Comparison of Effectiveness of Mask Ventilation and Endotracheal Tube in Pharynx (TTIP) in Patients with Potential Difficult Airway: A Prospective Randomized and Blind Trial.

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1. Background

In the past century, measures have been increasingly implemented in the field of anesthesia to combat the incidence of preoperative and perioperative complications. One such measure has been the development and subsequent modifications to airway management via the difficult airway algorithm (1). Difficulty with the airway management is a primary concern as an inability to oxygenate the patient can result in irreversible injury to vital organs and ultimately death (2).

Difficulties encountered with mask ventilation and intubation result in a significant portion of complications and mortality encountered during anesthesia (3). Among all patients undergoing general anesthesia, the rate of difficult intubation ranges from 0.5% to 10% depending on the exact definition (4). In addition, analysis conducted using closed claims spanning over 3 decades found that difficulties in airway management account for 6% of all claims during general anesthesia (5). The inability to perform effective mask ventilation or tracheal intubation can be due to a multitude of patient related factors. These factors include increasing age, increasing weight, history of snoring, lack of teeth, Mallampati class, limited mouth opening, protruding tongue, and beard presence (6). Establishing new airway management techniques and assessing which techniques lead to better outcomes (both efficiency and effectiveness) are necessary to reduce anesthesia-related morbidity and mortality. In the event that intubation proves to be difficult or impossible, mask ventilation is often used as a rescue technique to provide oxygenation and ventilation to a patient until the patient's airway can be successfully intubated. Therefore, clinicians should be made aware of the most effective techniques regarding difficult airway management and effective ventilation strategies.

On arrival to the operating room, the large majority of patients are ventilating and oxygenating without any airway adjuncts for assistance. Therefore, the inability to perform effective mask ventilation after induction of anesthesia likely occurs due to technical failure to generate positive ventilation and/or upper airway obstruction. When considering all causes of failure for adequate ventilation, it is often challenging to precisely determine the cause of failed mask ventilation. Failure of mask ventilation often occurs due to leaks around the mask from an inadequate seal, tongue and/or epiglottis obstructing the upper airway, laryngospasm, or aspiration. However, airway obstruction from redundant tissue likely accounts for the majority of failure. Understanding the underlying physiology of a difficult airway enables clinicians to proficiently manage a difficult airway.

In an effort to reduce morbidity and mortality associated with difficult airway management, adjustments to technique and innovations of ventilation have been studied extensively in patients with difficult airways. Recently, it was demonstrated that the approach to two-hand mask ventilation techniques had varying levels of success as measured by tidal volumes and rate of ventilator failure depending on the hand-grip used by the person attempting ventilation. (7). In addition to exploring the effect of hand grips on mask's ventilation success, further innovations in ventilation have been searched including the use of tracheal tube in pharynx (TTIP) ventilation. Ventilation using the TTIP technique is effective and can be used as a bridging technique for oxygenation **(this technique is illustrated in Figure 1)**. An endotracheal tube can be inserted via the nostril or oral cavity, and subsequently advanced until the tip of the tube reaches approximately the level of the glottis. By ventilating with the tip of an endotracheal tube near the glottis, the TTIP technique successfully provided ventilation within seconds after failed mask ventilation in all 4 difficult airway cases encountered in a study by Kristensen in 2005 (7). Unfortunately, there is a lack of well-designed and executed randomized trials to validate its efficacy in a true or potential difficult airway.

Moreover, this technique seems easy to learn, conceptualize, and use in any urgent or emergency difficult airway management situation. Potential advantages of TTIP technique are multiple and include: 1) bypasses the mask seal, 2) does not require successful laryngoscopy and tracheal intubation, 3) flexible laryngoscopy or surgical airway can be concurrently performed when the patient is ventilated or at least oxygenated, and more importantly, 4) it does not require the correct insertion of a conventional supraglottic airway (SGA), like a laryngeal mask airway (LMA). As long as the tip of the endotracheal tube reaches the level of the glottis, the positive pressure of ventilation should be enough to open a collapsed upper airway. Two scenarios that may render this technique ineffective are laryngospasm and massive aspiration. If laryngospasm is present as the potential cause, adequate muscle paralysis should be effective in correcting this obstruction. In massive aspiration, clearance of the debris should help with ventilation. Finally, the potential inadequate seal is a concern with this technique. Since the cuff is not placed in the lumen of the trachea and is not inflated, the seal must be achieved via the lips. The seal can be established with one or two hands as shown in **Figures 2 and 3**, respectively. Even if a complete seal is not achieved, holding the lips around the tube can create a seal sufficient for positive pressure ventilation.

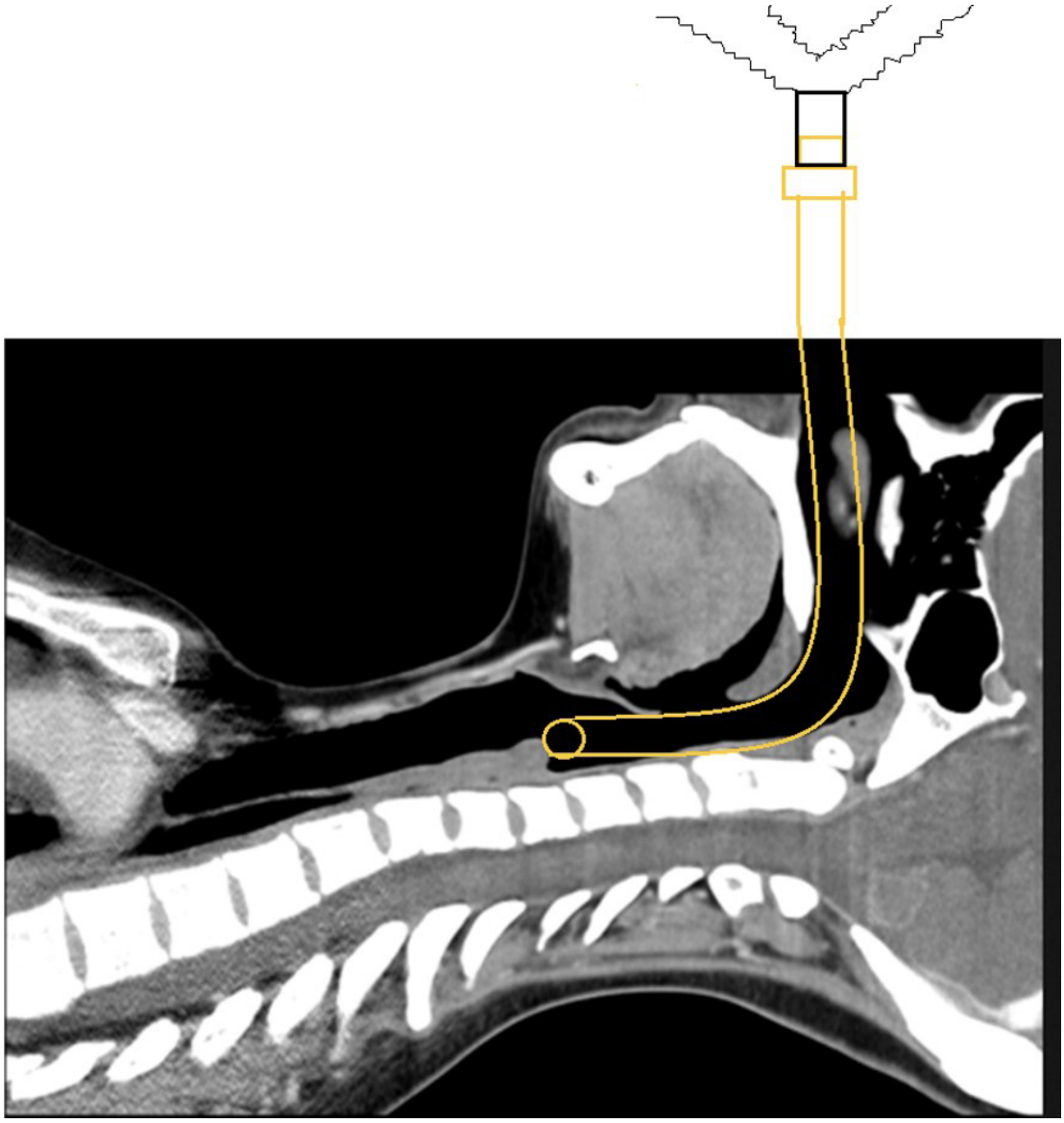

Figure 1. Illustration of endotracheal tube in pharynx technique.

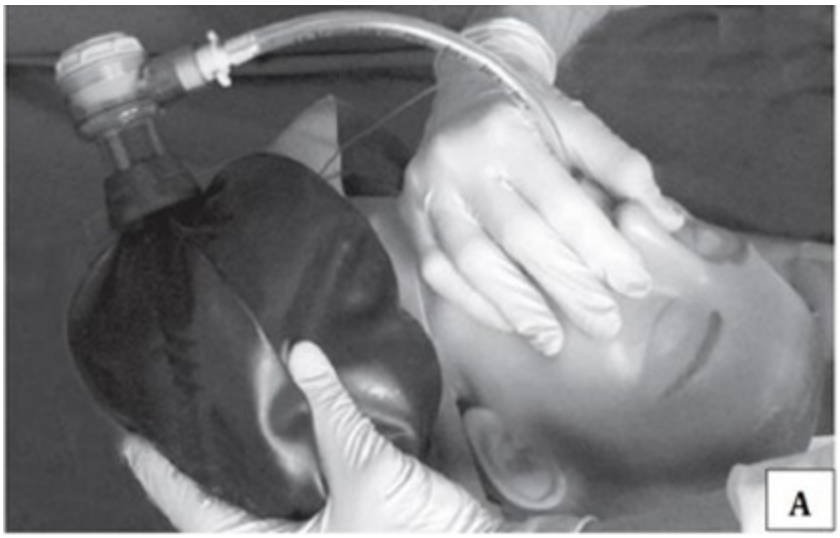

Figure 2. Tracheal tube in pharynx and seal at lips with one hand

Figure 3. ***Tracheal tube in pharynx and seal at lips with two hands***

While improvements in intubation technologies have been of primary focus, there has been relatively little consideration into comparing the effectiveness of traditional mask ventilation vs. TTIP. In other words, how do we optimize and improve the difficult airway protocol for use during urgent or emergent circumstances? Furthermore, little is known on the specific order that the two ventilation modalities are used during a difficult airway situation. The maintained consistency of order in the standard airway protocol can be attributed to the success the difficult airway algorithm has had in decreasing complications (6). However, rates of CICV (cannot intubate, cannot ventilate) have not seen a reduction despite new innovations (8). It is possible that alterations to the order of the current difficult airway procedure could lead to significant improvement of difficult airway management.

2. Hypothesis

TTIP ventilation is more effective than mask ventilation in patients with a potentially difficult airway

3. Specific aims

3.1 To determine the efficacy of TTIP-first ventilation

3.2 To compare the efficacy of TTIP first ventilation with the current practice of mask-first ventilation

4. Patient enrollment

This study will be carried out in the main operative rooms at Memorial Hermann Hospital in the Texas Medical Center (TMC). The study team will approach the patients in the respective preoperative holding area after reviewing their medical records to determine eligibility. Once the study team believes that a particular patient is eligible to participate in the study, the study team will provide that patient with detailed information about the study and obtain informed consent from the patient.

4.1. Inclusion criteria:

I. 18 or older years of age

II. BMI >30 kg/m^2

III. Mallampati class III or IV

IV. Requiring general anesthesia

4.2. Exclusion criteria:

I. Acute and chronic respiratory disorders, including COPD and asthma

II. ASA physical status classification ≥IV

III. Emergency surgery

IV. Induction requiring rapid sequence for intubation

V. Patients requiring awake intubation

VI. Pregnant women

VII. Untreated ischemic heart disease

VIII. Contraindication for mask ventilation

5. Outcomes

5.1 Primary outcome: The success rate of ventilation with TTIP vs. mask, defined as at least one of the first three breaths shows three phases of expired CO_2 profile.

5.2 Secondary outcomes:

5.2.1 Expired tidal volume of ventilation with TTIP vs mask.

5.2.2 Peak inspiratory airway pressure achieved with TTIP vs. mask ventilation

5.2.3 Dynamic airway resistance is defined as the peak inspiratory flow divided by the corresponding airway pressure.

5.2.4 Satisfaction of the providers obtained with post ventilation survey

6. Study protocol

After providing informed consent, the subjects will receive premedication in the usual manner. Subjects will be placed on the operating room table in the supine position with the head in the neutral position on a pillow and elevated ~10 cm. The operators who will be performing mask ventilation are familiar with bag–valve mask ventilation, including the physicians, residents, and Anesthesia assistants. Medical students and anesthesia assistant students will not be involved in airway manipulation for the purposes of this study. All the operators will not be a

part of the study team. The operators will be provided with brief instructions before the induction (with a demonstration of the two techniques), with a photograph for each, as shown in **Fig. 4A and 4B.**

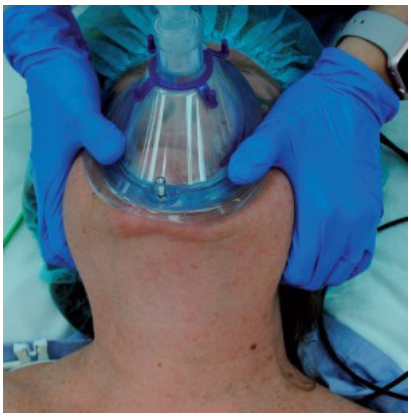

Figure 4A: Mask Ventilation using the V-E technique

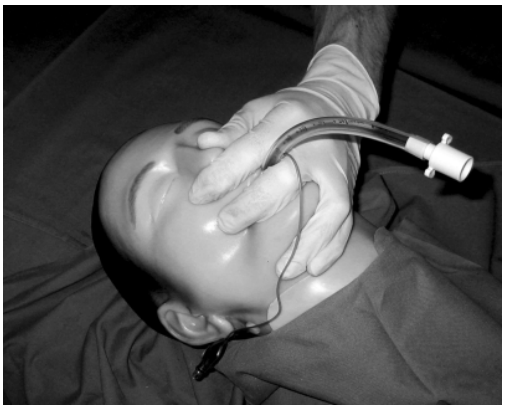

Figure 4B: Ventilation via TTIP

Standard monitors for general anesthesia will be applied, including ECG, blood pressure measurement, pulse oximetry, and capnography. Pre-oxygenation via a medium-sized plastic mask will be carried out with a flow rate of 10-liter min^{-1} of 100% O_2 until the expired O_2 concentration reaches ≥80%. The mask will be connected to the breathing circuit and used for pre-oxygenation in both ventilation techniques.

Induction of anesthesia will be achieved by an intravenous bolus injection of fentanyl (1-2µg/kg), propofol (1–2 mg/ kg). Thereafter, based on the clinical assessment of the care team, an appropriate level of sedation will be maintained with additional propofol.

When apnea is observed, the subjects will be ventilated with one of the two ventilation techniques in a randomized crossover manner. Ventilation will begin either with TTIP followed by mask ventilation (Group A) or with the reverse sequence, that is, mask ventilation followed by TTIP (Group B), as shown in **Fig. 5.** After induction, ventilation will be obtained with the ventilator set to pressure-control mode at a rate of 10 bpm, inspiratory-to-expiratory time ratio (I:E) of 1:2, peak inspiratory pressure (PIP) of 20 cm H_2O, and no PEEP. Subjects will start with one technique (Step 1) and cross over to the other technique (Step 2), as shown in **Fig. 5**. The subjects in Group A will first be ventilated with the TTIP technique. If the subjects are adequately ventilated, as defined by carbon dioxide measured during exhalation in at least one of the first three consecutive breaths, ventilation will continue until completion of 10 breaths, for 1 min (Step 1). Subjects will then be ventilated with mask ventilation (Step 2). In Step 1, if

ventilation fails with the TTIP technique for all of the first three consecutive breaths, the subject will be crossed over to the mask ventilation (Step 2). If ventilation fails again with all the first three consecutive breaths after crossover, the study will be terminated. The routine care is resumed including tracheal intubation or LMA insertion. Once Step 2 is completed, routine care will be applied, including oral or nasal airway placement or placement of a laryngeal mask airway. If tracheal intubation was planned, either rocuronium or succinylcholine will be given to facilitate muscle relaxation followed by subsequent intubation. Subjects in Group B will follow the same protocol as that in Group A, with the exception that the sequence of applying the two ventilation techniques will be reversed, as shown in **Fig. 5.**

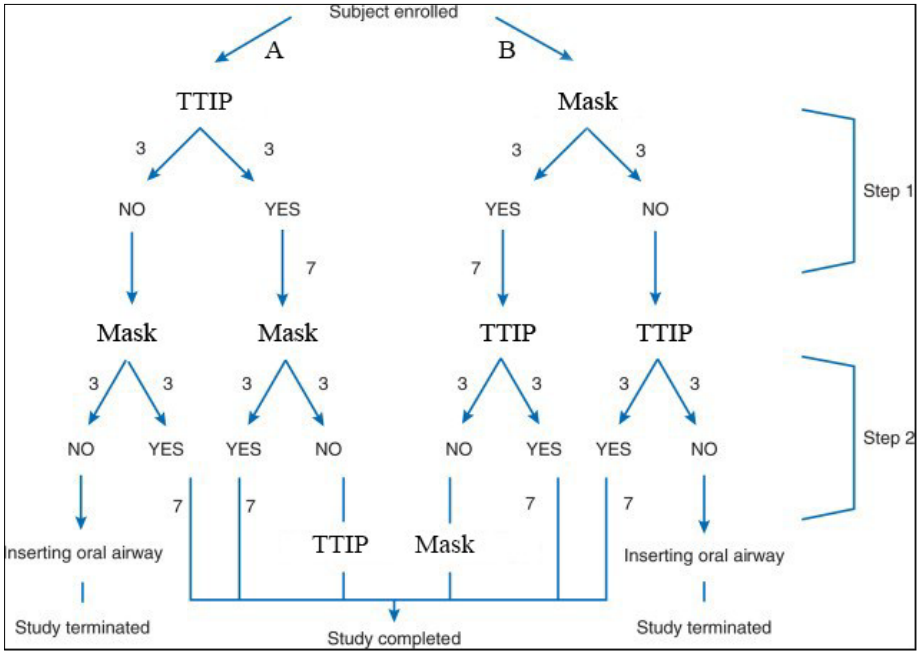

Figure 5: The algorithm of the study procedure. The numbers listed on the chart represent the number of breaths. At each Step, 10 breaths were targeted. NO= ventilation was not effective as assessed clinically; YES= ventilation was effective as assessed clinically.

Vital signs and parameters will continuously be recorded until the patient leaves the operating room. The monitor will not be masked, and the care team will be able to access it as they wish throughout the entire case. Once the patient arrives at PACU, the study team will assess the patient and record the vital signs 30 min after arrival and before discharge from the PACU. The study team will then call the patient 24 hours later to complete the QoR-15, which is a validated short form of the QoR-40 to assess any potential adverse effects. The data will include vital signs, incidence, and severity of nausea and vomiting, pain scale, sedation level, the satisfaction of the anesthesia, and medications administered in PACU. We will also record the

experience level of the attending, resident, or anesthesia assistant who is involved in the airway management with years of experience providing anesthesia.

7. Data acquisition and analysis

All ventilatory settings and measured parameters displayed on the operating room ventilator (Datex Ohmeda AS/5, Helsinki, Finland), including expired tidal volume (VTeVTe), flow waveforms, end-tidal carbon dioxide partial pressure, exhaled carbon dioxide waveforms, and vital signs displayed on the monitor will be preserved electronically intra-operatively and video recorded from the time of pre-oxygenation and 5 minutes after intubation. The target number for ventilation is 10 breaths for both TTIP and mask ventilation techniques. Only the last five breaths (only three breaths for failed ventilation) will be used for final analysis to calculate the VTe and PIP. The mean of five breaths (three breaths if mask ventilation failed) is used as a single data point. Study team members converting the video recorded data to digital data will be blind to the interventions and the sequence of interventions. Once the study is completed and the digital data is collected, the study team members will be unblinded.

The primary analysis is to perform the McNemar test on the paired outcomes of all subjects. In addition to the McNemar test, we will find odds ratio estimate of failure for TTIP versus mask ventilation, together with its 95% confidence interval (CI), by stratifying on subject to handle dependence. Further, we will find the estimate of failure rate difference and its 95% Wald CI. We will consider and evaluation the covariance when estimating the standard error of failure rate difference.

We will perform multivariable analysis by using GEE method to estimate adjusted odds ratio of failure for TTIP versus mask ventilation. We will let the GEE model to include an odds ratio to accommodate within-subject association. The regression equation of the GEE model will include treatment (TTIP, mask ventilation), period (1, 2) and treatment-by-period interaction. The last two factors facilitates different carry-over effects for these two ventilation methods. If all factors will be significant, we will report the odds ratios of failure for TTIP versus mask ventilation at periods 1 and 2 separately. P values less than 0.05 will be considered as significant.

All statistical analyses will be performed by using the SAS software (version 9.4, the SAS Institute, Cary, NC).

8. Predicted outcome and its significance

The study team assumes that TTIP-first ventilation (A) will be superior to mask first ventilation (B) as shown by a 50% reduction of failed ventilation. Additionally, we predict a significant improvement in the measured parameters (expired tidal volume, flow waveforms, exhaled carbon dioxide waveforms) with TTIP compared to that with mask ventilation. The study team hopes that TTIP will be an effective rescue technique for failed mask ventilation. Such a finding will provide evidence of the efficacy of TTIP and TTIP can be used as an alternative for rescuing failed mask ventilation and/or tracheal intubation. Its implication can be in the perioperative setting, emergency department, and pre-hospital resuscitation. We expect the implication of TTIP would improve the difficult airway management and therefore outcome.

9. Sample Size Calculation

9.1 Our primary outcome is the rate of failed ventilation with mask vs. TTIP. Literature demonstrated that the rate of failed mask ventilation for obese patients with potential difficult mask ventilation is 9/26 (34%). We assume this failure rate (34%) for the mask ventilation in the proposed crossover study. We believe that for ventilation with TTIP, the failure rate is at most 20%. We also assume that in the proposed crossover study a quarter of subjects yield discordant outcomes. Two-sided McNemar test is used to evaluate effectiveness ot two ventilation methods. At the 5% significance level, the size of 200 subjects provides 99.4% power for proving superiority of TTIP to the mask ventilation. We assume a dropout rate of 20% and a total of 250 subjects will be enrolled. The enrolled subjects will be randomized at 1:1 ratio to two groups. For Group 1 we will deliver ventilation in mask-TTIP order. For Group 2 the TTIP-mask order will be employed.

10. Risk Assessment

10.1. Pharyngeal airway injury and gastric insufflation: TTIP may cause gastric insufflation. However, we will limit peak inspiratory pressure to less than 20cmH_2O which is the lower

esophageal sphincter opening pressure. Because the cuff of the end tracheal tube will not be inflated, we do not expect the risk of TTIP for gastric insufflation/aspiration to be greater than the mask ventilation with insertion of an oral airway, used as routine care.

10.2. Adverse effect of medications: Propofol and fentanyl are routinely used for anesthesia care. We will exclude the patients who are allergic to these two medications. Midazolam is routinely used as pre-medication. Any risk associated with these three medications will not be altered due to the study. All other medications will not be restricted to use for patient care including anti-emetics.

11. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or others

Because the only alteration is the order of airway procedure, patients who may have otherwise had mask ventilation may complain of symptoms of pharyngeal injury. Therefore, dosing and the sedation level will not be altered in the proposed study. We do not anticipate the risk of intraoperative apnea and other complications associated with this study as compared with routine care.

11.1 Adverse events (AE) will be obtained and documented by the investigators performing data collection and by questioning or examining the patient. All new complaints and symptoms (i.e., those not existing before the signing of informed consent) will be recorded on the AE CRF.

11.2 AEs will be characterized in terms of their start and stop dates, start and stop times, intensity, action taken, relationship to research study, subject outcome, and whether or not the AE led to an SAE.

12. Privacy/Confidentiality Issues

Measures will be taken to prevent lapses in confidentiality from occurring. Only key study personnel will have access to identified information. Exported and extrapolated data will be stored on a password-protected UTHealth computer that only key study personnel can access. Any paper records will be kept in a drawer with a lock in Dr. Markham's office.

13. Follow-up and Record Retention

Records will be kept through the HIPAA compliant servers of McGovern Medical School. All the documents will be kept in Dr. Markham's office in the draw with a lock. All research tests will be performed under a code that protects the identity of the participants. Records of experimental procedures will be kept at least 6 years following the publication of the study results. At that time, research data will be destroyed.

14. Milestone of the study

- June 15, 2021. Approval of IRB application
- June 16, 2021. Initiation of the study
- June 18, 2021. Completion of the study - the first 10 patients
- July 16, 2021. Completion of the study - first100 patients

August 13, 2021. Completion of the study total 245 patients

15. Cost and resource

All the equipment needed for the study are for routine anesthesia care and is available in the operating room. Dr. Markham will provide an encrypted lap computer for the study team. Since this study imposes minimal risk, and little effort of the participants is needed, the participants will not be compensated and will be discussed at the time when consent is obtained.

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17 Appendix

1. QoR40 [44] and post-operation recall survey form.

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____ ____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time