Informed Consent Form

Project Title: Efficacy of Different Drugs Administered by Glottic Nebulization on Postoperative Sore Throat After Thyroidectomy with Nerve Monitoring: A Randomized Controlled Trial

Protocol Version & Date: Version V6.0 / 2025.02.05

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Dear Participant,

You are invited to voluntarily take part in the study entitled "Efficacy of Different Drugs Administered by Glottic Nebulization on Postoperative Sore Throat After Thyroidectomy with Nerve Monitoring", which is approved and conducted at The First Affiliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital). This study will be carried out at the above hospital, and a total of 243 participants will be enrolled voluntarily. This study has been reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital).

Before you decide whether to participate in this study, please read this document carefully. It will help you understand the purpose, procedures, and duration of the study, how your information will be used, as well as the potential benefits and risks of participation. If you have any questions, please consult the researcher who explains this informed consent form to you to ensure you fully understand the relevant content. Your participation in this study is completely voluntary. You may refuse to participate or withdraw at any stage of the study without discrimination or retaliation, and your medical treatment and rights will not be affected.

If you choose to participate in this study, please sign the participant statement on this informed consent form. Our research team will do its best to protect your safety and rights during the study.

1. Study Background

Postoperative sore throat (POST) is one of the common complications after general anesthesia with tracheal intubation, with a reported incidence of 30%–70%. Severe POST may be accompanied by cough, hoarseness, dysphagia and other symptoms, which seriously reduce patients' postoperative comfort and satisfaction and hinder the process of enhanced recovery after surgery.

Thyroidectomy requires a special position with shoulder padding and head backward hyperextension, which aggravates the glottic irritation caused by tracheal intubation. The thyroid gland is surrounded by abundant blood vessels and nerves, and surgical stimulation triggers the release of a large number of inflammatory mediators, thus aggravating throat pain. Nerve-monitoring endotracheal tubes have a larger diameter than ordinary tubes and deliver periodic electrical stimulation through nerve probes to collect feedback signals with minimal or no use of muscle relaxants. Glottic muscle tension and continuous electrical stimulation also aggravate throat pain.

Nebulization is a non-invasive clinical method that converts drugs and water into droplets to enter the oral cavity, pharynx and respiratory tract. It can quickly relieve inflammatory congestion and edema of the throat, exert anti-inflammatory, expectorant and antitussive effects, and provide certain moist heat therapy. When drugs act directly on the injured mucosa, it can effectively increase the local drug concentration in the respiratory tract, relieve respiratory spasm and eliminate respiratory inflammation. Nebulization therapy can quickly relieve throat complications and avoid systemic side effects to a certain extent, with remarkable clinical efficacy.

Budesonide is a type of glucocorticoid that significantly inhibits leukocyte infiltration and phagocytosis and reduces the release of local inflammatory mediators. In addition, nebulized glucocorticoids can improve vascular tone, reduce capillary permeability and congestion, thereby reducing throat inflammation and edema and relieving postoperative sore throat.

Lidocaine is an amide local anesthetic with strong tissue diffusion and mucosal penetration and rapid onset. It blocks the ion flow required for the generation and conduction of nerve impulses, inhibits the excitation of airway C sensory fibers, stabilizes nerve cell membranes, reduces central sensitivity, and relieves pharyngeal pain.

Esketamine hydrochloride, a novel anesthetic analgesic, is the active S-enantiomer of racemic ketamine and a non-selective N-methyl-D-aspartate receptor antagonist. Its anesthetic and analgesic effect is twice that of ketamine with milder effects on circulation and respiration. It was approved for intravenous anesthesia in humans by the U.S. Food and Drug Administration (USFDA) in 1970. Studies have found that

ketamine saline gargle or preoperative nebulized ketamine can reduce the incidence of postoperative sore throat.

2. Study Purpose

To evaluate the efficacy of different drugs administered by glottic nebulization on postoperative sore throat after thyroidectomy with nerve monitoring.

Primary Outcome Measure

Incidence of postoperative sore throat in participants.

Secondary Outcome Measures

1. Four-point sore throat scale score and Visual Analogue Scale (VAS) score at immediately after extubation, 12 hours and 24 hours after surgery.

2. Age, gender, weight, height, voice use habits (teacher or singer), anesthesia duration, postoperative catheterization time.

3. Incidence of adverse reactions within 24 hours postoperatively, including cough, hoarseness and dysphagia.

3. Study Procedures

Planned Enrollment: 98 participants

Study Content

To evaluate the efficacy of different drugs administered by glottic nebulization on postoperative sore throat after thyroidectomy with nerve monitoring.

Detailed Steps and Methods

3.1 Screening Phase

- Sign the informed consent form; collect general data: medical history, medication history, personal history, physical examination, vital signs and voice use habits.
- Randomization: Eligible participants will be randomly assigned to two groups by block randomization: Control Group (Group C) and Budesonide + Lidocaine Group (Group N), with 49 participants in each group.
- Nebulization: A research nurse is responsible for allocating and preparing intraoperative nebulized drugs. After routine anesthesia induction and tracheal intubation, a sterile suction catheter for nebulization is connected to the endotracheal tube and fixed above the testing electrode of the nerve-monitoring tube. Once the endotracheal tube is fixed, the nebulization catheter is positioned at the glottis. An anesthesiologist connects the wall-mounted nebulization device, and nebulization is performed at an oxygen flow rate of 2 L/min for 1 hour.

3.2 Observation Phase

• Anesthesia monitoring: Upon arrival in the operating room, participants receive routine monitoring of electrocardiogram (ECG), pulse oxygen saturation (SpO_2), non-invasive blood pressure (NIBP), skin temperature and bispectral index (BIS) for anesthetic depth.

• Anesthesia induction: midazolam 0.03 mg/kg, sufentanil 0.4 μg/kg, etomidate 0.4 mg/kg and atracurium 0.6 mg/kg. After pre-oxygenation via face mask, tracheal intubation is performed and the patient is connected to the anesthesia machine.

• Anesthesia machine parameters: tidal volume (VT) 6–8 mL/kg, respiratory rate (RR) 10–12 breaths/min, inspiratory to expiratory (I:E) ratio 1:2, oxygen concentration 60%, fresh gas flow 2 L/min, and end-tidal partial pressure of carbon dioxide ($PETCO_2$) maintained at 35–45 mmHg.

• Intraoperative management: Endotracheal tube cuff pressure is monitored every 15 minutes and maintained at 25–30 cmH_2O. Anesthesia is maintained by target-controlled infusion of propofol 0.5–2 μg/mL and remifentanil 0.2–0.3 μg/kg/min. Atracurium 0.15 mg/kg and sufentanil 0.2 μg/kg are supplemented as needed to maintain BIS value at 40–60. A warming blanket is used to keep the patient's body temperature not lower than 36℃. After surgery, participants are transferred to the Post-Anesthesia Care Unit (PACU) for recovery. No glucocorticoids or non-steroidal anti-inflammatory drugs are used during the perioperative period.

3.3 Postoperative Follow-up

A professional anesthesiologist conducts face-to-face follow-up in a blinded manner. The follow-up endpoint is 24 hours after surgery, and the follow-up time points are immediately after surgery, 12 hours and 24 hours after surgery. The follow-up contents include four-point sore throat scale score and Visual Analogue Scale (VAS) score at each time point, blood on the endotracheal tube at extubation, and the occurrence of postoperative cough, hoarseness and dysphagia. If the participant's NRS score is $\geqslant$ 4 at 24 hours, the researcher will conduct follow-up observation and symptomatic treatment until the NRS score is $<$ 4.

4. Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

Participants must meet all the following criteria to be enrolled:

1. Fully understand the purpose and significance of the trial, voluntarily participate and sign the informed consent form.

2. Undergo thyroidectomy with nerve monitoring under general anesthesia (successful tracheal intubation at the first attempt).

3. Aged 18–60 years, regardless of gender.

4. Body mass index (BMI) 18–30 kg/m^2.

5. Operation duration 1–4 hours.

6. American Society of Anesthesiologists (ASA) physical status Grade I–II.

7. No contraindications to the study drugs.

4.2 Exclusion Criteria

Participants will be excluded if they meet any of the following criteria:

1. Current smokers or patients with preoperative sore throat.

2. Recent upper or lower respiratory tract infection.

3. Patients who refuse to participate in this study.

4. Complicated with significant hepatic, renal or other organ dysfunction.

5. Pregnancy or lactation period.

6. Mallampati classification > 2.

7. Nasogastric tube required during surgery.

8. Reoperative thyroidectomy.

9. Preoperative use of non-steroidal anti-inflammatory drugs or analgesics.

10. Poor compliance and inability to cooperate with the study.

11. Patients with chronic pharyngitis or gastroesophageal reflux disease.

12. More than two attempts of tracheal intubation by an experienced anesthesiologist.

13. Patients with allergy to the study drugs.

5. Alternative Treatment

Additional nebulization therapy will be given after surgery.

6. Anticipated Benefits

1. A comprehensive and systematic evaluation of your overall physical condition and surgical comorbidities.

2. Expert assessment of in-hospital examination results and therapeutic guidance for abnormalities.

3. The results of this follow-up study are of great significance for relieving postoperative sore throat after thyroidectomy with nerve monitoring.

7. Compensation

This is an in-hospital follow-up study with no travel expenses or compensation involved.

8. Treatment Costs

This study uses routine anesthetic and analgesic drugs with no additional medical costs.

9. Compensation for Injury

This study uses routine nebulization and analgesic drugs. Transient dizziness, blurred vision and other mild symptoms may occur occasionally

with low-dose use. If any study-related side effects occur during the trial, the researcher will conduct follow-up observation and provide timely symptomatic treatment.

10. Pre-, Intra- and Post-Study Instructions

Before the study, you will be fully informed of the relevant content and sign the informed consent form. If you experience dizziness or other discomforts during and after the study, please contact us in time. The researchers will conduct follow-up and symptomatic treatment until your symptoms disappear.

11. Confidentiality

Your privacy will be protected, and your personal data will be kept confidential. Your personal information will not be disclosed except as required by law. Personal identification information obtained in the study will be coded or anonymized, stored in special locked cabinets in the department, kept strictly confidential and used only for this study. The research team will take measures to protect your personal information, and no identifiable content will appear in any research documents, reports or published articles. Research results including laboratory and other test results will be published for scientific purposes without disclosing your identity. We will make every effort to protect the privacy of your personal medical data within the scope permitted by law.

Collected blood or tissue samples will be stored in the departmental laboratory during the study, kept strictly confidential and used only for this study. These samples will be labeled with codes or anonymization instead of your name. After the study, your blood or tissue samples will not be retained or reused, and will be disposed of as medical waste.

Any records of you in this study will be kept strictly confidential at all times. However, researchers, competent authorities, the Ethics Committee and superior auditing departments may access your medical records and study-related information as required. By signing this informed consent form, you agree that your personal and medical information may be used for the purposes described above.

12. Voluntary Participation

Your participation in this study is completely voluntary. You may refuse to participate or notify the researcher to withdraw at any time for any reason. Your data will not be included in the study results, and your medical treatment and rights will not be affected. Your decision will not impact your future treatment.

If you decide to withdraw from this study, please notify your study doctor in advance. Relevant examinations may be required according to your health condition or for safety reasons, which is beneficial to protecting your health and safety.

Your study doctor may terminate your participation if you need other treatments, fail to comply with the study protocol, suffer study-related injury or for any other reasons.

You may obtain information and progress related to this study at any time. You will be notified promptly if new safety information related to this study occurs.

13. Participant Commitments

1. Provide truthful information about your medical history and current physical condition.

2. Inform the study doctor of your past or current participation in other studies, including the time and details, which is important for protecting your health and safety.

3. Promptly inform your study doctor of any changes in health conditions, symptoms or discomfort, regardless of whether you think it is related to this study.

4. Follow the instructions of the study doctor for clinical research and administration of study drugs.

5. Once enrolled in the study, inform your study doctor before using any other medications to avoid adverse effects on your health.

6. Do not take prohibited medications or foods.

14. Contact Information

If you have any questions about this study, or experience any discomfort or injury during the study, please contact:Dr. Yalei Gao. Tel: 17615838417

If your rights and interests are affected during the study, please contact the Ethics Committee of The First Affiliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital):Tel: 0531-89269890

Consent Signature Page

Study Title: Efficacy of Different Drugs Administered by Glottic Nebulization on Postoperative Sore Throat After Thyroidectomy with Nerve Monitoring: A Randomized Controlled Trial

If you fully understand the content of this study and agree to participate, please sign this informed consent form. The informed consent form shall be signed by the participant or their legal representative, in duplicate: one for the researcher and one for the participant or their authorized agent.

Statement of Consent

I confirm that I have read and understood the informed consent form for this study. The potential problems and solutions during the study have been explained to me, and I have had the opportunity to ask my own questions.

I clearly understand that participation in the study is voluntary, and refusal to participate will not prejudice any of my legitimate rights and interests.

I have been informed that the physicians participating in this study, the person in charge of this project at The First Affiliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital), and the Medical Ethics Committee of the hospital have the right to review the study records and medical data. I agree that the above personnel may directly access my study records, and I understand that such information will be kept confidential.

I agree to participate in this study.

Participant Full Name: _____**Date & Time**: _____

Legal Representative Full Name: _____**Date & Time**: _____

Relationship to Participant: _____(If the authorized agent is not an immediate family member, do you have the power of attorney from the participant: ☐ Yes ☐ No)

This section is to be completed by the physician who conducts the informed consent process.

Investigator Statement:I confirm that I have explained and discussed the nature, purpose, requirements and potential risks of this study with the patient, as well as alternative treatment options, and ensured that a copy of this informed consent form has been provided to the participant for retention.

Investigator Full Name: _____**Date & Time**: _____