Study Protocol

Title

Transcutaneous Auricular Vagus Nerve Stimulation for the Prevention of Emergence Agitation and Emergence Delirium After Adenotonsillectomy in Children: A Randomized, Double-Blind, Interventional Study

Background

Emergence agitation (EA) and emergence delirium (ED) refer to a cluster of negative behavioral symptoms occurring during the early recovery phase from general anesthesia in children, characterized by crying, restlessness, and disorientation. The reported incidence ranges from 25% to 80% [1-5].The occurrence of ED not only delays recovery, increases postoperative complications and healthcare costs, but also reduces parental satisfaction with anesthesia management [6],making it a pressing issue in pediatric anesthesia.

Although the exact etiology of ED remains unclear,it is strongly associated with exposure to volatile anesthetics. Several studies have demonstrated that inhalational agents such as isoflurane, halothane, sevoflurane, and desflurane are linked to a higher incidence of EA/ED, with sevoflurane showing the strongest association and significantly increasing the risk of pediatric anesthesia emergence delirium (PAED). In addition to anesthetic factors, the type of surgery plays an important role. EA is less frequent after tonsillectomy, thyroid, or circumcision surgeries, but occurs more commonly following ophthalmic and otolaryngologic procedures [6].Moreover, preoperative anxiety and postoperative pain are closely related to ED. Higher preoperative anxiety scores on the modified Yale Preoperative Anxiety Scale (mYPAS) are independently associated with an increased risk of ED, with each 10-point increase correlating to a 10% rise in risk [7].Postoperative pain has also been recognized as a major trigger for ED. Therefore, reducing anxiety and optimizing perioperative analgesia may help decrease the incidence of ED following sevoflurane anesthesia[3,8-10].

To prevent or manage ED,various pharmacological and non-pharmacological strategies have been explored [11-13], but their overall efficacy remains uncertain. Agents such as fentanyl, propofol, and dexmedetomidine may alleviate symptoms but can prolong emergence or induce respiratory depression. Midazolam has been shown to reduce the incidence of ED in children [14]. Intravenous administration is the most commonly used route for prevention[15],and a single bolus of 0.5 mL/kg midazolam administered at the beginning or end of surgery has demonstrated efficacy [14]. However, due to its relatively long half-life(0.79–2.83h) and active metabolite(1-hydroxymidazolam), its use may delay postoperative recovery [16,17].

Among non-pharmacological approaches, behavioral interventions such as handheld video games and video distraction can help relieve preoperative anxiety [18,19],but they are not suitable for anesthetized or unconscious children. Although parental presence during induction may reduce anxiety to some extent, this approach is often impractical in the operating room and may interfere with surgical workflow [19].

Recently, growing evidence has emphasized the role of the autonomic nervous system (ANS) in postoperative recovery. Increased vagal activity has been shown to improve physical performance[20], reduce postoperative pain scores [21-23], alleviate anxiety and depression [24]and improve sleep quality [25]. These effects are partly through the cholinergic anti-inflammatory pathway and related mechanisms [26-28].However, perioperative conditions such as systemic inflammation [29], regional anesthesia [30]and general anesthesia [31] may impair autonomic regulation, leading to decreased vagal tone and sympathetic overactivation [20,32,33].

Transcutaneous auricular vagus nerve stimulation (ta-VNS), a safe and non-invasive neuromodulatory technique, stimulates the auricular branch of the vagus nerve located in the cymba conchae [34], thereby activating vagal pathways to produce anti-inflammatory, analgesic, and anxiolytic effects while mitigating stress responses [21-23]. It represents a promising strategy to modulate autonomic balance and improve perioperative outcomes.

Based on these findings, we designed a randomized, double-blind, controlled trial to systematically evaluate the efficacy of ta-VNS in preventing emergence agitation and delirium following tonsillectomy and adenoidectomy in children. This study aims to provide a safe and non-invasive intervention for the prevention of ED in pediatric anesthesia and to offer new theoretical and clinical evidence supporting the use of neuromodulation in perioperative management.

Study Objective

To investigate the effect of transcutaneous auricular vagus nerve stimulation (ta-VNS) on emergence agitation (EA) and emergence delirium (ED) in children undergoing adenotonsillectomy.

Study Design and Methods

Study Population

This study will enroll pediatric patients scheduled for elective adenotonsillectomy under general anesthesia. The inclusion and exclusion criteria are as follows:

Inclusion Criteria

1. Children aged 3 to 8 years.
2. Diagnosed with tonsillar and/or adenoidal hypertrophy at The First Affiliated Hospital of Zhejiang Chinese Medical University, and scheduled to undergo adenotonsillectomy

under sevoflurane inhalational general anesthesia.

3. Classified as American Society of Anesthesiologists (ASA) physical status I–II.
4. Able to understand the study procedures and assessment scales, and communicate effectively with the research staff.

Exclusion Criteria

1. Children with ASA physical status III–IV, or with hepatic, renal, cardiovascular, or endocrine dysfunction.
2. Children with neuromuscular diseases or left auricular dermatitis.
3. Recent respiratory tract infection, developmental delay, or autism.
4. Children receiving specialized institutional care or living in social welfare facilities, or with any other condition that may interfere with study participation.
5. Participation in other ongoing clinical trials.

Study Content

Participant Grouping, Intervention, and Blinding

After obtaining written informed consent from the child's legal guardian, participants will be randomly assigned in a 1:1 ratio to either the active stimulation group or the sham stimulation group using a computer-generated random number table. Randomization will be completed prior to the first preoperative intervention. Group allocation information will be kept confidential by the study designer, while both the implementers and data analysts will remain blinded to group assignments to ensure a double-blind design.The sham stimulation device will be identical in appearance, wearing method, and operation procedure to the active stimulation device to ensure participants cannot distinguish the stimulation type.

In the active stimulation group, participants will receive active electrical stimulation on the left cymba conchae. The stimulation parameters are as follows: frequency 25 Hz, pulse width 300 μs, 30 s on/30 s off alternating mode. The stimulation will last for three consecutive days:

1. The first stimulation begins in the preoperative preparation area, applied by the guardian or parent under supervision.
2. The stimulation continues intraoperatively and in the post-anesthesia care unit (PACU).
3. The device will be turned off and removed upon discharge from PACU.

The stimulation intensity will start at level 1 and increase by one level at a time (each level ≈ 0.4 V) until the child reports a tingling sensation, after which the intensity will be adjusted to the highest comfortable level without pain. On postoperative days 1 and 2, stimulation will be applied twice daily (morning and afternoon), each lasting 30 minutes. An operator must be present throughout each stimulation session to supervise.

The sham group will receive an identical procedure, with electrodes placed on the left cymba conchae and stimulation adjusted similarly before being turned off. To monitor compliance, nursing staff will record the start and end time of each stimulation, completion of device placement, and child cooperation during the intervention.

Anesthesia Protocol

Standard monitoring includes continuous ECG, pulse oximetry (SpO_2), bispectral index (BIS), and noninvasive blood pressure, initiated before induction and recorded every 5 minutes.Anesthesia will be induced with fentanyl (2–2.5 $\mu g \cdot kg^{-1}$), propofol (2–2.5 $mg \cdot kg^{-1}$), and rocuronium bromide (0.6 $mg \cdot kg^{-1}$), with 100% oxygen (4 $L \cdot min^{-1}$). After successful induction and complete muscle relaxation, tracheal intubation will be performed using a video laryngoscope.

During anesthesia maintenance, the sevoflurane concentration (2–4%) will be dynamically adjusted to maintain BIS around 50 (range 40–60) and vital signs within ± 20% of baseline. The gas mixture will consist of air/oxygen (50%) at a flow rate of 2 $L \cdot min^{-1}$. The end-tidal CO_2 ($PETCO_2$) will be maintained at 35–45 mmHg by adjusting the respiratory rate and tidal volume.If blood pressure or heart rate exceeds 20% of baseline and inadequate anesthesia is excluded, fentanyl 0.5–1 $\mu g \cdot kg^{-1}$ may be administered as needed.At the end of surgery, all anesthetic agents will be discontinued, and neuromuscular blockade will be antagonized using sugammadex sodium.

Outcome Measures (All Are Routine Clinical Assessments)

a. Primary Outcome

(1) Incidence of Emergence Delirium (ED)

ED will be diagnosed when the Pediatric Anesthesia Emergence Delirium (PAED) score is ≥10 and the FLACC (Face, Legs, Activity, Cry, Consolability) score is <4.If the PAED score ≥10 and FLACC score ≥4, the child will first receive analgesic treatment: when FLACC ≥4, fentanyl 0.5 $\mu g \cdot kg^{-1}$ will be administered intravenously.Five minutes after analgesia, the evaluation will be repeated.If the PAED score remains ≥10 after reassessment, ED will be confirmed regardless of the FLACC score[35].

b. Secondary Outcomes

(1) Incidence of Postoperative Pain

Defined as FLACC score ≥4.

FLACC scores will be assessed at 0, 5, 10, 20, and 30 minutes after anesthesia emergence.

(2) Quality of Recovery in Children

On postoperative days 1–2, the Pediatric Quality of Recovery (PedSQoR) scale will be used to

evaluate postoperative recovery.

The PedSQoR (20-item) questionnaire comprehensively reflects children's physical, emotional, and psychological recovery after surgery and anesthesia.

Proxy Report: for children aged 2–7 years, completed by parents or caregivers.

Self-Report: for children aged 8–17 years, completed by the child.

The total score ranges from 20 to 100, with higher scores indicating better recovery quality[36].

(3) Recovery Time

Defined as the time interval from cessation of sevoflurane to the moment the child awakens and responds to their name when called in a normal tone, including any delay due to ED.

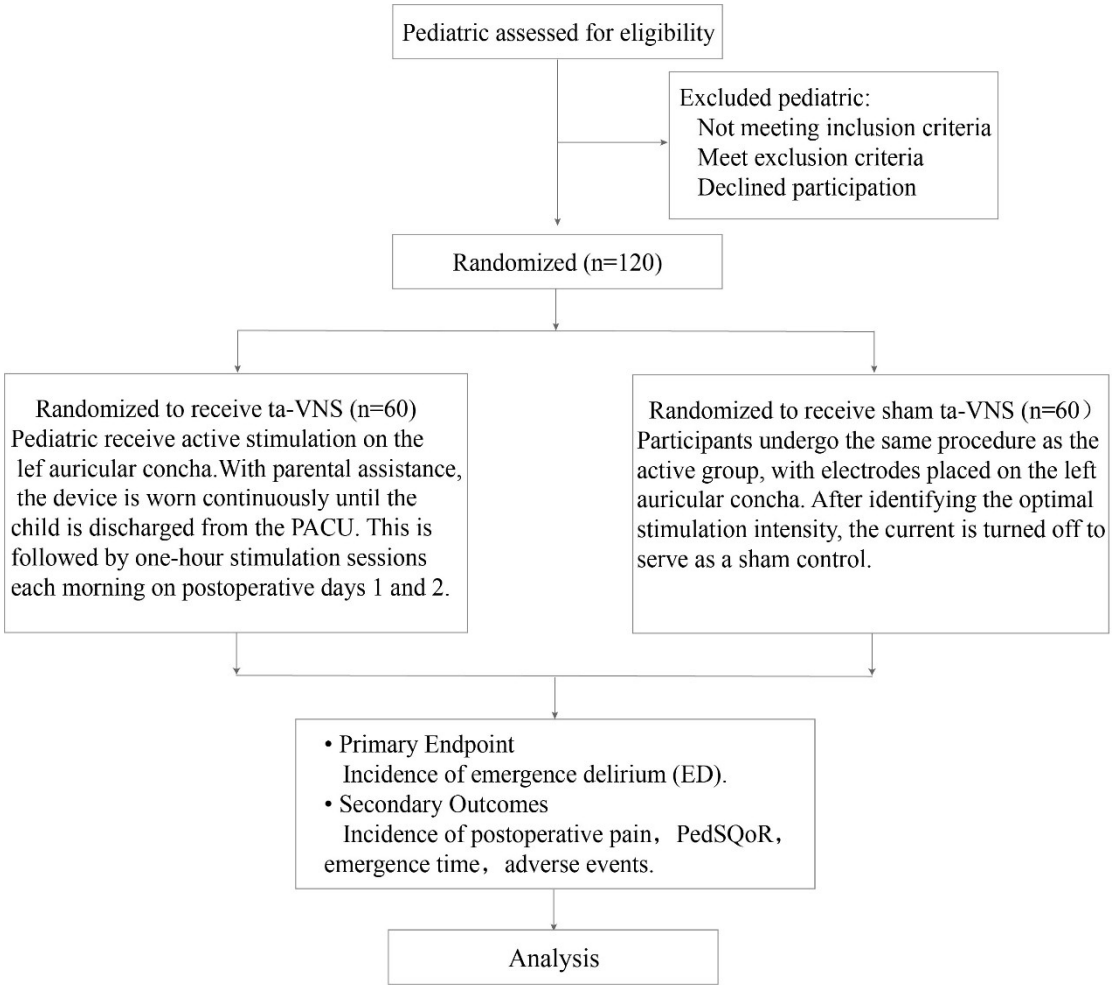
(4) Adverse Events

All adverse events during hospitalization will be recorded, including nausea, vomiting, pneumonia, and ta-VNS–related complications.

Sample Size Estimation

According to previous studies, the incidence of emergence delirium (ED) after tonsillectomy and adenoidectomy under sevoflurane anesthesia in children is approximately 44%.This study hypothesizes that ta-VNS will reduce the postoperative ED incidence to 20% in the intervention group.Using G*Power software (version 3.1.9.7), the required sample size is calculated to be 110 participants.Considering an estimated 10% dropout rate, a total of 120 children will be enrolled, with 60 participants in each group.

Research flowchart



Data Management and Confidentiality

A paper-based Case Report Form (CRF) will be designed to record clinical data and study results. All data will be stored on password-protected computers to ensure the confidentiality of patient privacy. The study will be conducted in strict accordance with the principles of Good Clinical Practice (GCP).

Only investigators authorized by the principal investigator will have access to review or analyze the data. Computers used for data management will be password-protected, and all paper records will be securely locked.

All information related to the identity of the participants will remain confidential and will not be disclosed to any third party beyond the scope permitted by relevant laws and/or regulations.

Informed Consent

Before enrollment, the investigator responsible for obtaining informed consent will provide the participant’s guardian or parents with a complete and detailed written explanation of the study’s purpose, nature, procedures, and possible benefits and risks. Participants will be informed

that they have the right to withdraw from the study at any time.Prior to inclusion, each participant must be fully informed and given sufficient time to decide whether to participate. Only those whose guardians or parents voluntarily agree and sign the informed consent form will be enrolled in this study.

Adverse Events and Management

Transcutaneous auricular vagus nerve stimulation (taVNS) is a selective, non-invasive, and low-risk form of vagus nerve stimulation. The main adverse events include mild pain, flu-like symptoms, and local skin discomfort, all of which typically resolve after discontinuation of taVNS. To date, no serious adverse events related to taVNS have been reported in the literature. In the event of any harm or adverse reaction, the research team will provide participants with prompt and appropriate medical care.

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