Research Protocol

Attachment 1(Version No.: V6.0 Date: 2025.02.05)

Project Title: Evaluation of the efficacy of nebulization of different drugs at the glottis on postoperative sore throat in thyroid surgery with neural monitoring

Project Source: The First Affiliated Hospital of Shandong First Medical University

Undertaking Department: Department of Anesthesiology and Perioperative Medicine

Principal Investigator: Liang Guo

Investigator Statement and Protocol Signature Page

As the principal investigator of this research project, I will comply with the ethical principles of the *Measures for Ethical Review of Life Science and Medical Research Involving Humans* (2023), the *Measures for Ethical Review of Biomedical Research Involving Humans* (2016), the WMA Declaration of Helsinki (2013), the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) and GCP. Under the guidance of Good Clinical Practice, I will conduct the research in accordance with the protocol approved by the Ethics Committee and the requirements of this protocol to ensure the scientific nature of the research and protect the health and rights of research participants.

Name: _____

Signature: _____

Date: _____

Protocol Summary

Item	Content
Protocol Title	Evaluation of the efficacy of nebulization of different drugs at the glottis on postoperative sore throat in thyroid surgery with neural monitoring
Version No./Date	V6.0/2025.02.05
Principal Investigator	Liang Guo
Research Nature	Interventional clinical study
Research Objectives	**Primary Objective**: To evaluate the efficacy of nebulization of different drugs at the glottis on postoperative sore throat in thyroid surgery with neural monitoring **Primary Outcome Measure**: Incidence of postoperative sore throat **Secondary Outcome Measures**: Four-point scale score and NRS score of postoperative sore throat at immediately after extubation, 12 h and 24 h after surgery in research participants; age, gender, weight, height, voice use habits (whether a teacher or singer), anesthesia duration, postoperative intubation duration, and occurrence of adverse reactions (cough, hoarseness, dysphagia) within 24 h after surgery in research participants
Sample Size	98 cases
Study Subjects	Research participants scheduled for thyroid surgery with neural monitoring under general anesthesia in The First Affiliated Hospital of Shandong First Medical University
Research Method	Randomized, double-blind, placebo-controlled trial
Inclusion Criteria	1. Research participants fully understand the purpose and significance of this trial, voluntarily participate and sign the informed consent form; 2. Undergo thyroid surgery with neural monitoring under general anesthesia (one-time successful tracheal intubation); 3. Aged 18－60 years, gender unlimited;

Item	Content
Exclusion Criteria	4. 18 kg/m² ≤ BMI ≤ 30 kg/m²; 5. Operation time 1－4 hours; 6. ASA Class Ⅰ－Ⅱ; 7. No contraindications to the use of study drugs. 1. Smokers or those with preoperative sore throat; 2. Recent upper or lower respiratory tract infection; 3. Patients refusing to participate in this study; 4. With significant dysfunction of liver, kidney and other organs; 5. Pregnancy or lactation; 6. Mallampati class > 2; 7. Surgery requiring nasogastric tube; 8. Repeated thyroid surgery; 9. Preoperative use of non-steroidal drugs or analgesics; 10.Patients with chronic pharyngitis or reflux esophagitis; 11.Tracheal intubation attempted by an experienced anesthesiologist > 2 times; 12.Patients allergic to study drugs.
Study Completion Criteria	Completion of trials with valid sample size
Early Withdrawal Criteria	**Withdrawal decided by investigators**: Withdrawal of research participants refers to the situation where enrolled research participants are not suitable to continue the trial during the trial, and the investigator decides to withdraw the participant from the trial. 1) The investigator deems it necessary to terminate the trial from the perspective of medical ethics. 2) A serious adverse event (SAE) occurs, and the investigator judges that the participant is not suitable to continue the trial. 3) The investigator judges that withdrawal from the study is most beneficial to the research participant. 4) Poor compliance of research participants, including: a. Failure to take drugs and accept examinations as required;

Item	Content
	b. Use of other drugs or foods affecting the efficacy and safety trial results; c. Other behaviors affecting trial results; d. Loss to follow-up. **Voluntary withdrawal by research participants**: According to the informed consent form, research participants have the right to withdraw from the trial midway, or fail to receive medication and testing without withdrawing informed consent (also regarded as withdrawal or dropout). The reason for withdrawal should be ascertained and recorded as much as possible.
Dosing Regimen	1) Control Group (Group C): Inhalation of 5 ml normal saline by nebulization at the glottis after conventional anesthesia induction and tracheal intubation 2) Experimental Group (Group N): Inhalation of 1 ml budesonide + 4 ml lidocaine by nebulization at the glottis after conventional anesthesia induction and tracheal intubation
Primary Outcome Measure	Incidence of sore throat
Secondary Outcome Measures	1) Four-point scale score and NRS score of postoperative sore throat at immediately after extubation, 12 h and 24 h after surgery in research participants. 2) Whether the tracheal tube is bloody at extubation 3) Operation duration 4) Postoperative intubation duration 5) Number of cases with postoperative cough, hoarseness and dysphagia
Statistical Analysis Method	A preliminary experiment was conducted with reference to previous literature. The incidence of postoperative sore throat in the control group and experimental group was 47% and 16% respectively. A two-sided α=0.05 and a power of 90% were set. The sample size was calculated according to

Item	Content
	$$n = \frac{2\bar{p}\bar{q}(z_\alpha + z_\beta)^2}{(p_1 - p_2)^2}$$ the following formula, and n1=42 cases and n2=42 cases were obtained. Considering 1:1 randomization, 42 participants were required in both experimental group and control group. Taking into account 15% loss to follow-up and refusal to visit, at least 49 participants were finally required in each group, with a total of 98 participants enrolled. Measurement data conforming to normal distribution were statistically described by mean ± standard deviation; measurement data not conforming to normal distribution were statistically described by median (interquartile range). Non-parametric rank sum test was used for comparison between two groups. Count data were statistically described by frequency and percentage, and chi-square test or Fisher's exact test was used for comparison between two groups. Repeated measures analysis of variance was used for sore throat score and NRS score at different time points. According to the basic principle of Intention-to-Treat (ITT) analysis, full analysis set was used for analysis. Statistical analysis was performed with SPSS 22.0 software, and two-sided test was adopted for statistical tests. P<0.05 was considered statistically significant.
Form of Research Achievement Publication	Treatise
Trial Schedule	Start Time: Q1 2025 End Time: Q1 2026

1. Research Objectives

To evaluate the efficacy of nebulization of different drugs at the glottis on postoperative sore throat in thyroid surgery with neural monitoring.

Primary Outcome Measure

Incidence of postoperative sore throat in research participants.

Secondary Outcome Measures

1)Four-point scale score and visual analogue scale score of postoperative sore throat at immediately after extubation, 12 h and 24 h after surgery; 2) Whether the tracheal tube is bloody at extubation; 3) Anesthesia duration; 4) Postoperative intubation duration; 5) Number of cases with postoperative cough, hoarseness and dysphagia.

2. Research Background

Postoperative sore throat (POST) is one of the common complications after general anesthesia with endotracheal intubation, with an incidence rate of 30%–70% reported in the literature (Mchard F E, Chung F. Postoperative sore throat: cause, prevention and treatment[J]. Anaesthesia. 1999,54(5):444-453.). Severe POST accompanied by cough, hoarseness, dysphagia, etc., seriously reduces patients' postoperative comfort and satisfaction, and is not conducive to rapid postoperative recovery. Thyroid surgery is performed in a special position with shoulder elevation and head hyperextension, which aggravates the stimulation of the glottis by tracheal intubation. In addition, the thyroid gland is surrounded by abundant blood vessels and nerves, and surgical stimulation can induce the release of a large number of inflammatory factors, thereby aggravating pharyngeal pain (CAI H D, LIN C Z, YU C X, et al. Bilateral superficial cervical plexus block reduces postoperative nausea and vomiting and early postoperative pain after thyroidectomy[J]. J Int Med Res,2012,40(4):1390-1398.). The neural monitoring tracheal tube has a larger diameter than ordinary tracheal tubes. Electrical stimulation is periodically emitted through neural probes to collect feedback signals with minimal or no use of muscle relaxants. Muscle tension at the glottis and continuous electrical stimulation also aggravate pharyngeal pain.

As a non-invasive clinical method, nebulized inhalation atomizes drugs and water into mist to enter the oral cavity, pharynx and respiratory tract through a nebulizer, which can rapidly relieve inflammatory congestive edema of the pharynx, exert anti-inflammatory, expectorant and even antitussive effects, and also has a certain damp-heat moistening effect. When drugs act directly on damaged mucosa, they can effectively increase the local drug concentration in the respiratory tract, thereby relieving respiratory spasm and eliminating respiratory inflammation. Nebulized inhalation therapy can rapidly alleviate pharyngeal complications and avoid side effects caused by systemic administration to a certain extent, with remarkable clinical effects (Farkas A, Balashazy I, Szoes K. Characterization of Regional and local deposition of inhaled aerosol drugs in The respiratory system by computational fluid and Particle dynamics methods[J]. J Aerosol Med,2006,19(3):329-343. Kleinstreuer C, Zhang Z, Donohue J F. Targeted drug aerosol delivery in the human respiratory system[J]. Annu Rev Biomed Eng,2008,10(8):195-220.).

Budesonide is a type of glucocorticoid, which can significantly inhibit leukocyte infiltration and phagocytosis, reduce the release of local inflammatory mediators. At the same time, nebulized inhalation of glucocorticoids can improve vascular tension, reduce capillary permeability and congestion, thereby reducing the occurrence of pharyngeal inflammation and edema and relieving postoperative sore throat (Cheng Zhe, Zheng Wanlai, Zhan Shilong, et al. Efficacy analysis of budesonide suspension for nebulized inhalation in the treatment of postoperative sore throat after general anesthesia for oral surgery[J]. Journal of Stomatology,2016,36(1):61-63.). Lidocaine is an amide local anesthetic with strong tissue diffusivity and mucosal penetrability and rapid onset. It inhibits the excitation of airway C sensory fibers by blocking ion flow required for the generation and conduction of nerve impulses, stabilizes nerve cell membranes, reduces central sensitivity, and alleviates pharyngeal pain (Moustafa M A. Nebulized lidocaine alone or combined with fentanyl as a premedication to general anesthesia in spontaneously breathing pediatric patients undergoing rigid bronchoscopy[J]. Paediatr Anaesth,2013,23(5):429-434. Zhou Yaru, Zha Jiaming, Jing Zhixin, et al. Determination of related substances in lidocaine aerosol by HPLC[J]. Chinese Journal of Pharmaceutical Analysis,2018,38(3):469-476. Wang Yuhong, Qiu Bo, Jiang Jiandong, et al.

Effect of lidocaine on hERG potassium channel[J]. Acta Pharmaceutica Sinica,2016,51(11):1698-1703.).

3. Research Basis

1. Mchard F E, Chung F. Postoperative sore throat: cause, prevention and treatment[J]. Anaesthesia. 1999,54(5):444-453.

2. CAI H D, LIN C Z, YU C X, et al. Bilateral superficial cervical plexus block reduces postoperative nausea and vomiting and early postoperative pain after thyroidectomy[J]. J Int Med Res,2012,40(4):1390-1398.

3. Farkas A, Balashazy I, Szoes K. Characterization of Regional and local deposition of inhaled aerosol drugs in The respiratory system by computational fluid and Particle dynamics methods[J]. J Aerosol Med,2006,19(3):329-343.

4. Kleinstreuer C, Zhang Z, Donohue J F. Targeted drug aerosol delivery in the human respiratory system[J]. Annu Rev Biomed Eng,2008,10(8):195-220.

5. Cheng Zhe, Zheng Wanlai, Zhan Shilong, et al. Efficacy analysis of budesonide suspension for nebulized inhalation in the treatment of postoperative sore throat after general anesthesia for oral surgery[J]. Journal of Stomatology,2016,36(1):61-63.

6. Moustafa M A. Nebulized lidocaine alone or combined with fentanyl as a premedication to general anesthesia in spontaneously breathing pediatric patients undergoing rigid bronchoscopy[J]. Paediatr Anaesth,2013,23(5):429-434.

7. Zhou Yaru, Zha Jiaming, Jing Zhixin, et al. Determination of related substances in lidocaine aerosol by HPLC[J]. Chinese Journal of Pharmaceutical Analysis,2018,38(3):469-476.

8. Wang Yuhong, Qiu Bo, Jiang Jiandong, et al. Effect of lidocaine on hERG potassium channel[J]. Acta Pharmaceutica Sinica,2016,51(11):1698-1703.

4. Research Content

1. Study Population

Research participants scheduled for thyroid surgery with neural monitoring under general anesthesia in The First Affiliated Hospital of Shandong First Medical University.

Sample Size Calculation

A preliminary experiment was conducted with reference to previous literature. The incidence of postoperative sore throat in the control group and experimental group was 47% and 16% respectively. A two-sided $\alpha=0.05$ and a power of 90% were set. The sample size was calculated

$$n = \frac{2\bar{p}\bar{q}\left(z_\alpha + z_\beta\right)^2}{(p_1 - p_2)^2}$$

according to the formula, and n1=42 cases and n2=42 cases were obtained. Considering 1:1 randomization, 42 participants were required in both experimental group 1 and control group. Taking into account 15% loss to follow-up and refusal to visit, at least 49 participants were finally required in each group, with a total of 98 participants enrolled.

5. Research Method

1. Inclusion Criteria

1. Research participants fully understand the purpose and significance of this trial, voluntarily participate and sign the informed consent form;

2. Undergo thyroid surgery with neural monitoring under general anesthesia (one-time successful tracheal intubation);

3. Aged 18–60 years, gender unlimited;

4. 18 kg/m² ≤ BMI ≤ 30 kg/m²;

5. Operation time 1–4 hours;

6. ASA Class I–II;

7. No contraindications to the use of study drugs.

2. Exclusion Criteria

1. Smokers or those with preoperative sore throat;

2. Recent upper or lower respiratory tract infection;

3. Patients refusing to participate in this study;

4. With significant dysfunction of liver, kidney and other organs;

5. Pregnancy or lactation;

6. Mallampati class > 2;

7. Surgery requiring nasogastric tube;

8. Repeated thyroid surgery;

9. Preoperative use of non-steroidal drugs or analgesics;

10. Patients with chronic pharyngitis or reflux esophagitis;

11. Tracheal intubation attempted by an experienced anesthesiologist > 2 times;

12. Patients allergic to study drugs.

3. Recruitment of Research Participants

After obtaining ethical approval, recruitment will be conducted in the thyroid surgery ward by researchers specially responsible for

recruitment, targeting patients meeting the inclusion and exclusion criteria who need thyroid surgery with neural monitoring.

4. Grouping of Research Participants

Eligible research participants will be randomly assigned to the control group and experimental group at a ratio of 1:1.

- Control Group (Group C):

  Drug Name: 0.9% Sodium Chloride Injection

  Storage Condition: Store at room temperature;

  Administration Method: Conventional anesthesia induction, inhalation of 5 ml normal saline by nebulization at the glottis after tracheal intubation

- Experimental Group (Group N):

  Drug Name: Budesonide Suspension for Inhalation

  Specification: 2mL; 1mg;

  Storage Condition: Store at 8–30℃, do not refrigerate;

  Drug Name: Lidocaine Hydrochloride Injection

  Specification: 5mL; 0.1g;

  Storage Condition: Sealed storage;

  Administration Method: Conventional anesthesia induction, inhalation of 1 ml budesonide + 4 ml lidocaine by nebulization at the glottis after tracheal intubation

5. Grouping and Blinding

5.1 Block Randomization Grouping

Patients were grouped by block randomization, and the sequence was concealed in opaque sealed envelopes. Drug blinding was performed by specialized personnel not directly involved in the clinical trial. Block randomization grouping was adopted (random number table generated by statistical software (SAS)), coded sequentially as 1,2,3,4…243, and divided into 2 groups according to block randomization.

5.2 Blinding

This trial is designed as double-blind, with research participants unaware of group allocation and investigators unaware of the drugs used. (1) The total random table is kept by specialized personnel responsible for statistics;(2) Pumped drugs are prepared by specialized nurses not directly involved in the clinical trial according to the total random table.

5.3 Unblinding

- **Overall Unblinding**: Unblinding will be performed after the completion of case report form entry and statistical analysis.
- **Emergency Unblinding**: Performed when a research participant experiences a serious adverse event and the investigator believes that knowing the drug used by the participant is necessary to take effective measures.

6. Rescue Medication and Supportive Treatment

For patients with severe postoperative sore throat, nebulization therapy will be continued.

7. Criteria for Early Withdrawal/Termination of Trial by Research Participants

7.1 Withdrawal Decided by Investigators

Withdrawal of research participants refers to the situation where enrolled research participants are not suitable to continue the trial during the trial, and the investigator decides to withdraw the participant from the trial.

1. The investigator deems it necessary to terminate the trial from the perspective of medical ethics.

2. A serious adverse event (SAE) occurs, and the investigator judges that the participant is not suitable to continue the trial.

3. The investigator judges that withdrawal from the study is most beneficial to the research participant.

4. Poor compliance of research participants, including:a. Failure to take drugs and accept examinations as required;b. Use of other drugs affecting the efficacy trial results, such as analgesics, non-steroidal anti-inflammatory drugs, etc.;c. Other behaviors affecting trial results;d. Loss to follow-up.

7.2 Voluntary Withdrawal by Research Participants

According to the informed consent form, research participants have the right to withdraw from the trial midway, or fail to receive medication and testing without withdrawing informed consent (also regarded as withdrawal or dropout). The reason for withdrawal should be ascertained and recorded as much as possible.

8. Adverse Events

Definition of Serious Adverse Event (SAE)

SAE refers to any adverse medical event meeting any of the following criteria (a–f):a. Resulting in death;b. Life-threatening (in the definition, life-threatening refers to an immediate risk of death for a critically ill patient, not hypothetical death in the future if the

condition worsens);c. Resulting in hospitalization or prolongation of hospital stay;Hospitalization or prolongation of hospital stay shall not be reported as SAE if meeting at least one of the following criteria:

- Hospital stay <12 hours after admission;
- Pre-planned admission (e.g., elective or scheduled surgery arranged before the first administration of study drugs; or admission is part of the study procedure);
- Hospitalization unrelated to adverse events (e.g., admission to social welfare institutions for temporary care). However, it should be emphasized that invasive treatment received during hospitalization may meet the criteria of "important medical event" and thus should be reported as SAE based on clinical judgment.d. Resulting in significant or permanent disability/functional impairment (disability refers to substantial damage to an individual's ability to perform normal life functions; functional loss does not include events of relatively minor medical importance, such as headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., ankle sprain)).e. Resulting in congenital malformation or birth defect: congenital malformation or birth defect in a newborn (fetus) born (or aborted) to a female research participant exposed to drugs or the female partner of a male research participant exposed to drugs.f. Other important medical events: events that may not immediately result in death, life-threatening conditions or hospitalization/prolongation of hospital stay, but according to medical judgment, may harm research participants or require medical intervention to prevent one of the above situations.

6. Trial Procedure

1. Screening Period

Sign informed consent form, collect general data: past medical history or medication history, personal history, physical examination, vital signs;

Randomization:Research participants are randomly divided into two groups: Control Group (Group C), Budesonide + Lidocaine Group (Gtoup N). Block randomization grouping is adopted, with 49 people in each group.

Nebulization:A research nurse is responsible for allocating and preparing intraoperative nebulization drugs. After conventional anesthesia induction and tracheal intubation, a sterile suction tube for nebulization is connected to the tracheal tube and fixed at the upper end of the test electrode of the neural monitoring tracheal tube. After the tracheal tube is fixed, the nebulization tube is located at the glottis. The anesthesiologist connects the wall-mounted nebulization device and performs nebulization at an oxygen flow rate of 2 L/min for 1 hour.

2. Observation Period

Anesthesia:After entering the operating room, research participants receive routine monitoring of ECG, SPO2, NIBP, skin temperature and BIS anesthesia depth monitoring. The anesthesia method is the same in all groups. Anesthesia induction is performed with midazolam 0.03 mg/kg, sufentanil 0.4 ug/kg, etomidate 0.4 mg/kg and atracurium 0.6 mg/kg. Mask oxygenation and denitrogenation are performed before intubation, followed by connection to the anesthesia machine. Anesthesia machine parameters: VT 6–8 ml/kg, RR 10–12 times/min, inspiratory-expiratory ratio 1:2, oxygen concentration 60%, fresh gas flow 2 L/min, maintaining end-tidal partial pressure of carbon dioxide at 35–45 mmHg.

Intraoperative Management:Tracheal cuff pressure is monitored every 15 minutes with a cuff manometer, maintaining pressure at 25–30 cmH_2O. Anesthesia maintenance is performed with target-controlled infusion of propofol 0.5–2 ug/ml, remifentanil 0.2–0.3 ug/kg/min, and additional atracurium 0.15 mg/kg and sufentanil 0.2 ug/kg as needed, maintaining BIS value at 40–60. A warming blanket is used intraoperatively to keep the body temperature of research participants not lower than 36℃. After surgery, patients are sent to PACU for resuscitation. No hormonal drugs or non-steroidal anti-inflammatory drugs are used in all research participants during the perioperative period.

3. Postoperative Follow-up

Research participants are interviewed face-to-face by a professional anesthesiologist unaware of group allocation. The follow-up endpoint is 24 h after surgery, and follow-up time points are immediately after surgery, 12 h and 24 h; follow-up contents include four-point scale score and visual analogue scale score of postoperative sore throat at each time point, whether the tracheal tube is bloody at extubation, and occurrence of postoperative cough, hoarseness and dysphagia. If the NRS score $\geqslant 4$ at 24 h after surgery, the investigator will track and observe the research participant and provide symptomatic treatment until the NRS score <4.

4. Rescue and Supportive Treatment

Record the four-point scale score and NRS score of pharyngeal pain at any follow-up time point. Terbutaline nebulization is given if the four-point scale score > grade 2 and NRS score >4.

5. Data Collection

Record age, gender, weight, height, BMI index, whether a teacher or singer of research participants; record anesthesia duration,

postoperative intubation duration (from the end of surgery to extubation of tracheal tube), whether the tracheal tube is bloody at extubation; record four-point scale score and visual analogue scale score of pharyngeal pain at immediately after surgery, 12 h and 24 h after surgery, and the number of cases with postoperative cough, hoarseness and dysphagia in research participants.

6. Data Management

Electronic information entry is performed by two data entry administrators, and all information required by the research protocol must be provided. Investigators must keep the original documents of each participant in the trial, and all data must be derived from the original documents. Cases with missing data or illogical data will be deleted during data processing.

7. Compliance with Ethical Principles and Relevant Regulations

7.1 Ethics Committee Review

This protocol, written informed consent form, case report form and materials directly related to research participants must be submitted to the Ethics Committee, and the study can be officially carried out only after obtaining written approval from the Ethics Committee. The investigator shall notify the Ethics Committee in writing when the study is suspended and/or completed; the investigator shall promptly report all changes occurring in the research work (such as revisions of the protocol and/or informed consent form) to the Ethics Committee, and shall not implement these changes without obtaining approval from the Ethics Committee, unless the changes are made to eliminate obvious and immediate risks to research participants. In such cases, the Ethics Committee will be notified.

7.2 Procedure for Obtaining Informed Consent

The investigator provides the research participant or his legal representative with an easy-to-understand informed consent form approved by the Ethics Committee, and gives sufficient time for the research participant or his legal representative to consider the study. No research participant shall be enrolled before obtaining the signed written informed consent form from the research participant. During the participation of research participants, all updated versions of the informed consent form and written information will be provided to them. The informed consent form shall be kept as an important document of the clinical trial for future reference.

8. Statistical Analysis Plan

Sample Size Calculation

A preliminary experiment was conducted with reference to previous literature. The incidence of postoperative sore throat in the control group and experimental group was 47% and 16% respectively. A two-sided α=0.05 and a power of 90% were set. The sample size was calculated

$$n = \frac{2\bar{p}\bar{q}(z_\alpha + z_\beta)^2}{(p_1 - p_2)^2}$$

according to the formula, and n1=42 cases and n2=42 cases were obtained. Considering 1:1 randomization, 42 participants were required in both experimental group 1 and control group. Taking into account 15% loss to follow-up and refusal to visit, at least 49 participants were finally required in each group, with a total of 98 participants enrolled.

Statistical Analysis

Measurement data conforming to normal distribution were statistically described by mean ± standard deviation; measurement data not conforming to normal distribution were statistically described by median (interquartile range). Non-parametric rank sum test was used for comparison between two groups. Count data were statistically described by frequency and percentage, and chi-square test or Fisher's exact test was used for comparison between two groups. Repeated measures analysis of variance was used for sore throat score and NRS score at different time points.

According to the basic principle of Intention-to-Treat (ITT) analysis, full analysis set was used for analysis. Statistical analysis was performed with SPSS 22.0 software, and two-sided test was adopted for statistical tests. $P<0.05$ was considered statistically significant.

9. Quality Control

The principal investigator shall train the personnel participating in the research. Investigators shall strictly follow the trial protocol and adopt corresponding standard operating procedures to ensure the implementation of the quality control and quality assurance system of the clinical trial.

10. Form of Research Achievement Publication

Treatise.

11. Trial Schedule

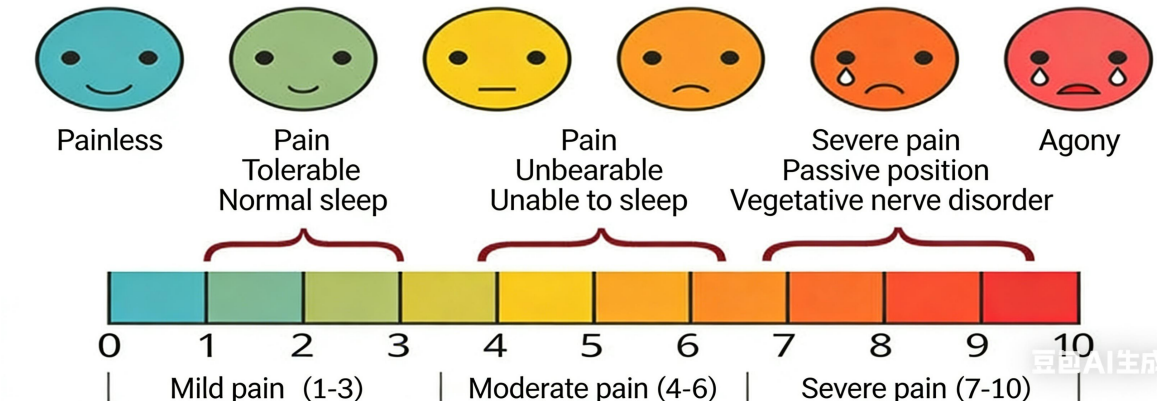
Start Time: Q1 2025

End Time: Q1 2026

12. Appendices

NRS Score

0: No pain1－3: Mild pain (pain does not affect sleep)4－6: Moderate pain (pain affects sleep)7－9: Severe pain (unable to fall asleep, awakened by pain during sleep or unable to sleep)10: Excruciating pain



Four-point Scale Score Classification for Postoperative Sore Throat

Grade 1: No sore throat.

Grade 2: Mild sore throat (complains of sore throat only when asked).

Grade 3: Moderate sore throat (complains of sore throat repeatedly).

Grade 4: Severe sore throat (hoarseness or voice change caused by sore throat).