

A Feasibility Study to
Investigate Lidocaine as an ETT
Cuff Media in the Cardiac
Surgery ICU Patient Population,
and its Effect on Sedation
Requirements

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Title of Study: A FEASIBILITY STUDY TO INVESTIGATE LIDOCAINE AS AN ETT CUFF MEDIA IN THE CARDIAC SURGERY ICU PATIENT POPULATION, AND ITS EFFECT ON SEDATION REQUIREMENTS

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Principal Investigator: Troy Seelhammer, M.D.

Co-Principal Investigators: Erica Wittwer, M.D.

Co-Investigators: Katelynn Kressin, RN, Ellen Borhart, RN, Jenna Steege, CRNA., Eric DuBois, RN, Marci Newcome, APRN.

Statistician: Darrell Schroeder

Background and Significance

Patients who undergo general anesthesia with tracheal intubation frequently suffer from multiple adverse events with the endotracheal tube (ETT) itself a frequent source of pain and discomfort.¹ Tracheal mucosal inflammation and irritation caused by the ETT may exacerbate many of these symptoms which create a variety of respiratory challenges including difficulty maintaining patient-ventilator synchrony. Generally speaking, this problem can be treated with sedation and analgesia medications. These medications however, can subsequently increase the total time of intubation, length of intensive care unit (ICU) stay, as well as increase morbidity and mortality.²

Additionally, other adverse events often occur once the patient is extubated including sore throat, cough, restlessness, dysphagia, and dysphonia. When considered in their entirety, these adverse events are referred to as, emergence phenomena (EP).^{1,3,4} EP can subsequently lead to setbacks regarding surgical procedures. Setbacks arise often due to increases in intra-thoracic or intra-abdominal pressure, intraocular pressure, and intracranial pressure. Increases in these various pressures may result in post-operative bleeding, bronchospasms, vitreous loss, or possibly wound dehiscence.⁵

Pharmacological support includes; NSAIDS, opioids, or sedation and analgesia medications (while intubated). Among these medications, lidocaine has recently been emerging as a superior method of choice.⁵ Recent evidence-based literature (randomized controlled trials [RCTs], systematic reviews, Cochrane review, and expert opinion) has shown that lidocaine as an intracuff media for patients who are mechanically ventilated, can reduce sedative requirements thereby improving ETT tolerance, and can reduce EP.⁵⁻⁸ Reducing sedation may result in: less side effects of the sedation medication, a quicker extubation time leading to a shorter stay in the ICU, and a reduction in overall cost.

The proposed study seeks to investigate the efficacy of instillation of buffered lidocaine as an endotracheal tube cuff medium on post-operative sedative requirements, time to extubation, and frequency of emergence phenomena in a population of adult patients undergoing cardiac surgical procedures requiring endotracheal intubation.

After completion of a thorough review of the current literature, the optimal route for investigating the above clinical question is a prospective feasibility study to determine the effect of 1.8% lidocaine/0.76% sodium bicarbonate in the ETT cuff for the stated outcomes. The proposed research project will be called, the lidocaine project and will be conducted in the cardiac surgery ICU at Saint Mary's Hospital (Mayo Clinic), in Rochester, MN. This setting is highly desired due to the high volume of cardiac surgeries being performed at Mayo Clinic. This population of patients proves to be consistent in their post-operative recovery period and quite often is extubated within 6 hours. This will provide a substantial window of opportunity to study the effects of the intervention.

References

1. Biro P, Seifert B, Pasch T. Complaints of sore throat after tracheal intubation: a prospective evaluation. *Eur. J. Anaesthesiol.* 2005;22(04):307-311.
2. Basuni A. Intracuff alkalized lidocaine reduces sedative/analgesic requirements for mechanically ventilated patients. *Saudi J. Anaesth.* 01 Oct 2014;8(4):451-455.
3. Scuderi PE. Postoperative sore throat: more answers than questions. *Anesth. Analg.* 2010;111(4):831-832.
4. Jaensson M, Olowsson LL, Nilsson U. Endotracheal tube size and sore throat following surgery: a randomized-controlled study. *Acta Anaesthesiol. Scand.* 2010;54(2):147-153.
5. Lam F, Lin Y-C, Tsai H-C, Chen T-L, Tam K-W, Chen C-Y. Effect of Intracuff Lidocaine on Postoperative Sore Throat and the Emergence Phenomenon: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PloS one.* 2015;10(8):e0136184.
6. Mallick A, Smith S, Bodenham A. Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation. *Br. J. Anaesth.* 1996;77(6):731-734.
7. Tanaka Y, Nakayama T, Nishimori M, Sato Y, Furuya H. Lidocaine for prevention of a sore throat following an operation under general anaesthetic. *Health (N. Y).* 2007.
8. Altıntaş F, Bozkurt P, Kaya G, Akkan G. Lidocaine 10% in the endotracheal tube cuff: blood concentrations, haemodynamic and clinical effects. *Eur. J. Anaesthesiol.* 2000;17(7):436-442.
9. Abbasi A, Mahjobipoor H, Kashefi P, et al. The effect of lidocaine on reducing the tracheal mucosal damage following tracheal intubation. *J. Res. Med. Sci.* 2013;18(9).

Specific Aims

1. The primary outcome is to determine if 1.8% lidocaine/0.76% Sodium Bicarbonate in the ETT cuff will improve ETT tolerance thereby reducing sedation requirements.
2. A secondary outcome is to determine if 1.8% lidocaine/0.76% Sodium Bicarbonate in the ETT cuff will decrease the total amount of time the patient requires mechanical ventilation.
3. Secondary outcomes are to determine if 1.8% lidocaine/0.76% Sodium Bicarbonate in the ETT cuff decreases post-extubation sore throat, cough, dysphonia, dysphagia, restlessness, and agitation.

Design and recruitment:

This project will be carried out as a small feasibility study. It will be carried out in the Cardiovascular Surgical Intensive Care Unit (CVSICU) of Saint Mary's Hospital, in Rochester, MN. After obtaining approval by the Institutional Review Board (IRB), patients will be recruited by the research assistant during their initial outpatient appointment for their upcoming cardiac surgical procedure, as well as pre-operatively the day of surgery. Patients who are deemed in the clinic as, "rapid recovery," meet the inclusion criteria, and are expected to require ventilatory support for a period of less than 5 hours post-operatively in the cardiac ICU will be enrolled in this small feasibility study.

Inclusion Criteria:

- All patients > 18 years of age (male and female) who will receive general anesthesia for cardiac surgery at St. Mary's Hospital (SMH) in Rochester, MN
- Cardiac surgery includes: single valve repair, myectomy, CABG, pericardectomy.
- Patients who are anticipated to be deemed, "rapid recovery," in the cardiac surgery ICU at St. Mary's Hospital
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Exclusion Criteria:

- Age < 18 years old at time of surgery
- Patients who cannot consent themselves or non-English speaking patients who require an interpreter
- Patients who are not sent to the cardiac ICU post-operatively
- Patients who are anticipated to have a difficult tracheal intubation
- Patients having risk factors of postoperative aspiration of gastric contents
- Patients who have respiratory disease or recent respiratory tract infection
- > 2 attempts to secure an airway
- Patients undergoing TAVR procedures or any form of "robotic," procedures

Methods:

Patients will be chosen based on their inclusion/exclusion criteria. Patients during their clinic appointment prior to surgery were provided a thorough explanation of the intervention and study, if the patient agrees to participate; he or she will be included in the study. The day of the procedure, the patient will have the intervention take place while in the operating room by the Registered Respiratory

Therapist (RRT), Certified Registered Nurse Anesthetist (CRNA) or Anesthesiologist. The patient will remain intubated after the surgery is complete and will be taken to the cardiac surgical ICU.

At the induction of anesthesia, patients will be breathing 100% oxygen via a face mask and then, become anesthetized according to a standard protocol and at the discretion of the attending anesthesiologist. Patients will be receiving fentanyl, lidocaine (as an IV anesthetic preventing uncomfortable side effect Propofol can create in the arm) and either succinylcholine or vecuronium to facilitate tracheal intubation. Laryngoscopy will then be performed and the trachea intubated with a standard cuffed ETT. ETT tubes from 6.0mm to 8.0mm in diameter will be used. Inflation of the ETT cuff will be performed in accordance with the randomization of either air or 1.8% lidocaine/0.76% solution until such time as there is no air leak around the tube when administering positive pressure to 20 cm H₂O. Checking for intermittent leaks to ensure a minimum seal is present will be done as needed per standard of care. Anesthesia will be maintained with volatile anesthetic with or without a Propofol infusion. Vecuronium will be used to maintain the ulnar nerve train-of-four at 0–3 of four twitches. Anesthesia maintenance will occur until the near end of the surgical procedure. The volatile anesthetic will be discontinued and Propofol will be initiated via a continuous infusion to facilitate transportation to the intensive care unit (ICU). After arrival to the ICU, Neuromuscular blockade will then be antagonized with suggamadex reversal agent, and the pharynx being gently suctioned under direct vision. Mechanical ventilation to be maintained until swallowing or spontaneous respiration begins, and then, converted to assisted manual ventilation. Extubation will be performed at ICU provider's discretion once the extubation protocol criteria are met.

The patient then will be closely monitored as a 1:1 by the room nurse, and by other staff (respiratory therapist, and ICU fellows and consultants) for toleration of the ventilator (coughing, double triggering, "bucking," etc.) on the cardiac surgical intensive care unit. Sedation amount will be recorded electronically from initiation of the mechanical ventilation weaning protocol until the time of extubation. The RRT will physically record "yes," or "no," on the form provided regarding the patient coughing, complaining of a sore throat or difficulty swallowing, having hoarseness or difficulty speaking.

Sample Size:

The sample size for this investigation is determined for the primary endpoint of total propofol dose in the first 4 hours. Basuni (2014) reported differences in propofol dose of approximately 0.7 SD for patients receiving saline vs lidocaine+bicarb.

The current investigation is considered a randomized Phase II study, with the objective of determining whether or not additional studies of the current treatment intervention are warranted. Although debate exists regarding the value of formal statistical comparisons in phase II trials, we agree with those who propose that a one-sided test with a false-positive (type I error) rate of 0.10 for the primary endpoint is an appropriate criterion to use to help guide the decision-making process. In general, a sample-size of N=20 patients per group will provide statistical power (one-tailed, alpha=0.10) of 80% to detect a difference between groups of 0.7 standard deviation units.

Data Collection:

Regarding the primary outcome, total sedation required from the time of the patient entering the ICU until extubation, will be recorded in the electronic charting documentation.

Regarding a secondary outcome, the total amount of time the patient is intubated (from the time they enter their room in the ICU from surgery) will be recorded by the RRT on the assessment form provided.

Regarding the secondary outcomes, patient assessment forms will be provided in the envelopes (attached to patients chart) for the study team, SRNA, to fill out. Completed assessments will be collected at the end of each day and will be manually analyzed at the end of the study once the sample size is reached.

Data Analysis

Data will be summarized using mean \pm SD, or median [25th, 75th] for continuous variables and frequency counts and percentages for nominal variables. The primary endpoint will be sedative dose (Propofol, precede, fentanyl, ketamine) amount from the mechanical ventilation weaning protocol initiation until ETT extubation. This endpoint will be compared across groups using the two-sample t-test, or rank sum test. Secondary endpoints will include; time to extubation (from initiation of the mechanical ventilation weaning protocol); and coughing, restlessness, hoarseness, and dysphagia. Sedative dose will be treated as continuous variables and analyzed using ANOVA. Post-extubation endpoints will be dichotomized and analyzed using logistic regression. In all cases, distributional assumptions will be assessed with transformations or nonparametric methods used as appropriate.

Statistical Analysis:

Recorded characteristics will be presented using mean \pm SD or median (IQR) for continuous variables and frequency percentages for categorical variables. Summaries of these variables will be presented overall. The primary outcome will be compared using analysis of variance (ANOVA). Secondary analyses will also be performed and analyzed using logistic regression. Two-tailed p-values ≤ 0.05 will be considered statistically significant in all analyses.

Strengths

Despite variation in co-morbidities and surgery types, all patients deemed rapid recovery eligible have necessarily undergone screening for complications, hemodynamic stability, adequacy of hemostasis, and anticipated readiness for extubation within 2 to 6 hours. This improves the generalizability of study results. All patients have the added benefit of being closely and safely monitored by the cardiac ICU team during the entire duration of the intervention. There will be a pharmacist on the ICU as well to help with any discrepancies that may arise. The study is using a sample size with sufficient enough power to gain a greater separation of results between the control and intervention arms.

Limitations

Our team acknowledges several limitations. Only a single lidocaine concentration and a single sodium bicarbonate concentration will be studied. Previous studies have compared various concentrations of sodium bicarbonate; results have not shown a difference in patient outcomes. Future projects could investigate other instillation solutions to further optimize therapeutic efficacy. There is data that the heart rate can be lower in patients receiving alkalinized lidocaine. However it is common for postoperative cardiac surgical patients to have paced rhythms and vasoactive drug infusions, both of which can derange the HR. HR will not be included as a secondary outcome, however could be something to consider in future studies. Oxygen saturation proves difficult to record as many factors can give a false reading (transient face mask, turning up of nasal cannula not often charted), so this was left out as a potential secondary outcome. Hypercarbia could be included in future studies as a secondary outcome. This study left it out because it requires ensuring that a post-extubation arterial blood gas is obtained. This quite often is not reliably obtained nor is the time to obtain the sample standardized. Future research regarding the use of lidocaine as an ETT cuff media could certainly entertain the idea of incorporating some of these potentially important outcomes.

Budget

After first obtaining IRB approval, funding will be applied for through the Mayo Clinic Center for Clinical and Translational Science (CCaTS) 2017 Small Grants Program (SGP) allocation for the Department of Anesthesiology. CCaTS Research Resources will assist with the statistical analysis.

Should a poster be generated to disseminate results, under the new institutional guidelines for poster development and preparation, Media Support Services will provide support and print the poster at no charge.

Human Subjects

Description

This study will be conducted as a feasibility study prospectively comparing a single group of patients receiving lidocaine, respectively via the ETT cuff.

Research Materials:

No biological specimens will be obtained.

Confidentiality and Data Management

The confidentiality of all study participants will be maintained. After the outcome measures are collected, data will be abstracted and entered into an electronic database. At the time of data entry, all personal identifiers will be removed. When not in use, the electronic database will be securely housed in the administrative offices of the Anesthesia Clinical Research Unit.

Informed Consent

Written informed consent will be obtained from all study participants prior to involvement in the study protocol. All potential study subjects will be told that declining to participate in the research project will in no way impact their medical care at Mayo Clinic.

Potential Risks:

There is an extremely rare chance the ETT cuff could rupture. There has been a recent documented incidence however, involving a patient who received an unknown amount of lidocaine in their ETT during a non-study, off-label use of lidocaine. The patient did have a negative outcome regarding vocal cord injury, although it should be known that this could have occurred due to a variety of reasons ranging from improper ETT placement, coughing, cuff/tube migration, pain/light anesthetic agent, etc. In case of ETT cuff rupture, and to avoid potential systemic toxicity, we will be using a dose which is well under the toxic level, as documented by previous literature. Other potential risks are none greater that would otherwise normally occur to a typical cardiac surgery ICU patient.

In addition, the potential risks that have been investigated in the literature for this topic are comprised of: two meta-analyses, many randomized-controlled trials, and one retrospective case-control study. The majority of this evidence is level II, with two level I meta-analysis on the Ackley level of evidence scoring tool, indicating a high level of quality, reliability, and generalizability, with a low risk of bias among the evidence.¹ For over 20 years, researchers have been experimenting with lidocaine to help patients overcome the various side effects and complications of being intubated. There have been a few studies conducted to determine the safety and efficacy of lidocaine diffusion across the polyurethane cuff of the endotracheal tube.^{2,3} Both Estebe et al.⁴ and Huang et al.³ determined that alkalinization of lidocaine is safe to use, without compromising the integrity of the cuff and improves the diffusion when compared to lidocaine alone. Since these studies, most researchers have utilized alkalinized lidocaine in intracuff studies, and there have even been a few studies that have compared different concentrations of lidocaine.^{4,5} This high level of evidence will guide a protocol for the

anesthesia and intensive care staff at Mayo Clinic caring for rapid recovery cardiac surgery patients. This study will improve and elaborate on the science behind intracuff lidocaine and the positive impact on lowering patient sedation requirements, as well as, bridge the gap between current studies with endotracheal lidocaine and decreased sedation in the intensive care setting. While reviewing the literature, there were no reported cases of sentinel events or tube rupture.

With the scientific evidence, our team has also consulted with multidisciplinary groups across the campus to ensure safety and efficacy of this study. The critical care respiratory therapists group has been educated on the science behind this study, and their role in protecting the patient's airway. The respiratory therapists will continue to do all of their normal safety assessments, in addition to monitoring how much lidocaine is in the cuff upon arrival to the ICU and at extubation to ensure there is not over or under inflation. The team has also obtained approval from the Critical Care Service consultant group. This group of highly experienced physicians was briefed on the exact procedures that will take place throughout this study, including the benefits and potential risks.

1. Melnyk BF-O, E. *Evidence-Based Practice in Nursing & Healthcare*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2011.
2. Estebe JP, Treggiari M, Richebe P, Joffe A, Chevanne F, Le Corre P. In vitro evaluation of diffusion of lidocaine and alkalinized lidocaine through the polyurethane membrane of the endotracheal tube. *Ann Fr Anesth Reanim*. 2014;33(4):e73-77.
3. Huang CJ, Tsai MC, Chen CT, Cheng CR, Wu KH, Wei TT. In vitro diffusion of lidocaine across endotracheal tube cuffs. *Canadian journal of anaesthesia = Journal canadien d'anesthesie*. 1999;46(1):82-86.
4. Estebe J-P, Dollo G, Le Corre P, et al. Alkalinization of intracuff lidocaine improves endotracheal tube-induced emergence phenomena. *Anesthesia & Analgesia*. 2002;94(1):227-230.
5. Soares SMF, Arantes VM, Módolo MP, et al. The effects of tracheal tube cuffs filled with air, saline or alkalinised lidocaine on haemodynamic changes and laryngotracheal morbidity in children: a randomised, controlled trial. *Anaesthesia*. 2017;72(4):496-503.

Benefits:

Direct benefits of this study are the potential to decrease the need for sedation and analgesia medication in the mechanically ventilated post-op patients. This would decrease cost, as well as the morbidities that go along with sedation and analgesia medication usage. Another benefit is the decrease in EP symptoms; sore throat, cough, dysphagia, dysphonia, and restlessness. A decrease in these symptoms would make a more comfortable recovery for patients, as well as potential to

decrease any hindrance in their recovery, as many of these symptoms can disrupt healing in their respective surgical sites. These outcomes would add to the body of literature.

Gender/Minority Mix

Subjects will be eligible for enrollment, regardless of race or gender with distribution reflecting the practice at Mayo Rochester.