A Randomized Controlled Study to Explore the Clinical Effect of Intermittent Oro-esophageal Tube Feeding vs. Nasogastric Tube Feeding on Cerebral Small Vessel Disease Patients with Dysphagia

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Statement

This trial protocol is confidential and intended for distribution to medical experts, researchers involved in the trial, and other staff members associated with the trial, as well as the medical institutions, ethics committees, and contracted research organizations involved in the trial. Except for providing information to the participants, no content of this trial protocol shall be disclosed or made available to any third party without prior written consent from the sponsor. Furthermore, any partial or complete results of this clinical trial, when published externally in societies, journals, etc., require written consent from the sponsor.

CATALOGUE

Co-organizer

N/A

Abstract

Title	**A Randomized Controlled Study to Explore the Clinical Effect of Intermittent Oro-esophageal Tube Feeding vs. Nasogastric Tube Feeding on Cerebral Small Vessel Disease Patients with Dysphagia**
Drugs	N/A
Approval number of durgs	N/A
Aims	This study aims to explore the clinical effect of IOE vs. NGT on CSVD Patients with Dysphagia.
Design	This was a randomized controlled study
Indications	CSVD Patients with Dysphagia
Total cases	60 CSVD Patients with Dysphagia who received comprehensive rehabilitation therapy. Patients enrolled were randomly divided into the observation group (with IOE, n=30) and the control group (with NGT, n=30)
Center	*The First Affiliated Hospital of Zhengzhou University*
Research period	2023.1-2023.6
Case selection	The inclusion criteria were: 1) Meeting the diagnostic criteria for CSVD, confirmed by MRI; 2) Able to cooperate with treatment and questionnaire investigation, (Generally with a Mini-Mental State Examination (MMSE) score ≥ 24) ; 3) Diagnosed with dysphagia through the Functional Oral Intake Scale (FOIS) and Video Fluoroscopic Swallowing Study (VFSS); 4) Aged between 40 and 70 years; 5) Enteral nutrition support was required and feasible. 5) No history of prior stroke.
Study drug	N/A
Plan	During the treatment period, both groups of patients received conventional treatment and enteral nutrition support. Conventional treatment included health

	education, dietary adjustments, control of risk factors (blood pressure, lipids, etc.), and psychological support. The observation group used IOE for enteral nutrition support. The control group's nutritional support was administered via NGT.
Visit timing	N/A
Procedures	Patients enrolled were randomly divided into the observation group (with IOE, n=30) and the control group (with NGT, n=30). At admission and after treatment, Video Fluoroscopic Swallowing Study (VFSS) and Functional Oral Intake Scale (FOIS), body mass index (BMI), serum albumin (Alb), and hemoglobin (Hb), Modified Barthel Index (MBI) and World Health Organization Quality of Life Assessment Instrument Brief Version (WHOQOL-BREF) were recruited to assess and compare dysphagia, nutritional status, activities of daily living (ADL) and quality of life (QOL). The incidence of pneumonia was recorded and compared.
Assessment	At admission and after treatment, Video Fluoroscopic Swallowing Study (VFSS) and Functional Oral Intake Scale (FOIS), body mass index (BMI), serum albumin (Alb), and hemoglobin (Hb), Modified Barthel Index (MBI) and World Health Organization Quality of Life Assessment Instrument Brief Version (WHOQOL-BREF) were recruited to assess and compare dysphagia, nutritional status, activities of daily living (ADL) and quality of life (QOL). The incidence of pneumonia was recorded and compared.
Safety indicator	AEs

1. Background

Cerebral small vessel disease (CSVD) refers to a heterogeneous group of pathological changes affecting the small arteries, arterioles, capillaries, venules, and small veins within the brain. These changes are attributed to various etiological factors[1]. According to a study conducted in Rotterdam, it has been observed that CSVD comprised a significant proportion, specifically 83.8%, of all cases of cerebrovascular diseases while epidemiological surveys have revealed that approximately half of the incidence of dementia and 25% of ischemic strokes can be attributed to cerebral small vessel disease[2, 3]. Radiologically, CSVD is characterized by enlarged perivascular spaces, cortical subcortical infarcts, white matter lesions, microbleeds, and cerebral atrophy observed on magnetic resonance imaging (MRI)[4]. According to the previous study, it has been demonstrated that CSVD patients exhibit an insidious onset with diverse clinical presentations, encompassing symptoms such as dysphagia, cognitive impairment, anxiety, and depression. Notably, in China, approximately 25% of CSVD patients experience varying degrees of dysphagia, mainly in the cognitive, oral, and pharyngeal phases[5].

The occurrence of subcortical lacunar infarction in the brain can give rise to a range of lacunar syndromes. When the pathological changes involve the knee of the internal capsule and basal part of the brainstem, it can lead to dysphagia in the oral and pharyngeal phrase[6]. Furthermore, CSVD-related negative psychological state may also cause dysphagia in the cognitive phrase. Besides, it has been reported that approximately 60% of individuals with CSVD experienced limb movement disorder, which can also contribute to the development of dysphagia[5]. In patients with dysphagia, various complications may arise, including aspiration, pneumonia, progressive weight loss, malnutrition, edema, impaired gastrointestinal absorption

function, and psychological and social communication disorders[7]. Hence, comprehensive and individualized treatment plan should be conducted for CSVD patients with dysphagia. Nevertheless, during the initial phase of hospitalization, it is frequently observed that patients' swallowing function is inadequate to sustain oral intake. Consequently, tube feeding presents itself as a temporary solution to provide patients with essential nutritional support especially at the early stage, which forms the backbone of the overall treatment process, and therefore, its selection is critical[8].

Currently, for CSVD patients with dysphagia, the primary nutritional supports available are enteral nutrition and parenteral nutrition[9]. Parenteral nutrition involves intravenous administration of essential nutrients, ensuring rapid nourishment for patients in the short term. Nonetheless, prolonged reliance on this method may disrupt gastrointestinal function and lead to gastrointestinal disturbances[10]. Enteral nutrition mainly encompasses NGT and gastrostomy, with each approach has its own disadvantages[11]. Both NGT and gastrostomy are viable options in the short term. However, prolonged use can result in various complications including gastroesophageal reflux, pharyngitis, aspiration pneumonia and electrolyte imbalances[12]. In China, due to the invasive nature of gastrostomy, patients generally exhibit lower acceptance[13]. Moreover, NGT poses a risk of recurrent pneumonia, significantly impacting the patient's functional recovery and potentially leading to increased risk of anxiety and depression[14]. Therefore, the selection of a secure and comfortable approach becomes paramount.

IOE, as an alternative enteral nutrition mode, was introduced in the "Expert Consensus on Assessment and Treatment of Swallowing Disorders in China" in 2017[15]. It was pointed out that IOE maintains the normal physiological structure of the digestive tract with its intermittent insertion mode, which is safe, simple, and less likely to cause mucosal damage[16]. In recent years, the practice of IOE has gradually increased in China, and it has achieved satisfying clinical results in improving nutritional status[17]. However, the application of IOE in CSVD patients is relatively insufficient, and further research is needed to explore the relationship between IOE and ADL, QOL.

2.Objective

Therefore, this study was carried out to explore the clinical effect of IOE vs. NGT in CSVD patients with dysphagia, mainly on nutritional status, swallowing function, pneumonia, ADL and QOL.

3.Design

3.Type：This was a multicenter randomized controlled study

3.2 Study patient population

This was a multicenter randomized controlled study, including CSVD patients with dysphagia who received comprehensive rehabilitation therapy in the department of rehabilitation medicine from 3 hospitals in China from January 2023 to June 2023. Through literature review, it was found that when estimating the expected sample size using VFSS as an indicator of dysphagia, the maximum target sample size was achieved. In this case, M1=7.96, M2=6.51, S=1.90, α= 0.05, (1-β) =80%, it was calculated the following:

N1= N2 = \frac[{2 \times (Z_{\alpha/2} + Z_{\beta})^2 \times S^2}][{(M1 - M2)^2}]≈27

To assume a 10% dropout rate, the estimated sample size for this study was calculated as 27*110%, which is approximately 30.

A total number of 60 CSVD patients with dysphagia was finally enrolled. With a random number table, cases enrolled were divided into the observation group (with IOE, n=30) and the control group (with NGT, n=30).

3.3Intervention

During the treatment, all patients were provided with comprehensive rehabilitation therapy

as follows:

1) Basic treatment, including corresponding control of risk factors and education on healthy lifestyles.
2) Swallowing training, including lemon ice stimulation, Mendelsohn maneuver, empty swallowing training, and pronunciation training.
3) Pulmonary function training, including standing training, cough training, and diaphragm muscle training.

Besides, the control group was given enteral nutritional support with NGT according to the relevant guidelines. Within 4 hours after admission, the placement of the feeding tube was conducted by professional medical staffs and after intubation, the tube was secured to the patient's cheek with medical tape. The feeding was conducted once every 3-4 hours, with 200-300ml each time. The total feeding volume was determined based on daily requirements[18].

The observation group was given enteral nutritional support with IOE according to the following procedure[19]: Before each feeding, inside and outside of the tube was cleaned with water. During feeding, the patient should maintain a semi-reclining or sitting position with mouth opened, and the tube was inserted slowly and smoothly into the upper part of the esophagus by medical staffs while the appropriate depth of intubation was checked with the calibration markings on the tube wall. The distance from the incisors to the head part of the tube should be between 22-25 cm (Appendix). However, the specific depth should be evaluated based on patients' feedback and adjusted accordingly. After insertion, the tail part of the tube should be put into a container full of water and the absence of continuous bubbles indicated a successful intubation. Then, the feeding was to be conducted three times per day with 50 ml per minute and 400-600ml for each feeding. After each feeding, the nutrition tube was removed and placed in a container filled with 20% solution of vinegar for rinsing and storage. For patients with sensitive pharyngeal reflex, a small amount of 2% Lidocaine can be applied to the pharyngeal area for surface anesthesia before tube insertion.

The feeding content was formulated by the nutritionists based on the patient's condition and relevant guidelines to reach the energy demand as 20-25 kcal/kg/day and protein supplementation of 1.2-2.0 g/kg/day for both two groups[18]. For patients with limited tube feeding compliance, we made appropriate adjustments to ensure that they were not at risk of severe malnutrition as much as possible.

4、Case selection

4.1 **The inclusion and exclusion criteria**

The inclusion criteria were: 1) Meeting the diagnostic criteria for CSVD, confirmed by MRI; 2) Able to cooperate with treatment and questionnaire investigation, (Generally with a Mini-Mental State Examination (MMSE) score ≥ 24) ; 3) Diagnosed with dysphagia through the Functional Oral Intake Scale (FOIS) and Video Fluoroscopic Swallowing Study (VFSS); 4) Aged between 40 and 70 years; 5) Enteral nutrition support was required and feasible. 5) No history of prior stroke. The exclusion criteria were: 1) With dysphagia related to other cerebrovascular diseases or caused by neurodegenerative diseases; 2) Complicated with severe liver and kidney failure, tumors, or hematological disorders; 3) Simultaneously in need to undergo other therapy that might affect the outcomes of this study; 4) Unable or unwilling to undergo VFSS; 5) pregnant or nursing females.

4.2 **The dropout criteria**

Dropout and termination criteria were: 1) a patient or family members requested to withdraw voluntarily; 2) development of intolerance; 3) emergence of unexpected events requiring adjustment of treatment. 4) the patient's condition deteriorated severely.

4.3 Termination criteria

If more than half of the subjects experience mild or higher adverse reactions (such as 3/6, 4/8), the trial should be terminated.

5、Study management

5.1 Ethical Considerations and Informed Consent

5.1.1 Approval by an Independent Ethics Committee

Prior to the commencement of the trial, the researcher/research institution should obtain written approval from the independent ethics committee regarding the trial protocol, informed consent form, subject recruitment procedures, and any other written materials to be provided to the subjects. During the course of the trial, if there are any additions or revisions to the trial protocol, informed consent form, etc., written approval from the independent ethics committee should be obtained again.

5.1.2 Informed Consent

The researcher or their designated representative will be responsible for explaining the background of the study, the pharmacological characteristics of the investigational medication, the trial protocol, as well as the potential benefits and risks of participating in the trial to each subject, the subject's legally authorized representative, or witness. They should obtain written informed consent signed by the subject or their legally authorized representative and the investigator before the subject enters the trial (before screening).

The final text of the informed consent form should include the following: the purpose of the trial, trial procedures, the subject's obligations, the foreseeable benefits and risks and inconveniences of participating in the trial, treatment and appropriate insurance compensation available to the subject in case of trial-related harm, access to trial data, and confidentiality of subject information.

The informed consent form should obtain written approval from the ethics committee and be written in a language that is understandable to the subject. The subject or their legally authorized representative, the researcher conducting the informed consent process, or their representative should all sign and date the informed consent form. The original copy of the informed consent form should be retained by both the researcher and the subject. If important new information related to the investigational drug in a clinical trial is discovered, the informed consent form must be modified in writing, submitted for approval to the ethics committee, and re-obtained from the subject.

5.2 Protection

Prior to the start of the clinical trial, the trial protocol must be reviewed and approved by the ethics committee of the responsible research institution before implementation. Any modifications to the trial protocol during the course of the clinical trial should also be approved by the ethics committee before they can be executed.

Clinical researchers must inform subjects that participation in the clinical trial is voluntary and that they have the right to withdraw from the trial at any stage without facing discrimination or retaliation. Subjects must be made aware that their participation in the trial and their personal information will be kept confidential. They should also be informed about the nature of the clinical trial, the trial objectives, the potential anticipated benefits, and the possible risks and inconveniences. Subjects should be informed of their rights and obligations as outlined in the Helsinki Declaration, and given sufficient time to consider whether they wish to participate in the trial.

5.3 Management Unit

This study will be conducted at the First Affiliated Hospital of Zhengzhou University and will be overseen by the ethics committee of the hospital and the clinical trial institution.

6. References

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