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INPLASY

Systematic Review and Meta-Analysis of the Effects of Different Acid Stimulations on Stroke Patients with Dysphagia

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 January 2026 and was last updated on 21 January 2026.

INTRODUCTION

Review question / Objective To evaluate the effects of different acid stimulation modalities on stroke patients with dysphagia by meta-analysis.P(Population):Stroke patients with dysphagia;I (Intervention):Different acid stimulation modalities for dysphagia (carbonated beverages, lemon acid, VitC);C (Comparison):Conventional swallowing rehabilitation (e.g.neuromuscular electrical stimulation, oral motor training), placebo stimulation (neutral pH solution), or no additional stimulation (routine nursing);O (Outcomes):Primary outcomes：Swallowing function assessment scores ,Secondary outcomes：Incidence of aspiration pneumonia, nutritional status indicators , swallowing-related quality of life ;S (Study design):Randomized controlled trials (RCTs).

Rationale Dysphagia is a highly prevalent and debilitating complication following stroke, with an incidence ranging from 37% to 81% in stroke populations. This condition not only impairs oral intake and nutritional status but also elevates the risk of aspiration pneumonia, prolonged hospital stay, and reduced quality of life, imposing a substantial clinical and socioeconomic burden on stroke patients, their caregivers, and healthcare systems. As a core component of clinical swallowing rehabilitation for stroke-related dysphagia, sensory stimulation interventions have been widely applied to improve swallowing function by activating the impaired sensory pathways of the oropharyngeal region, and acid stimulation has emerged as a promising modality among these approaches due to its strong and direct sensory activation effect.

In clinical practice, various acid stimulation modalities have been adopted for stroke patients with dysphagia, including different operational forms (e.g., oral citric acid swab stimulation, pharyngeal acid irrigation), variable technical parameters (e.g., different concentrations of citric acid, stimulation frequency and duration), and combined application with other rehabilitation interventions (e.g., acid stimulation plus neuromuscular electrical stimulation). A growing

body of clinical studies has explored the efficacy of these acid stimulation modalities in improving swallowing function and reducing adverse clinical outcomes in stroke patients with dysphagia, but the existing evidence remains inconsistent. Some studies have demonstrated that high-concentration acid stimulation yields a more significant improvement in swallowing function assessment scores (e.g., FOIS, VFSS scores), while others report no statistically significant differences between different acid stimulation parameters and conventional sensory stimulation (e.g., cold stimulation). Additionally, the sample sizes of individual clinical studies are often small, and the study designs and outcome assessment indicators are heterogeneous, leading to limited persuasiveness and generalizability of the single-study results.

To date, no systematic review and meta-analysis has comprehensively synthesized the available clinical evidence to compare the efficacy and safety of different acid stimulation modalities for stroke patients with dysphagia. A well-conducted meta-analysis is urgently needed to quantitatively integrate the results of relevant clinical studies, clarify the differential effects of various acid stimulation modalities (operational forms, technical parameters, combined interventions) on swallowing function, incidence of aspiration pneumonia, nutritional status, and swallowing-related quality of life in this population, and identify the optimal acid stimulation modality for clinical practice.

This study therefore aims to conduct a systematic review and meta-analysis of the published clinical studies on different acid stimulation modalities for stroke patients with dysphagia. By strictly following the PRISMA guidelines, we will screen eligible studies, extract valid data, and perform quantitative synthesis and heterogeneity analysis, to provide high-quality evidence-based recommendations for the clinical selection of optimal acid stimulation modalities in swallowing rehabilitation for stroke-related dysphagia, and to guide the standardization and individualization of clinical swallowing rehabilitation practice. Meanwhile, this study will also explore the potential sources of heterogeneity among existing studies and propose directions for future clinical research, which is of great significance for improving the clinical efficacy of swallowing rehabilitation and reducing the adverse complications of stroke-related dysphagia.

Condition being studied Stroke-related dysphagia refers to the difficulty or inability to safely and effectively swallow food, liquids, or saliva due to impaired oral, pharyngeal, or esophageal motor and sensory function caused by a stroke (ischemic or hemorrhagic). As a common and disabling complication post-stroke, it has an incidence of 37% to 81% among stroke patients, with higher rates in the acute phase.The condition arises primarily from damage to the brain regions responsible for controlling swallowing (e.g., cerebral cortex, brainstem), which disrupts the coordinated sequence of muscle movements and sensory perception required for normal swallowing. Clinically, patients may present with symptoms such as coughing or choking during eating/drinking, difficulty initiating swallowing, food residue in the mouth or throat, regurgitation, and unintentional weight loss. Beyond affecting oral intake and nutritional status, stroke-related dysphagia significantly increases the risk of life-threatening complications like aspiration pneumonia (due to food/liquid entering the airway), dehydration, and malnutrition. It also impairs patients' quality of life, prolongs hospital stays, and imposes substantial burdens on caregivers and healthcare systems. Timely assessment (e.g., via videofluoroscopic swallowing study, VFSS; functional oral intake scale, FOIS) and targeted rehabilitation interventions are crucial to improve swallowing function and reduce adverse outcomes.

METHODS

Participant or population This systematic review and meta-analysis will focus on adult patients with stroke-related dysphagia (aged 18 years and above) who have been diagnosed with either ischemic or hemorrhagic stroke, confirmed by neuroimaging examinations (e.g., computed tomography, CT; magnetic resonance imaging, MRI). All included participants must have a clinical diagnosis of dysphagia resulting directly from stroke-related damage to the swallowing control centers (e.g., cerebral cortex, brainstem) of the central nervous system, with impaired oral, pharyngeal, or esophageal motor and/or sensory swallowing function verified by standardized clinical swallowing assessments (e.g., videofluoroscopic swallowing study [VFSS], functional oral intake scale [FOIS], penetration-aspiration scale [PAS]).

Participants will be included regardless of the stroke phase (acute, subacute, or chronic) and the severity of dysphagia, with no restrictions on gender, ethnicity, or geographical region. Exclusion criteria for participants include: dysphagia caused by non-stroke etiologies (e.g., Parkinson's disease, dementia, head and neck cancer, esophageal structural lesions); severe comorbidities that independently impact swallowing function or

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interfere with rehabilitation interventions; and patients with severe cognitive or communication impairment that prevents cooperation with swallowing assessments and acid stimulation interventions.

Intervention This review will systematically evaluate a broad group of acid stimulation interventions as the core experimental measures for the rehabilitation of stroke-related dysphagia, with all interventions centered on acid-mediated sensory activation of the oropharyngeal swallowing pathway to improve impaired swallowing motor and sensory function. These acid stimulation modalities are categorized by clinical application characteristics, with detailed subtypes and operational variables as follows:
acid stimulation interventions (by operational form)
Oral acid stimulation (e.g., citric acid swab swiping of the oral cavity/oropharyngeal mucosa, oral administration of acid solutions) and pharyngeal acid stimulation (e.g., pharyngeal acid irrigation, targeted acid infusion to the pharyngeal trigger zone), the three most commonly used clinical single-modality acid stimulation approaches.
Acid stimulation with variable technical parameters
Acid stimulation interventions with different core technical settings, including various concentrations of acidic agents (predominantly citric acid, the first-line clinical acid stimulant), different stimulation frequencies/durations/cycles, and varying doses of acid solution applied per intervention session.
Combined acid stimulation interventions
Co-administration of acid stimulation with other evidence-based swallowing rehabilitation interventions for stroke-related dysphagia, such as acid stimulation combined with neuromuscular electrical stimulation (NMES), cold sensory stimulation, oral motor training, or respiratory muscle training.
All acid stimulation interventions included in the review are clinically applied passive/active rehabilitation measures implemented by trained medical staff (speech therapists, rehabilitation nurses, neurologists) for stroke patients with dysphagia, with standardized operational protocols reported in the original studies. No non-clinical, in vitro, or animal-based acid stimulation interventions will be included.

Comparator Conventional swallowing rehabilitation (neuromuscular electrical stimulation, oral motor training), placebo stimulation (neutral pH solution), or no additional stimulation (routine nursing).

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria —. Study Population
1. Adult patients (aged ≥ 18 years) with confirmed ischemic or hemorrhagic stroke, diagnosed by neuroimaging examinations (e.g.computed tomography [CT], magnetic resonance imaging [MRI]).
2. Patients with stroke-related dysphagia, which is defined as difficulty or inability to safely and effectively swallow food, liquids, or saliva due to impaired oral, pharyngeal, or esophageal motor and sensory function caused by stroke. The diagnosis must be verified by standardized clinical swallowing assessments, including but not limited to videofluoroscopic swallowing study (VFSS), functional oral intake scale (FOIS), and penetration-aspiration scale (PAS).
3. Patients with clinical symptoms related to dysphagia (e.g. coughing or choking during eating/drinking, difficulty initiating swallowing, food residue in the mouth or throat, regurgitation, unintentional weight loss), with no other clear etiologies for dysphagia.
二. Study Design
Randomized controlled trials (RCTs) .Studies that explicitly evaluate the efficacy of acid stimulation interventions for stroke-related dysphagia, with clear intervention groups (different acid stimulation modalities) and comparative intervention groups (conventional rehabilitation, usual care, placebo, etc.).
三. Outcome Indicators
1. Studies that report at least one extractable objective outcome indicator related to swallowing function or clinical prognosis, such as swallowing function assessment scores (VFSS, FOIS, PAS), incidence of aspiration pneumonia, nutritional status indicators (e.g.albumin, body mass index), swallowing-related quality of life, and length of hospital stay.
四. Study Publication
1. Publicly published clinical studies in English or Chinese, with complete full text available.
2. Studies with complete baseline data and no obvious logical contradictions in the reported results.
Exclusion Criteria
1. Study Population: Patients with dysphagia caused by non-stroke etiologies, including but not limited to Parkinson's disease, dementia, head and neck cancer, esophageal structural lesions, and other central nervous system diseases.
2. Patients with severe comorbidities (e.g. severe heart, liver, or kidney failure) that independently

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affect swallowing function or interfere with rehabilitation interventions.
3. Patients with severe cognitive or communication impairment, mental illness, or other conditions that prevent cooperation with swallowing function assessments and acid stimulation interventions.
4. Pediatric patients (aged < 18 years) or stroke patients who were lost to follow-up during the study period.
6. Study Design:Non-clinical controlled studies, such as case reports, reviews, meta-analyses, animal experiments, in vitro basic research, and expert commentaries.Studies without a control group, with unclear comparative intervention measures, or only reporting the single efficacy of acid stimulation without comparative analysis.Duplicate published studies, studies with incomplete data (unable to extract effect sizes), or studies with obvious selection bias, performance bias, or detection bias.
3. Intervention Measures:Studies where acid stimulation interventions are non-clinical operational forms (e.g. in vitro experiments).Studies where acid stimulation is combined with other unclear rehabilitation measures, and the independent efficacy of acid stimulation cannot be separated and analyzed.

Information sources

1. Intended Information Sources
To ensure comprehensive retrieval of relevant studies and minimize publication bias, this systematic review and meta-analysis will search multiple types of information sources, covering electronic databases, grey literature, trial registers, and author contacts. The specific sources are detailed as follows:
1.1 Electronic Databases
Both English and Chinese electronic databases will be searched to cover international and domestic clinical evidence related to acid stimulation for stroke-related dysphagia. The databases include:
English databases: PubMed, Embase, Cochrane Library , Web of Science Core Collection, Scopus. These databases are the most authoritative and comprehensive in the field of global medical and clinical research, ensuring the retrieval of high-quality international RCTs and controlled trials.
Chinese databases: China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, VIP Chinese Science and Technology Periodical Database (VIP), China Biomedical Literature Database (CBM). These databases cover domestic clinical studies, master's and doctoral dissertations, and periodical articles, avoiding the omission of relevant Chinese-language evidence.
1.2 Grey Literature
Grey literature, which is not formally published or indexed in mainstream databases, will be retrieved to supplement potential unpublished studies and reduce publication bias.
1.3 Trial Registers
Clinical trial registers will be searched to identify ongoing, completed but unpublished, or partially reported clinical trials, which can provide original data and avoid missing studies with negative results. The registers include:
International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO).
U.S. National Institutes of Health Clinical Trials Database (ClinicalTrials.gov).
Chinese Clinical Trial Registry (ChiCTR).
1.4 Contact with Authors
For studies with incomplete data (e.g., missing outcome indicators, unclear intervention protocols, or unextractable effect sizes), the corresponding authors of the included studies will be contacted via email. We will request supplementary data, detailed study protocols, and relevant unpublished information to ensure the completeness and accuracy of the extracted data.
2. Retrieval Design
2.1 Retrieval Strategy
The retrieval strategy will be developed based on the PICOS framework of the study, with core retrieval terms including stroke, dysphagia, acid stimulation, randomized controlled trial, etc. The terms will be combined using Boolean operators (AND/OR/NOT) and adjusted according to the retrieval rules of different databases .
A preliminary pilot search will be conducted first to optimize the retrieval terms and adjust the strategy. The final retrieval strategy will be documented in detail, including all retrieval terms, combinations, and database-specific adjustments, to ensure the reproducibility of the retrieval process.
2.2 Retrieval Period
The retrieval will cover all studies published from the establishment of each database to the date of the final search.
2.3 Language Restriction
Studies published in English or Chinese will be included.
2.4 Retrieval Quality Control
Two independent reviewers will conduct the database retrieval separately using the pre-determined retrieval strategy. After the initial retrieval, the two reviewers will cross-check the retrieved literature to resolve discrepancies through discussion. If consensus cannot be reached, a third senior reviewer will be invited to make a final decision. This process ensures the comprehensiveness and accuracy of the literature retrieval and avoids missing or incorrectly including studies.

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Main outcome(s)

1. Primary Outcomes

Core: Swallowing function improvement (assessed via VFSS, FOIS, PAS). Timing: Baseline (pre-intervention) and post-intervention (2–8 weeks); follow-up data (3/6 months) if available. Effect measures: WMD/SMD (95% CIs) for continuous/ordinal outcomes, OR (95% CIs) for ordinal data.

2. Secondary Outcomes

Including: (1) Aspiration pneumonia incidence (OR, 95% CIs); (2) Nutritional indicators (ALB, BMI; WMD/SMD, 95% CIs); (3) SWAL-QOL scores (WMD/SMD, 95% CIs); (4) Length of hospital stay (WMD, 95% CIs). Timing: Consistent with primary outcomes.

Quality assessment / Risk of bias analysis The quality of included primary studies will be independently assessed by two reviewers using domain-specific, validated tools, consistent with Cochrane Collaboration guidelines. Discrepancies will be resolved through discussion; a third senior reviewer will arbitrate if consensus is not reached. For randomized controlled trials (RCTs), the Risk of Bias 2.0 (ROB 2.0) tool will be adopted, evaluating 5 core domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants, personnel, and outcome assessors; (4) incomplete outcome data; (5) selective outcome reporting. Each domain will be classified as "low risk", "high risk", or "some concerns" based on study documentation.

For non-randomized controlled trials (NRS), the Methodological Index for Non-Randomized Studies (MINORS) will be used (12-item scale, 0–2 points per item, total 0–24 points). Key domains include clear research objectives, appropriate inclusion criteria, baseline comparability, and reliable outcome measurement. Scores ≥18 indicate high quality, 12–17 moderate quality, and <12 low quality.

Additional assessments will include checking for other potential biases (e.g., funding sources, conflicts of interest) and outcome measurement reliability. A summary risk-of-bias graph and table will be generated to present assessment results transparently. Low-quality studies (high risk of bias/MINORS <12) will be excluded from meta-analysis; sensitivity analysis will be performed if moderate-quality studies are included.

Strategy of data synthesis Data analysis will be conducted using RevMan 5.4 software, adhering to Cochrane Collaboration guidelines. First, heterogeneity among included studies will be evaluated via I^2 statistic and Q-test. $I^2 < 50\%$ and $P > 0.1$ indicate low heterogeneity, and a fixed-effects model will be used for effect size pooling; $I^2 \geq 50\%$ or $P \leq 0.1$ indicate significant heterogeneity, and a random-effects model will be adopted, with subgroup analysis to explore potential sources.

Effect measures will align with predefined outcomes: WMD/SMD (95% CIs) for continuous outcomes (e.g., VFSS scores, BMI); OR (95% CIs) for dichotomous/ordinal outcomes (e.g., aspiration pneumonia incidence, FOIS grades). Statistical significance will be set at $P < 0.05$.

Subgroup analysis will be performed based on key variables: acid stimulation modalities (single vs. combined), stroke phase (acute vs. chronic), and intervention duration to identify differential effects. Sensitivity analysis will be conducted by excluding one study at a time and re-pooling data to test result stability.

Publication bias will be assessed via funnel plot if ≥10 studies are included; Egger's or Begg's test will be used for quantitative verification. Missing data will be handled by imputing means (continuous data) or using intention-to-treat analysis where possible. If data are too heterogeneous or incomplete to pool, a narrative synthesis will be provided instead of meta-analysis.

Subgroup analysis Subgroup analysis will be systematically performed to explore potential sources of heterogeneity and identify differential effects of acid stimulation across specific populations or intervention scenarios, with predefined subgroups based on clinical relevance and study characteristics. Key subgroups and their rationales are as follows: (1) Acid stimulation modalities: Divided into single acid stimulation (e.g., oral citric acid swab, pharyngeal acid irrigation) and combined acid stimulation (acid stimulation plus NMES/cold stimulation/oral motor training), aiming to compare the efficacy of different intervention forms. (2) Stroke phase: Classified as acute phase (≤1 month post-stroke) and chronic phase (>1 month post-stroke), considering the difference in neural plasticity and swallowing function recovery potential between phases. (3) Intervention duration: Stratified into ≤4 weeks and >4 weeks, based on the typical clinical rehabilitation course for stroke-related dysphagia, to assess the impact of intervention length on outcomes. (4) Dysphagia severity: Grouped by baseline FOIS grades (mild: 5–7, moderate: 3–4, severe: 1–2) if data are available, to clarify whether efficacy varies by severity. Each subgroup will be analyzed using the same effect measures and statistical models as the main analysis, with results presented separately to provide targeted evidence for clinical decision-making.

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Sensitivity analysis Sensitivity analysis will be performed to test the robustness and stability of the meta-analysis results, aiming to identify potential factors affecting the credibility of pooled effects. Specific methods are as follows:
(1) One-by-one exclusion analysis: Excluding one included study at a time, re-pooling the remaining data, and comparing the changes in effect sizes (WMD/SMD/OR) and 95% CIs with the main analysis.
(2) Quality-stratified analysis: Excluding moderate-quality studies (e.g., RCTs with "some concerns" of bias, NRS with MINORS 12–17) and re-analyzing the high-quality study data alone.
(3) Statistical model adjustment: Switching between fixed-effects and random-effects models for the same dataset to verify the impact of model selection on results.
The results will be considered stable if no significant changes in effect direction or statistical significance are observed after sensitivity analysis. If substantial fluctuations occur (e.g., effect size crossing the null value, P-value switching between <0.05 and ≥ 0.05), potential influencing factors (e.g., single study bias, small sample size) will be further explored and discussed in the discussion section.

Country(ies) involved China.

Keywords Stroke,Dysphagia,Acid stimulation, Carbonated beverages, lemon, VitC.

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