inability to swallow and/or lack of interest in food can be a critical symptom prompting decisions to forgo treatment and seek end-of-life care. Dysphagia refers to difficulty swallowing food or liquids, including medications in liquid or pill form. Post-stroke dysphagia (Post-Stroke Dysphagia, PSD) may arise from motor or sensory dysfunction in neurological processes, potentially causing problems with eating certain types of food or liquids, or even an inability to swallow altogether. Patients may complain of food sticking in the upper

gastrointestinal tract from the throat to the distal esophagus, and experience coughing or choking when eating or drinking. Chronic dysphagia affects the efficiency of oral intake, leading to physical weakness, loss of appetite, weight loss, dehydration, and malnutrition. Furthermore, airway protection or swallowing safety can be threatened by swallowing disorders. Food or liquid may enter the trachea, leading to aspiration, choking, or in severe cases, asphyxiation. Aspiration pneumonia is an infectious process caused by the aspiration of oropharyngeal secretions colonized by pathogenic bacteria, with Gram-negative enteric bacilli and anaerobes being the most common causative microorganisms. Aspiration of sterile acidic gastric contents can also cause acute chemical injury to the lungs.

Therefore, improving post-stroke dysphagia is particularly important for treating SAP, as it addresses the underlying cause, significantly reduces the incidence of SAP, and improves outcomes. Swallowing is not a voluntary act but a complex reflex that requires specific stimuli to initiate. Although the swallowing action can be started voluntarily, its completion is a complex reflex. A single simple swallow requires the coordination of 25 pairs of muscles in the oral cavity, pharynx, larynx, esophagus, and face, involving at least 6 pairs of cranial nerves, the speech system, and the respiratory system. Swallowing is a typical, complex reflex action consisting of a sequence of interlinked stages, each composed of a series of processes, where the activity of one stage can trigger the next. Receptors for swallowing are located in the

soft palate, posterior pharyngeal wall, epiglottis, esophagus, etc. Afferent nerves include fibers from the soft palate (Cranial Nerves V, IX), posterior pharyngeal wall (CN IX), epiglottis (CN X), and esophagus (CN X). The central pattern generator is located in the medulla oblongata. Efferent nerves are in Cranial Nerves V, IX, X, XI, and XII, and the effector organs include the tongue, larynx, pharyngeal muscles, esophageal muscle groups, etc. Every stage of swallowing is interconnected and indispensable. After a stroke, if the lesion involves the medulla oblongata, swallowing and breathing difficulties can occur.

Domestic research has primarily focused on the prevention of SAP-related risk factors, bundled care, rehabilitation training, and traditional Chinese medicine acupuncture, with a lack of reports on bronchoscopy for treating post-stroke dysphagia. Bedside bronchoscopy can clear airway secretions, pass directly through the glottis, stimulate cough and swallowing muscles to produce contractions, playing a positive role in preventing aspiration and alleviating dysphagia. Bronchoscopy can directly stimulate the trigeminal nerve in the soft palate, the glossopharyngeal nerve in the posterior pharyngeal wall, and the vagus nerve in the epiglottis, promoting contraction of the masticatory muscles, suprahyoid muscles, infrahyoid muscles, facial muscles, tongue muscles, and soft palate muscles, thereby training the swallowing muscle groups, exercising swallowing function, improving swallowing disorders, and significantly reducing the incidence and mortality rate of SAP.

Currently, there are no reports domestically or internationally on bedside bronchoscopy for the treatment of post-stroke dysphagia and SAP. This study aims to explore the application value and clinical safety of portable fiber bronchoscopy in non-severe SAP patients with dysphagia, and to evaluate whether bronchoscopic treatment can alleviate dysphagia symptoms, improve hypoxia, pulmonary infection, and SAP prognosis.

II. Study Objectives

Primary Objective: To observe the efficacy of bronchoscopic sputum suction + lavage therapy on post-stroke dysphagia and stroke-associated pneumonia.

Secondary Objectives: To compare National Institutes of Health Stroke Scale(NIHSS scores)(It is a standardized tool used to assess the degree of neurological deficits in patients with acute stroke, consisting of 15 items covering consciousness level, visual field, facial paralysis, limb movement, ataxia, sensory, language, and articulation disorders. The scoring range for each project is 0 to 4 points, with 0 indicating no defects and higher scores indicating more severe neurological deficits; The total score ranges from 0 to 42 points, with 0 indicating no neurological deficits and 42 indicating extremely severe deficits), Acute Physiology and Chronic Health Evaluation (APACHE) II scores(It includes three parts: acute physiology score (APS), chronic physiology score (CPS), and patient age score, with a total score of 0-

71 points. The higher the score, the more severe the patient's condition, the worse the prognosis, and the higher the mortality rate), CPIS scores (Clinical Pulmonary Infection Scores), Water Swallow Test scores(Grade I: able to drink without coughing within 5 seconds; Grade II: No coughing after drinking twice or more; Grade III: Can be consumed in one go but accompanied by coughing; Grade IV: Drink twice or more with coughing; Grade V: Frequent coughing and inability to finish all drinks. Grade I indicates normal, Grade II indicates suspicious, and Grade III or above indicates abnormal), C-reactive protein (CRP), Length of hospital stay, arterial partial pressure of oxygen (PaO_2), Height(m), Weight(Kg),Body Mass Index（BMI, Report BMI in kg/m ^ 2 by combining weight and height）,and overall clinical treatment efficacy between the two groups.

III. Study Plan

1. Study Population Selection

This is a single-center, prospective, randomized, controlled clinical trial. The control group will receive conventional anti-infective and expectorant therapy, plus suction via suction catheter as needed (i.e., when dyspneic or when phlegm sounds are heard in the airway). The observation group will receive, in addition to the control group's treatment, bronchoscopic treatment 1-2 times, including sputum suction under endoscopy, lavage, and drug

instillation. This study will enroll 60 patients with post-stroke dysphagia and stroke-associated pneumonia, randomly divided into an experimental group and a control group.

1.1 Inclusion Criteria

- Meets the diagnostic criteria for acute stroke and is clearly diagnosed through head MRI or CT examination.

- According to the Wada drinking water test, there is indeed difficulty swallowing.

- Pneumonia occurs within 72 hours after stroke, confirmed by chest imaging examination, and meets the diagnostic criteria for stroke-related pneumonia.

- Clear consciousness, stable vital signs, and able to cooperate with bronchial examination.

1.2 Exclusion Criteria

- The condition is critical, with severe hemiplegia and mental disorders that cannot tolerate bronchoscopy treatment.

- Combined lung tumors, open pulmonary tuberculosis, coagulation dysfunction, severe cardiovascular and cerebrovascular diseases, severe heart, liver, and kidney dysfunction, and pulmonary infection before stroke.

- Not willing to undergo bronchoscopy examination.

- Individuals with previous esophageal functional structural abnormalities.

- Disagree with participating researchers.

1.3 Withdrawal/Early Termination from Study

If a patient discontinues the study before completing the assessments specified in the study protocol, they will be considered withdrawn/terminated early. Patients may withdraw/terminate early for any of the following reasons:

- Adverse Event (AE)
- Inability to complete the bronchoscopy procedure

A final assessment of the patient should be conducted at this time, and the reason for early termination should be recorded on the appropriate page of the Case Report Form (CRF). For patients who withdraw due to an adverse event, the investigator must follow up with them.

2. Subject Recruitment Number

This single-center, prospective, randomized controlled clinical trial plans to enroll 60 patients.

3. Investigator Selection Criteria

The study center should have a standard Intensive Care Unit (ICU) with a sufficient volume of critically ill patients. It is planned to include 24 large general hospital ICUs.

4. Study Timeline

4.1 Study Implementation Period: September 2019 --- September 2021

4.2 Study Observation Period: Observation for 7 days starting from enrollment.

5. Study Execution

This is a single-center, prospective, randomized, controlled, clinical study.

5.1 Enrollment

Before the study begins, the investigator must clearly and verbally explain the study's circumstances, potential risks, and benefits to the patient or their authorized representative. The patient or their authorized representative and the investigator must sign and date the informed consent form. The patient can only enter the screening process and subsequently participate in the study after signing the informed consent form.

After signing the written informed consent, the patient will be assessed to determine if they meet the study criteria:

1. Patient's medical history;
2. Vital signs;

5.2 Randomization and Blinding

According to the principle of complete randomization, 60 patients will be assigned to the experimental group and the control group.

5.3 Research Methods

The control group will receive conventional anti-infective and expectorant therapy, plus suction via suction catheter as needed (i.e., when dyspneic or when phlegm sounds are heard in the airway). The observation group will receive, in addition to the control group's treatment, bronchoscopic treatment 1-2 times, including sputum suction under endoscopy, lavage, and drug instillation. Specific procedure steps: Prepare for the bronchoscopy procedure. Under continuous nasal cannula oxygen and vital sign monitoring via ECG, administer Atropine Injection 0.5mg (National Drug Approval No. H37021468, Shandong Huaxin Pharmaceutical Group Co., Ltd.) combined with Lidocaine Injection (National Drug Approval No. H20065387, China Otsuka Pharmaceutical Co., Ltd.) 0.1g via nebulization for local anesthesia. Insert the Olympus BF-P180 fiber bronchoscope routinely through the nostril, sequentially entering various levels of bronchi. Under direct vision, clear airway secretions, collect lavage fluid for bacterial culture and drug sensitivity testing. If sputum is thick and difficult to suction, lavage with normal saline

can be used. Simultaneously, select sensitive antibiotics for instillation therapy based on the bacterial culture results of the airway secretions. After completion, slowly withdraw the bronchoscope. Both groups will receive continuous treatment for 1 week. Throughout the process, closely monitor the patient's vital signs. If oxygen saturation falls below 80% or heart rate exceeds 130 beats/min, immediately withdraw the fiber bronchoscope and provide symptomatic treatment. Resume the subsequent procedure after vital signs stabilize.

5.4 Adverse Events

Record adverse events, the number of and reasons for trial dropouts in detail.

IV. Adverse Events

1. Classification of Adverse Events and Serious Adverse Events

Common adverse reactions during bronchoscopy include: laryngospasm, airway bleeding, pneumothorax, cardiac arrest, aspiration, hoarseness.

Medical Device Adverse Event: Any harmful event unrelated to the intended effect of a medical device that occurs during the normal use of an approved, qualified medical device, leading or potentially leading to human injury.

Among these, **death** and **serious injury events** must be reported to the monitoring agency. Serious injury refers to any of the following:

① Life-threatening;

② Resulting in permanent impairment of a body function or permanent damage to a body structure;

③ Necessitating medical or surgical intervention to prevent such permanent impairment or damage.

Subject Death: An event resulting in the death of a subject.

Life-Threatening: An event which, in the investigator's judgment, places the subject at immediate risk of death without medical intervention. It does not include an event that might have caused death had it occurred in a more severe form.

Hospitalization: An event resulting in admission to the hospital, regardless of length of stay. This does not include emergency room observation or outpatient clinic visits.

Prolongation of Hospitalization: An event that results in or prolongs a subject's hospitalization.

Persistent or Significant Disability/Incapacity: An event resulting in a condition that substantially disrupts the subject's ability to conduct normal life functions. This does not include relatively minor symptoms such as headache, nausea, vomiting, diarrhea, influenza, or accidental injury.

Important Medical Event: An event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., subject death, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent disability/incapacity).

2. Severity

Physicians can use the following definitions to judge the severity of all adverse events and serious adverse events, serving as study endpoints/data cut-off points.

[Mild] The adverse event is transient, and the patient tolerates it easily.

[Moderate] The adverse event causes discomfort to the subject and interferes with the subject's normal activities.

[Severe] The adverse event significantly affects the subject's daily activities, may cause incapacitation, or is life-threatening.

3. Reporting of Serious Adverse Events

In the event of a Serious Adverse Event, regardless of whether it is related to the device or the control device, the physician must notify Olympus (China) Co., Ltd. within 24 hours of becoming aware of the event.

V. Ethics and Quality

Ethics committee approval will be obtained prior to the initiation of this study.

Before enrolling a patient, authorization must be obtained for the use and/or disclosure of personal and/or health data. To protect patient privacy, the patient's age will be recorded on the Case Report Form instead of the date of birth, and the patient's initials will be recorded on the Case Report Form.

The consistency of the collected Case Report Form data will be checked. Data queries will be issued for inconsistent data, requiring clarification by the physician.

VI. Data Management

Investigators must fill in the collected data into the Case Report Form according to the study protocol requirements. At the end of the study, the investigator will submit the Case Report Forms for all patients enrolled in this study to the data management center. These Case Report Forms must be complete and signed. The consistency of the collected Case Report Form data will be checked. Data queries will be issued for inconsistent data, requiring clarification by the physician.

VII. Statistical Analysis

1. Statistical Software

The data statistical work will be completed by a biostatistician using the statistical software SPSS 22.0.

2. Data Description

Measurement data will be expressed as mean ± standard deviation ($\bar{x} \pm s$), using normality tests and t-tests. Enumeration data will be expressed as n (%), using the Chi-square test (X^2 test). A P-value < 0.05 will be considered statistically significant.

3. Data Statistics

All hypothesis tests will be two-sided, and a P-value < 0.05 will be considered statistically significant. Baseline data will be evaluated for comparability between groups, using two-tailed statistical tests at the α=5% level. Group comparisons for enumeration data will use the Chi-square test, and group comparisons for measurement data will use the t-test.

4. Statistical Analysis Plan

Will be completed by professional statistical personnel. After all data entry and verification are completed, the statistician shall promptly complete the statistical analysis work and produce a written statistical analysis report.

VIII. Final Report and Publication

After the study concludes, the principal investigator will lead the collaboration with investigators from all study centers to compile the study final report. Investigators from all study centers will sign the study final report. The study report will include a description of the study objectives, the methods used in the study, as well as the results and conclusions.

The Upjohn Company will archive the study final report. Without the explicit written consent of The Upjohn Company, investigators cannot disclose it in any form (publication or presentation) to unauthorized personnel.

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