Effects of Dexmedetomidine Combined With Lidocaine Topical Administration on Cough Reflex During Extubation in Thyroidectomy Patients: A Randomized Clinical Trial

Research Study Protocol

IRB Registration Number: Soh-Med-26-6—15PD

14 June 2026

Effects of Dexmedetomidine Combined With Lidocaine Topical Administration on Cough Reflex During Extubation in Thyroidectomy Patients: A Randomized Clinical Trial

Introduction

Thyroidectomy is one of the most commonly performed endocrine surgical procedures worldwide, indicated for various thyroid pathologies including malignancy, benign nodules, and hyperthyroidism [1]. While generally safe, the perioperative management of thyroidectomy patients presents unique challenges related to airway management and emergence from anesthesia [2].

The endotracheal tube, while essential for airway maintenance during surgery, stimulates mechanoreceptors and irritant receptors in the larynx and trachea, triggering cough reflexes during emergence and extubation [3]. This cough reflex, while protective under normal circumstances, becomes problematic in the immediate post-thyroidectomy period due to several anatomical and surgical considerations.

Clinical Significance of Cough Suppression in Thyroidectomy

Coughing during extubation following thyroidectomy carries specific risks that distinguish it from other surgical procedures [4]:

Cervical Hematoma Formation: The violent increase in intrathoracic and central venous pressure during coughing episodes can precipitate bleeding from surgically sealed vessels, potentially leading to expanding cervical hematoma—a life-threatening complication that can cause airway

compromise requiring emergency intervention [5].

Hemodynamic Instability: Coughing provokes sympathetic activation with tachycardia and hypertension, increasing myocardial oxygen demand and risking cardiovascular complications in susceptible patients [6].

Surgical Site Disruption: The anterior neck dissection creates tissue planes that may be disrupted by vigorous coughing, potentially contributing to postoperative pain, edema, and delayed healing [7].

Patient Discomfort: Coughing causes significant patient distress and may exacerbate postoperative pain, leading to increased analgesic requirements and prolonged recovery [8].

Pharmacological Approaches to Cough Suppression

Multiple pharmacological strategies have been investigated to attenuate the cough reflex during emergence from anesthesia [9]:

Intravenous Lidocaine: Administered systemically, lidocaine suppresses airway reflexes through central and peripheral mechanisms, though optimal timing and dosing remain debated [10].

Dexmedetomidine: This highly selective alpha-2 adrenergic agonist provides sedation, analgesia, and sympatholysis without significant respiratory depression, making it attractive for emergence management [11]. It attenuates airway reflexes through both central sedative effects and modulation of sympathetic outflow [12].

Topical Airway Anesthesia: Direct application of local anesthetics to airway mucosa provides targeted sensory blockade of cough trigger zones [13]. The laryngopharynx, particularly the supraglottic, glottic, and subglottic regions, contains dense concentrations of cough-mediating receptors [14].

Rationale for Combination Therapy

While each approach has demonstrated efficacy individually, the concept of multimodal analgesia—combining agents with different mechanisms of action—has gained traction in perioperative medicine [15]. The theoretical advantages of combining dexmedetomidine with topical lidocaine include:

1. Complementary Mechanisms: Lidocaine provides rapid-onset sensory blockade of peripheral cough receptors, while dexmedetomidine offers central sedative and sympatholytic effects [16]

2. Synergistic Effect: Alpha-2 agonism may enhance local anesthetic efficacy through vasoconstriction, prolonging tissue retention [17]

3. Reduced Individual Drug Requirements: Combination may allow lower doses of each agent, minimizing dose-dependent adverse effects [18]

Study Objectives and Hypotheses

Primary Objective: To investigate the inhibitory effect of dexmedetomidine combined with lidocaine topical administration on cough reflex during extubation in patients undergoing thyroidectomy.

Secondary Objectives: To evaluate effects on cough severity, postoperative

sore throat, hemodynamic stability, sedation levels, recovery profiles, and adverse events.

Study Hypothesis: The combination of dexmedetomidine and lidocaine administered as laryngopharyngeal topical spray provides superior suppression of extubation cough reflex compared to lidocaine alone or placebo, without compromising recovery or increasing adverse events.

Methods:

After approval by the Ethics Committee at the Faculty of Medicine, Sohag University, the study will commence.

A written informed consent will be obtained from all patients

Study Design and Setting

This prospective, randomized, double-blind, placebo-controlled clinical trial will be conducted at the Department of Anesthesiology.

Participant Selection

Inclusion Criteria:

· Female patients aged 18-65 years

· American Society of Anesthesiologists (ASA) physical status I-II

· Scheduled for elective thyroidectomy under general anesthesia with endotracheal intubation

· Will provide written informed consent

Exclusion Criteria:

· Known allergy or contraindication to dexmedetomidine, lidocaine, or study medications

· Pre-existing cough or respiratory tract infection within 2 weeks

· History of chronic cough or reactive airway disease (asthma, COPD)

· Significant cardiovascular disease (arrhythmias, uncontrolled hypertension, heart failure)

· Hepatic or renal dysfunction (liver enzymes >2× upper normal limit, creatinine >1.5 mg/dL)

· Pregnancy or breastfeeding

· Anticipated difficult airway (Mallampati class III-IV, limited neck extension)

· Preoperative use of antitussive medications or opioids

· Body mass index >35 kg/m^2

· Emergency surgery

· Participation in another interventional trial within 30 days

Sample Size Calculation: Sample size will be determined based on the primary outcome of cough incidence during extubation. Based on previous studies reporting cough incidence of approximately 65% in control groups and expecting a reduction to 30% in the combination group (absolute reduction 35%), with α = 0.05 (two-sided) and power = 0.90, a minimum of 35 patients per group will be required. Accounting for potential dropouts (approximately 15%), 40 patients per group (total 120) will be enrolled.

Randomization and Blinding

Eligible patients will be randomly assigned in a 1:1:1 ratio to one of three groups using a computer-generated random number sequence prepared by an independent statistician not involved in patient care or outcome assessment. Randomization will be stratified by surgeon to account for potential surgical technique variations.

Group allocations will be concealed in sequentially numbered, opaque, sealed envelopes. The study drugs will be prepared by an anesthesia nurse not involved in patient management or data collection. All patients, anesthesiologists performing the interventions and extubation, outcome assessors, and statisticians will be blinded to group allocation. The topical sprays will be identical in appearance, volume, and packaging to maintain blinding.

Study Interventions

Group Allocation:

1. Dex-Lido Group (n=40): Will receive topical spray containing dexmedetomidine 1 μg/kg combined with 2% lidocaine (total volume 5 mL)

2. Lido Group (n=40): Will receive topical spray containing 2% lidocaine alone (5 mL)

3. Control Group (n=40): Will receive topical spray containing 0.9% normal saline (5 mL)

Preparation of Study Solutions:

· Dex-Lido solution: Dexmedetomidine 100 µg/mL (concentration) will be diluted with 2% lidocaine to achieve final concentration of dexmedetomidine 1 µg/kg in 5 mL total volume

· Lido solution: 2% lidocaine, 5 mL

· Control solution: 0.9% normal saline, 5 mL

All solutions will be prepared under aseptic conditions immediately before use and will be loaded into identical 5 mL syringes attached to a mucosal atomization device (MADgic™, Teleflex Medical) capable of delivering fine-particle spray.

Anesthesia Protocol

Preoperative Preparation:

All patients will fast for 8 hours prior to surgery. No premedication will be administered. Upon arrival in the operating room, standard monitoring will be applied including non-invasive blood pressure, electrocardiography (lead II and V5), pulse oximetry, and capnography.

Induction of Anesthesia:

Anesthesia will be induced with intravenous propofol 2-2.5 mg/kg, remifentanil 1-2 µg/kg, and rocuronium 0.6 mg/kg to facilitate tracheal intubation. Following loss of consciousness and adequate muscle relaxation, direct laryngoscopy will be performed, and the study intervention will be administered.

Study Drug Application:

Immediately prior to intubation, the pre-loaded atomizer will be used to

spray the study solution directly onto the supraglottic (aryepiglottic folds, false vocal cords), glottic (true vocal cords), and subglottic (immediately below the vocal cords) areas under direct vision using a laryngoscope. The atomizer tip will be positioned to ensure uniform distribution across these regions. Total application time was approximately 30 seconds.

Tracheal Intubation:

Following study drug application, tracheal intubation will be performed using a appropriately sized cuffed endotracheal tube (internal diameter 6.5-7.0 mm). Tube placement will be confirmed by capnography and bilateral chest auscultation.

Maintenance of Anesthesia:

Anesthesia will be maintained with sevoflurane (1.0-1.3 MAC) in an oxygen/air mixture (FiO_2 0.5) and remifentanil infusion (0.1-0.3 μg/kg/min) titrated to maintain hemodynamic parameters within 20% of baseline. Additional rocuronium boluses (0.15 mg/kg) will be administered as guided by neuromuscular monitoring (train-of-four count). Mechanical ventilation will be adjusted to maintain end-tidal CO_2 between 35-40 mmHg.

Intraoperative Monitoring:

Throughout surgery, heart rate, mean arterial pressure, oxygen saturation, end-tidal sevoflurane concentration, and train-of-four ratio will be continuously monitored and recorded at 5-minute intervals.

Emergence and Extubation Protocol

Approximately 10 minutes before the anticipated end of surgery, sevoflurane will be adjusted to maintain adequate anesthesia while

preparing for emergence. Remifentanil infusion will be continued until skin closure. At surgical wound closure, sevoflurane and remifentanil will be discontinued simultaneously.

Neuromuscular Reversal:

At the end of surgery, residual neuromuscular blockade will be reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg when train-of-four ratio will be <0.9.

Extubation Criteria:

Extubation will be performed when all following criteria will have been met:

· Spontaneous ventilation with regular respiratory pattern

· Respiratory rate 10-20 breaths/min

· End-tidal CO_2 <45 mmHg

· Oxygen saturation ≥95% on FiO_2 0.4

· Train-of-four ratio ≥0.9

· Ability to open eyes or respond to verbal commands

· Presence of intact airway reflexes (gag, swallow)

Extubation Procedure:

Oropharyngeal suctioning will be performed gently under direct vision. Patients will be positioned with head elevated 30 degrees. The endotracheal tube cuff will be deflated, and the tube will be removed smoothly during positive pressure inspiration. Supplemental oxygen (6 L/min) will be administered via face mask immediately following extubation.

Outcome Measures

Primary Outcome:

· Incidence of cough reflex during extubation: Will be defined as any visible or audible cough occurring from the time of endotracheal tube cuff deflation until 2 minutes following complete tube removal. Cough will be assessed by a blinded observer.

Secondary Outcomes:

1. Cough Severity: Graded on a 4-point scale [19]:

· Grade 0: No cough

· Grade 1: Single cough (mild)

· Grade 2: Multiple coughs lasting <5 seconds (moderate)

· Grade 3: Sustained coughing >5 seconds or severe paroxysms (severe)

2. Hemodynamic Parameters:

· Heart rate and mean arterial pressure will be recorded at: baseline (pre-induction), immediately before extubation, immediately after extubation, and at 1, 3, 5, and 10 minutes post-extubation

3. Postoperative Sore Throat:

· Will be assessed at 1, 6, 24, and 48 hours postoperatively using a 0-10 numerical rating scale (0 = no sore throat, 10 = worst imaginable sore throat)

· Incidence of moderate-to-severe sore throat (score ≥4)

4. Hoarseness:

· Will be assessed at 1, 6, 24, and 48 hours postoperatively using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe)

5. Sedation Scores:

· Richmond Agitation-Sedation Scale (RASS) will be assessed upon arrival in post-anesthesia care unit (PACU) and at 30-minute intervals until discharge [20]

· RASS scores range from -5 (unarousable) to +4 (combative), with 0 indicating alert and calm

6. Postoperative Nausea and Vomiting (PONV):

· Incidence and severity will be assessed at 1, 6, 24, and 48 hours postoperatively

· Need for rescue antiemetics will be recorded

7. Pain Scores:

· Numerical rating scale (0-10) for incisional pain assessed at rest and with swallowing at 1, 6, 24, and 48 hours postoperatively

· Cumulative analgesic consumption (morphine equivalents) will be recorded

8. Recovery Parameters:

· Time to awakening (from discontinuation of anesthetics to eye opening)

· Time to extubation (from discontinuation of anesthetics to tracheal extubation)

· PACU length of stay

· Hospital length of stay

9. Adverse Events:

· Bradycardia (heart rate <50 bpm requiring treatment)

· Hypotension (mean arterial pressure <60 mmHg requiring intervention)

· Desaturation (SpO_2 <90%)

· Laryngospasm

· Bronchospasm

· Reintubation

· Postoperative bleeding or hematoma formation

Data Collection

Data will be collected by trained research assistants blinded to group allocation using standardized case report forms. Preoperative data will include demographics, medical history, and baseline vital signs. Intraoperative data will include surgical details, anesthetic drug doses, fluid administration, and hemodynamic parameters. Postoperative data will be will be collected at specified time points in the PACU and surgical ward.

Statistical Analysis

Statistical Software: All analyses will be performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive Statistics: Continuous variables will be presented as mean ± standard deviation or median (interquartile range) based on distribution normality assessed by Shapiro-Wilk test. Categorical variables will be presented as frequencies and percentages.

Comparative Analyses:

· Primary outcome (cough incidence): Will be compared among groups using chi-square test or Fisher's exact test as appropriate. Pairwise comparisons with Bonferroni correction for multiple testing (significance threshold $P < 0.017$).

· Cough severity: Will be analyzed using Mann-Whitney U test for ordinal data.

· Hemodynamic parameters: Repeated measures ANOVA with post-hoc Bonferroni correction to assess between-group differences over time.

· Continuous secondary outcomes: One-way ANOVA with post-hoc Tukey HSD for normally distributed data; Kruskal-Wallis test with Dunn's post-hoc test for non-normally distributed data.

· Categorical secondary outcomes: Chi-square or Fisher's exact test.

Adjusted Analyses: Logistic regression will be performed to identify independent predictors of cough incidence, adjusting for potential confounders including age, surgical duration, and intraoperative remifentanil dose.

Subgroup Analyses: Pre-specified subgroup analyses will be conducted based on age (<50 vs ≥50 years), surgical duration (<2 vs ≥2 hours), and type of thyroidectomy (total vs partial).

Missing Data: Multiple imputation using chained equations will be planned for missing outcome data if >5% missingness occurred.

Sample Size Recalculation: The study will be powered for 40 patients per group based on initial calculations. No interim analyses will be performed.

Statistical Significance: Two-sided $P < 0.05$ will be considered statistically significant unless otherwise specified for multiple comparisons.

References :-

1. Chen AY, Bernet VJ, Carty SE, et al. American Thyroid Association statement on optimal surgical management of thyroid disease. Thyroid. 2021;31(3):349-374.

2. Bajwa SJ, Sehgal V. Anesthesia and thyroid surgery: The never ending challenges. Indian J Endocrinol Metab. 2013;17(2):228-234.

3. Canning BJ. Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):33S-47S.

4. Irwin RS. Complications of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):54S-58S.

5. Shaha AR, Jaffe BM. Practical management of post-thyroidectomy hematoma. J Surg Oncol. 1994;57(4):235-238.

6. Leech P, Barker J, Fitch W. Proceedings: changes in intracranial pressure and systemic arterial pressure during the termination of anaesthesia. Br J Anaesth. 1974;46(4):315-316.

7. Kim ES, Bishop MJ. Cough during emergence from isoflurane anesthesia. Anesth Analg. 1998;87(5):1170-1174.

8. Bidwai AV, Bidwai VA, Rogers CR, Stanley TH. Blood-pressure and pulse-rate responses to endotracheal extubation with and without prior injection of lidocaine. Anesthesiology. 1979;51(2):171-173.

9. Tung A, Fergusson NA, Ng N, Hu V, Dormuth C, Griesdale DEG. Medications to reduce emergence coughing after general anaesthesia with tracheal intubation: a systematic review and network meta-analysis. Br J Anaesth. 2020;124(4):480-495.

10. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Sato Y, Yamada Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015;2015(7):CD004081.

11. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893-913.

12. Guler G, Akin A, Tosun Z, Eskitascoglu E, Mizrak A, Boyaci A. Single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation. Acta Anaesthesiol Scand. 2005;49(8):1088-1091.

13. Sakae TM, Souza RLP, Brandão JCM. Impact of topical airway anesthesia on immediate postoperative cough/bucking: a systematic review and meta-analysis. Braz J Anesthesiol. 2023;73(1):91-100.

14. Widdicombe JG. Sensory neurophysiology of the cough reflex. J Allergy Clin Immunol. 1996;98(5 Pt 2):S84-S90.

15. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77(5):1048-1056.

16. Zhang J, Zhang X, Wang H, Zhou H, Tian T, Wu A. Dexmedetomidine as a neuraxial adjuvant for prevention of perioperative shivering: meta-analysis of randomized controlled trials. PLoS One. 2017;12(8):e0183154.

17. Kosugi T, Mizuta K, Fujita T, Nakashima M, Kumagai M. High concentrations of dexmedetomidine inhibit compound action potentials in frog sciatic nerves without alpha(2) adrenoceptor activation. Br J Pharmacol. 2010;160(7):1662-1676.

18. Lee JH, Koo BN, Jeong JJ, Kim HS, Lee JR. Differential effects of lidocaine and remifentanil on response to the tracheal tube during emergence from general anaesthesia. Br J Anaesth. 2011;106(3):410-415.