Superiority of Sodium Hyaluronate Gel over Lidocaine Cream for Endotracheal Tube Lubrication in Reducing Postoperative Throat Numbness: A Randomized Controlled Trial

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CLINICAL STUDY PROTOCOL

Protocol Information

Department: Department of Anesthesiology

Collaborating Institution: Beijing Tsinghua Changgung Hospital

Study Category: Clinical study

1. Background

1.1 Study Purpose and Significance

This study aims to evaluate the clinical effectiveness and safety of sodium hyaluronate gel used to lubricate an endotracheal tube in patients undergoing general anesthesia, compared with conventional lidocaine cream, and to determine its superiority in improving postoperative throat numbness and reducing sore throat and hoarseness, as well as its potential safety advantages.

The theoretical significance is the introduction of medical sodium hyaluronate gel for endotracheal tube lubrication and systematic evaluation of its clinical effects, providing evidence for this new application. Clinically, a lubricant that effectively reduces these discomforts may improve perioperative comfort and reflect the patient-centered principles of Enhanced Recovery After Surgery (ERAS) and comfort-oriented care. The potential inhibitory effect of lidocaine on protective airway reflexes is a safety concern in anesthesia. Sodium hyaluronate gel, as an alternative without local anesthetic pharmacological activity, may offer a safety advantage in older or frail patients and those at risk of aspiration if it does not interfere with recovery of airway reflexes. This may help reduce postoperative pulmonary complications. The study may also improve patients' postoperative experience and encourage the development of biomaterial-based medical consumables that improve comfort and safety.

1.2 Current Evidence

Endotracheal intubation is essential for establishing an artificial airway during general anesthesia, but it inevitably causes mechanical irritation and injury to the oropharyngeal, laryngeal, and tracheal mucosa. Postoperative sore throat, hoarseness, coughing during emergence, and throat numbness are common intubation-related complications, with reported incidence rates ranging from 12.1% to 70% **[1,2]**. Although generally self-limiting, these symptoms can impair postoperative oral intake, communication, and sleep, prolong post-anesthesia care unit (PACU) stays, and reduce patient satisfaction, thereby affecting the overall quality of perioperative care.

Applying lubricants to the endotracheal tube is a common strategy to reduce friction-related mucosal injury. Lidocaine gel or cream is widely used because it provides both lubrication and topical anesthesia. However, its effectiveness remains controversial. A systematic review reported postoperative sore throat rates of 41.1% and 22.6% at 1 and 24 hours, respectively, following endotracheal tube lubrication with lidocaine cream. The review also suggested that hoarseness may be no less common, and potentially more common, in patients receiving lidocaine gel than in control groups, although the differences were not necessarily statistically significant **[3]**. Another study reported higher postoperative sore throat scores with lidocaine gel than with K-Y jelly **[4]**. Furthermore, prolonged local anesthetic effects may delay the recovery of pharyngeal sensation **[5]** and impair protective airway reflexes, such as coughing and swallowing, potentially increasing the risk of postoperative aspiration **[6]**. Mechanistically, lidocaine produces local anesthesia by blocking sodium channels and may temporarily relieve pain **[7]**; however, it does not directly prevent mechanical mucosal injury or the associated inflammatory response caused by intubation.

Sodium hyaluronate, the sodium salt of hyaluronic acid, is a natural component of the extracellular matrix and is widely distributed in synovial fluid, skin, and connective tissues. It has favorable biocompatibility and safety profiles, and medical-grade products have undergone ISO 10993 biocompatibility testing **[8]**. Sodium hyaluronate is currently used in ophthalmic surgery, intra-articular injections, wound care, and oral mucosal repair. Its distinctive

viscoelastic properties may make it particularly suitable for dynamic intubation procedures: under high-shear conditions, it exhibits reduced viscosity and may facilitate insertion by decreasing friction, whereas under static, low-shear conditions, it can form a protective gel layer over the mucosal surface **[9]**. In addition to its physical lubricating properties, hyaluronic acid may promote mucosal epithelial regeneration, fibroblast migration, and inflammatory regulation through interactions with cell-surface receptors, thereby maintaining a moist wound environment and supporting tissue repair **[10]**. Animal studies have also shown that exogenous hyaluronic acid can accelerate intestinal mucosal re-epithelialization and reduce ulcer size **[11]**. Therefore, sodium hyaluronate gel may provide both mechanical lubrication during intubation and additional mucosal protection during early postoperative recovery. As a physiologically degradable endogenous substance, it may also offer favorable biocompatibility.

Despite the established applications of sodium hyaluronate in ophthalmology, orthopedics, and oral mucosal repair, clinical evidence regarding its use specifically as an endotracheal tube lubricant remains limited. To our knowledge, no published clinical study has directly compared sodium hyaluronate gel with lidocaine cream for this purpose. Previous research has mainly examined different routes of lidocaine administration, such as spray, gel, and intracuff administration, or compared lidocaine with other agents, including corticosteroids and licorice extracts. The potential of lubricants that provide physical and biological protection without local anesthetic activity, such as sodium hyaluronate gel, has not been adequately investigated.

To address this gap, our research team conducted a preliminary study involving 10 patients undergoing laparoscopic surgery. Sodium hyaluronate gel was used to lubricate the endotracheal tube and compared with lidocaine cream. The median throat numbness visual analog scale (VAS) score at 30 minutes after extubation was 3.0 in the sodium hyaluronate gel group, compared with 6.0 in the lidocaine cream group. No serious adverse events occurred in either group. These preliminary findings support the feasibility and initial safety of sodium hyaluronate gel in this setting and provide preliminary data for selecting the primary outcome and estimating the sample size of the present trial.

Accordingly, this prospective randomized controlled trial will enroll patients undergoing laparoscopic surgery and compare medical sodium hyaluronate gel with conventional lidocaine cream for endotracheal tube lubrication. The primary outcome is the dynamic assessment of postoperative throat numbness during the first 2 hours after surgery. Throat numbness, rather than the conventional sore throat score, was selected as the primary endpoint for two reasons. First, it is an early and clearly perceived symptom following endotracheal intubation and may be closely associated with mechanical injury to mucosal sensory nerve endings, making it a potentially sensitive indicator of mucosal protection. Second, its severity is associated with postoperative swallowing recovery, willingness to resume oral intake, and subjective comfort, all of which are relevant to perioperative recovery and patient satisfaction.

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1.3 Institutional and Quality Assurance

The project will undergo review and approval by the hospital ethics committee and will follow the Declaration of Helsinki and Good Clinical Practice (GCP). Before study initiation, all personnel will receive standardized protocol training. A three-level quality-control system will include investigator self-checks, review by the study group leader, and monitoring by the GCP office. Data will be independently entered by two personnel and checked for logical consistency. Adverse events will be recorded, assessed, and reported to the ethics committee in a timely manner.

2. Study Objectives and Content

In this prospective randomized controlled clinical trial, using lidocaine cream as the active comparator, the study will evaluate the superiority of sodium hyaluronate gel for endotracheal tube lubrication in reducing postoperative throat numbness in patients undergoing general anesthesia. Effects on other throat complications (sore throat and hoarseness) and perioperative safety will also be assessed.

3. Study Methods

3.1 Study Design

A prospective, randomized, single-blind, head-to-head, parallel-group, single-center clinical trial. Participants, data collectors/outcome assessors, and data analysts will be blinded; anesthesiologists and anesthesia nurses will not be blinded.

3.2 Study Population

Patients scheduled for laparoscopic surgery with endotracheal intubation at a tertiary hospital will be selected. The anesthesia technique will be combined intravenous-inhalational general anesthesia.

3.3 Sample Size and Rationale

In a preliminary experiment, the early post-extubation throat-numbness score was 6 points in patients receiving lidocaine cream; the anticipated score with sodium hyaluronate gel was 3 points. The minimum clinically important difference was 2 points. Sample size was estimated using the superiority analysis procedure in PASS 25.0, with $\alpha=0.025$, power $(1-\beta)=90\%$, and a pooled standard deviation of 1.6 points. The calculated sample size was 54 participants per group. Allowing for 10% loss to follow-up or dropout, 60 participants will be enrolled per group, for a total of 120.

3.4 Inclusion Criteria

1. Age 18–65 years, any sex.
2. American Society of Anesthesiologists (ASA) physical status I–II.

3. Scheduled laparoscopic surgery under general anesthesia with endotracheal intubation.
4. Expected surgical duration of 1–4 hours.
5. Able to understand and sign the informed consent form.

3.5 Exclusion Criteria

1. Expected postoperative transfer to the intensive care unit (ICU).
2. Known or anticipated difficult airway.
3. History of severe respiratory disease, such as asthma or chronic obstructive pulmonary disease.
4. High risk of reflux and aspiration, such as a full stomach or a history of severe gastroesophageal reflux disease.
5. Allergy to sodium hyaluronate, lidocaine, or any other study-related medication.
6. Pre-existing sore throat or hoarseness before surgery.
7. Pregnancy or breastfeeding.

3.6 Study Interventions

3.6.1 Sodium Hyaluronate Gel Group

An appropriate amount (2–3 mL) of sterile medical sodium hyaluronate lubricating gel (Bloomage Biotechnology) will be evenly applied to the distal tip and cuff surface of the endotracheal tube. The medical device registration certificate is identified as Appendix 1 in the source protocol.

3.6.2 Lidocaine Cream Group

An equal amount (2–3 mL) of lidocaine cream will be evenly applied to the distal tip and cuff surface of the endotracheal tube.

3.6.3 Standardized Anesthesia Protocol

(1) Anesthesia induction: Remimazolam 0.2–0.3 mg/kg will be administered. Propofol or etomidate may be added when necessary. Sufentanil 0.3–0.5 μg/kg will be administered, together with rocuronium 0.6–0.9 mg/kg or cisatracurium 0.2–0.3 mg/kg. Intravenous lidocaine and corticosteroids will not be used. Endotracheal intubation will follow a standardized procedure. The lubricant volume will be 2–3 mL and applied to the cuff surface. An appropriately sized endotracheal tube and a video laryngoscope will be used. Intubation will be performed by anesthesiologists with comparable experience (e.g., attending physicians or above), aiming to minimize the number of attempts and procedure duration. The number of intubation attempts will be recorded. Cuff pressure will be adjusted and maintained at 25–30 cmH_2O during intubation.

(2) Anesthesia maintenance: Combined intravenous-inhalational anesthesia will be used. The inhaled anesthetic will be sevoflurane or desflurane at a minimum alveolar concentration (MAC) of 0.5–1. The intravenous sedative will be dexmedetomidine 0.3–0.5 μg/kg/h or propofol 3–5 mg/kg/h. Remifentanil 0.1–1 μg/kg/min will be used for intravenous analgesia. Additional sufentanil will be administered according to surgical progress, with an additional 0.1–0.2 μg/kg at the end of surgery. Neuromuscular blocking agents will be supplemented every 1–2 hours or according to surgical progress, at one-third to one-half of the induction dose. Patient-controlled analgesia will not be routinely used postoperatively. Surgical duration and patient position will also be recorded.

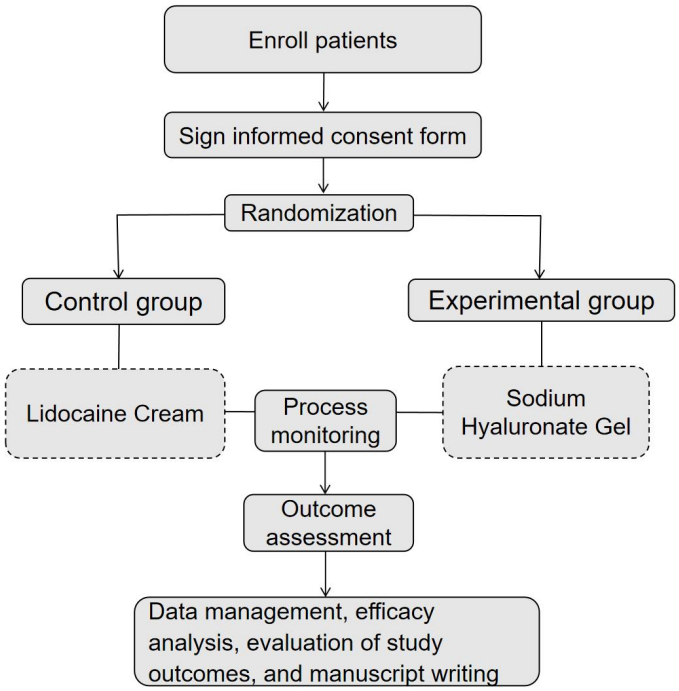
3.7 Statistical Analysis

Data will be analyzed using SPSS version 26.0. Continuous variables will be assessed for normality using the Shapiro–Wilk test and for homogeneity of variance. Normally distributed continuous variables will be analyzed using the independent-samples t test. Categorical variables will be analyzed using the chi-square test or Fisher's exact test. Continuous variables measured at multiple time points will be analyzed using a mixed-effects model, with participant as a random effect and group, measurement time point, and their interaction as fixed effects, to address imbalance due to loss to follow-up or missing data; baseline values and prespecified covariates will also be adjusted for. Between-group comparisons will use the independent-samples t test for normally distributed data or the Mann–Whitney U test otherwise. A P value <0.05 will be considered statistically significant.

3.8 Data Collection and Management

Paper-based and electronic data management will be used in parallel. Data will be collected using a structured case report form (CRF), including demographic information, perioperative variables, primary and secondary outcomes (throat-numbness visual analog scale [VAS] scores, coughing, sore-throat scores, hoarseness grades, endotracheal tube cuff pressure, hemodynamic parameters, adverse events, etc.), and safety follow-up records. Trained investigators will complete each item to ensure completeness and traceability.

4. Study Flow



5. Outcome Measures

5.1 Primary Outcome Measure

Throat numbness at 30 minutes after extubation, assessed using a visual analog scale (VAS).The visual analog scale (VAS) ranged from 0 to 10, with higher scores indicating more severe.

5.2 Secondary Outcome Measures

1. Incidence and severity of throat numbness during recovery, assessed using the VAS immediately after extubation and at 1, 8, 16, and 24 hours.
2. Postoperative throat numbness, assessed using the VAS immediately after extubation and at 1 hour.
3. Time to the first oral water intake and occurrence of coughing during the first oral water intake.
4. Grade of coughing during emergence: suctioning before extubation may be performed as clinically necessary and the number of suctioning episodes recorded. No active suctioning will be performed at the moment of extubation or within 5 minutes after extubation, to allow accurate assessment. Cough grade: 0 = no cough; 1 = mild, single cough; 2 = moderate, more than one cough lasting less than 5 seconds; 3 = severe, cough lasting more than 5 seconds.
5. Incidence and severity of sore throat during recovery, assessed using the VAS immediately after extubation and at 30 minutes, 1, 8, 16, and 24 hours.

6. Incidence and severity of hoarseness during recovery, assessed using the VAS immediately after extubation and at 30 minutes, 1, 8, 16, and 24 hours.
7. Endotracheal tube cuff pressure, measured at 1, 2, and 3 hours after intubation and at extubation.
8. Incidence of abnormal responses to intubation and extubation: heart rate >100 beats/min or <60 beats/min; systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; or a decrease in systolic blood pressure of >20% from baseline.
9. Satisfaction: anesthesiologists' satisfaction with use of the lubricant and patients' overall satisfaction with the emergence/recovery process.
10. Incidence of adverse events, including allergic reactions, nausea, and vomiting.