The Safety and Efficacy of the Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) for Laser Laryngeal Surgery

Study Protocol

NCT03086265

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STUDY PROTOCOL: THRIVE AND LASER LARYNGEAL SURGERY

STUDY OBJECTIVES

1. DETERMINING THE SAFETY OF THRIVE FOR LASER LARYNGEAL SURGERY. Current practice involves the use of specialized ETTs or jet ventilation catheter (JVC) that are laser resistant, but not laser proof. One of the major concerns with their use is the possibility of airway fire. The "fire triangle" requires the presence of an oxidizer (O_2), the ignition source (laser) and the "fuel" (ETT or JVC). If high oxygen concentration (FiO_2) is administered to the patient, the airway fire may happen, with devastating consequences. Thus, a decrease in oxygen concentration (FiO_2) below 30% constitutes current standard of care when ETT or JVC are used. Such low FiO_2 may not be well tolerated by all the patients.

In contrast, during THRIVE the fuel source (ETT or JVC) is removed, the "fire triangle" is disrupted, and safe administration of a higher FiO_2 is possible. Importantly, a completely "tubeless", non-instrumented surgical field will be greatly enlarged, providing superior operating conditions and access to all parts of the glottis. This should improve operating conditions, decrease surgical time, and potentially lead to better patient outcomes. The safety of THRIVE for laser laryngeal surgery has not been formally investigated, and will be explored in this study.

2. DETERMINING THE SAFE DURATION OF THRIVE FOR VOCAL CORD LASER SURGERY. With the patient anesthetized, apneic, and adequately oxygenated with THRIVE, the build up of carbon dioxide in patient's blood ($PaCO_2$) and ensuing acute hypercapnic acidosis will be the main factors limiting the duration of THRIVE administration. At present, the rate of $PaCO_2$ rise with THRIVE is suggested to be between 1.1 – 1.8 mm Hg per minute. By using the serial ABG measurements, we will be able to determine the rate of $PaCO_2$ rise during THRIVE and provide clinical guidance for safe administration of THRIVE in the future. We will allow $PaCO_2$ to rise to 75 mm Hg, which is considered a safe level for moderate hypercapnia in patients without significant comorbidities (see Exclusion Criteria).

3. DETERMINING THE OPTIMAL VENTILATORY STRATEGY FOR MAINTAINING SAFE $PACO_2$ LEVEL DURING THRIVE ADMINISTRATION ITRAOPERATIVELY. Once $PaCO_2$ has exceeded 75 mm Hg, we will administer either the low-frequency or high-frequency supraglottic jet ventilation (LFJV, HFJV) through the in situ operating surgical laryngoscope, in order to counteract hypercapnia. The administration of JV modality will be conducted in a randomized fashion, and will continue for at least 10 min, or until $PaCO_2$ has decreased below 65 mm Hg,

after which THRIVE will be resumed. The comparative efficacy of these two supraglottic JV modalities in eliminating CO_2 in anesthetized patients is unknown. Determining the optimal mode of JV during THRIVE will allow to establish safe anesthetic protocols for future use. To obtain more robust data, we will cross each patient over to an alternative JV modality, if JV needs to be repeated intraoperatively. For example, if a patient started with supraglottic low-frequency JV, the second JV run will be high-frequency, the third low-frequency again, etc. By having the patient serve as a self-control, we should be able to obtain more robust PaCO2 data and determine better which frequency works best for counteracting THRIVE-induced deliberate hypercapnia.

4. DETERMINING THE HEMODYNAMIC CHANGES THAT OCCUR DURING THRIVE IN PATIENTS ANESTHETIZED WITH TOTAL INTRAVENOUS ANESTHESIA USING PROPOFOL AND REMIFENTANIL. The administration of THRIVE requires the conduct of total intravenous anesthesia (TIVA), as delivery of anesthetic gases to the patient is not possible. TIVA with propofol and remifentanil is commonly used for VC laser surgery, and will be employed in this study. Acute hypercapnia and hypercapnic acidosis have been shown to produce an increase in cardiac output, cardiac index, a decrease in systemic vascular resistance, without associated tachycardia and myocardial depression with $PaCO_2 \leq 70$ mm Hg in patients who do not have significant comorbidities. These hemodynamic responses will be modified by TIVA with propofol and remifentanil, and we will investigate the extent of these changes to determine cardiovascular safety of THRIVE used in conjunction with TIVA. We will be continuously monitoring the heart rate, arterial blood pressure, cardiac output, cardiac index, and systemic vascular resistance during the surgery using Edwards EV1000 Clinical Platform with FloTrack sensor. Determining hemodynamic changes that accompany THRIVE that is conducted under TIVA with propofol and remifentanil will promote safe use of this technique in clinical anesthesia practice. Using Edwards EV1000 Clinical Platform we also will assess acute hemodynamic changes that may be associated with supraglottic LFJV and HFJV under the conditions of deliberate moderate hypercapnia. Demonstrating the safety and efficacy of THRIVE may make this technique a simple, safe and effective alternative to conventional use of ETT or JV during laser laryngeal surgery in selected patients.

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EXCLUSION CRITERIA

1. Patients with significantly decreased myocardial function (ejection fraction < 50%)
2. Patients with abnormal cardiac rhythm and conduction abnormalities, except for patients with isolated, asymptomatic premature atrial and ventricular contractions.
3. Patients with significant peripheral vascular disease, such as those with the symptoms of intermittent claudication.
4. Patients with known significant cerebrovascular disease, such as history of cerebrovascular accidents (CVAs) and transient ischemic attacks (TIAs).
5. Patients with significant renal insufficiency, as manifested by estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2.
6. Patients with electrolyte (K+, Ca++) abnormalities, as determined by the lab values outside of a normal range.
7. Patients with the history or symptoms of increased intracranial pressure or reduced intracranial compliance (e.g. headaches, nausea and vomiting, visual changes, mental changes).
8. Patients with skull base defects.
9. Patients with pulmonary hypertension who have pulmonary artery pressures above the normal range.
10. Patients with significant chronic obstructive or restrictive lung diseases, as manifested by known history of baseline chronic hypoxia and/or hypercapnia, and/or baseline room air SpO2 < 95%.
11. Obese patients with BMI > 35 kg/m^2.
12. Patients with severe and poorly controlled gastroesophageal reflux disease despite medical treatment.
13. Patients with hiatal hernia and full stomach patients.
14. Patients on immunosuppressive medications.
15. Patient's refusal to participate in the study.
16. Patients who do not understand English or mentally handicapped.
17. Pregnant or breastfeeding patients.

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PROTOCOL AT A GLANCE AND STUDY END-POINTS

18. Patients will be randomly assigned to either THRIVE or Control group (conventional management with laser ETT or jet ventilation catheter – infraglottic jet ventilation – if required). Patients within THRIVE group will be further randomly assigned to either low- or high-frequency supraglottic JV for intraoperative $PaCO_2$ > 75 mmHg.
19. Patients in both groups will have peripheral A-line started prior to induction. Central hemodynamic parameters will be monitored using Edwards system.
20. Patients in THRIVE group will be monitored with serial ABGs, to determine changes in PaO_2, $PaCO_2$, and electrolytes.
21. Anesthetic management is standardized for both groups.
22. **For both groups, and particularly for THRIVE, assure fully moistened pledgets, and no cotton material/other fuel left in airway before firing the laser.**
23. Study end-points:
    a. THRIVE GROUP
        i. Changes in PaO_2, $PaCO_2$, pH, electrolytes, and FiO_2 (tracheal)
        ii. Hemodynamic changes during permissive hypercapnia
        iii. Comparative effectiveness of JV modalities on CO_2 elimination
        iv. Comparative effect of JV modalities on hemodynamics during permissive hypercapnia
    b. BOTH GROUPS
        i. Total apnea time
        ii. Anesthesia time: from induction to awake (opening eyes to command)
        iii. Surgical time: from picking up suspension laryngoscope to laryngoscope withdrawal
        iv. Time to suspension: from picking up suspension laryngoscope to full suspension
        v. Number of required repositions for suspension laryngoscope
        vi. Lowest SpO_2
        vii. Total doses of anesthetic drugs used, including vasopressors, etc.
        viii. PACU recovery profile
        ix. Functional recovery profile after surgery

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OPERATING ROOM PREPARATION

1. All drugs, airway supplies, suction, eye tape, etc. per routine.
2. 5.0 laser ETT with two pre-filled 10 ml NS syringes: use a methylene blue tinged syringe for a proximal cuff.
3. A long pediatric ETT stylet and a pediatric gum-elastic bougie.
4. 5.0 MLT tube for apneic intermittent ventilation (AIV), if required (see protocol, below).
5. Precut large Tegaderm strips for securing ETT to the chin in left corner of patient's mouth.
6. Video laryngoscopy system: either a Glidescope or a Storz CMAC system.
7. Monsoon JV with connection tubing for suspension laryngoscope, and full humidifcation set up.
8. Sterile tracheal suction catheter assembly for tracheal FiO_2 sampling.
9. Four channel Alaris pump with:
    a. NS carrier at 50 ml/hr
    b. Propofol drip
    c. Remifentanil drip
    d. Check to assure tight connections throughout
10. IV LR/NS loading 5 ml/kg prior to induction, and 5 ml/kg x 1 as required intraop.
11. 20 ml NS syringe in line for chasing the induction and IVP drugs intraop. **Please minimize total IVF due to high incidence of urinary retention in male patients.**
12. Edwards system.
13. I-STAT with sufficient number of cartridges.
14. Working PNS with pads (make sure the battery is fresh).
15. BIS/Sedline monitor.

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<table>
<tr><th></th><th>THRIVE GROUP</th><th>CONTROL GROUP</th></tr>
<tr><td>PREOP and PREMEDICATION</td><td colspan="2">
• Obtain patient's consent. Make 2 copies: one for the chart, and another for the patient.
• Place a copy of consent into patient's folder, together with postop diary. Place patient's sticker on folder.
• Give a surgeon a folder with postop QoR15. Place patient's sticker on folder.
• Your study folder should contain consent, preop QoR15, intraop and PACU data collection sheets. Place patient's sticker on folder.

• Randomize the patient to either THRIVE or CONTROL group.
• Obtain preop QoR15 and VAS pain score.
• Peripheral IV, 20 g R upper extremity (preferred), tape securely straight out.
• Midazolam 0.007 mg/kg incremental doses to achieve sufficient anxiolysis, not to exceed 0.025 mg/kg total dose, unless severe anxiety. For elderly patients (70-80 y.o), limit total dose of Midazolam to 0.5 mg.
• Start an awake A-line for both groups in OR, and draw baseline ABG and i-STAT Troponin I level #1 for THRIVE group only.
</td></tr>
<tr><td rowspan="4">PRE-INDUCTION:
<u>CONSECUTIVE STEPS</u></td><td>Start with OR table 180°.</td><td>OR table in standard position.</td></tr>
<tr><td colspan="2">Place standard ASA monitors, BIS/Sedline, and peripheral nerve stimulator (TOF ulnar nerve).
Connect A-line to Edwards EV1000 Clinical Platform for automated monitoring of ABP, HR, CO/CI, SVR.</td></tr>
<tr><td>• Pre-O_2 with THRIVE (FiO_2 1.0) at 40 l/min for 5 min.
• Maintain patient's head is elevated 30-40° (table in BACK UP position, <u>not</u> reverse Trendelenburg).
• Obtain ABG after 5 min of THRIVE, per THRIVE protocol.</td><td>Preoxygenate for 5 min or until FeO_2 > 0.9.</td></tr>
<tr><td colspan="2">• Pre-induction:
○ IV fluid loading completed: 5 ml/kg.
○ IV Glycopyrrolate 0.2 mg if HR ≤ 50 bpm for elderly patients (70-80 y.o.).
○ Assure all surgical supplies are ready for immediate use in THRIVE group.
○ Both anesthesia and surgical time-outs completed.</td></tr>
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<table>
<tr><td>INDUCTION</td><td colspan="2">• IV Remifentanil 1 mcg/kg, Propofol 2mg/kg IV, Rocuronium 1.2 mg/kg IV, no IV lidocaine.
• Additional Remifentanil 0.5 mcg/kg and/or Propofol 0.5 mg/kg IV boluses, as required during video or suspension laryngoscopy, per hemodynamic responses and BIS/Sedline readings.
• Obtain tracheal FiO_2 once patient is suspended, before the start of surgery, per THRIVE protocol.</td></tr>
<tr><td></td><td>• Turn THRIVE to 70 l/min.
• Maintain jaw thrust, with oral airway as necessary, before surgeon starts suspension laryngoscopy. Continue, as necessary until patient is in full suspension.
• Suspension laryngoscopy by surgeon in 1 min.</td><td>• Mask ventilation, if required.
• Intubate in 1 min with laser 5.0 ETT, using acute angle video laryngoscopy system (Glidescope or Storz D-blade), secure ETT to chin in left corner of the mouth.</td></tr>
<tr><td rowspan="2">MAINTENANCE</td><td>• TIVA + THRIVE (FiO_2 1.0) at 70 l/min.
• If SpO_2 < 90%, or ventricular arrhythmias, discuss with surgeon converting to the following options:
○ Supraglottic or Infraglottic JV
○ 5.0 laser ETT
○ 5.0 MLT tube with apneic intermittent ventilation
• Obtain ABGs per THRIVE protocol.
• If $PaCO_2$ > 75 mmHg, randomize patients to JV protocol, and institute JV accordingly. Crossover each patient to an alternative JV frequency for repeated JV rounds.</td><td>• TIVA + O_2:Air; FiO_2 < 0.3
• Mechanical ventilation to normocapnia: $EtCO_2$ 35-40 mmHg.
• Vt 8 ml/kg of predicted body weight (PBW), PEEP 5 cmH_2O.
• PBW Males = 50 + 2.3 (Height”- 60)
• PBW Females = 45.5 + 2.3 (Height”- 60)
• FiO_2 < 0.3 unless SpO_2 < 90% (increase FiO_2 to 0.4, and coordinate subsequent FiO_2 decrease with surgeon during laser timeout).</td></tr>
<tr><td colspan="2">• A-line and Edwards monitoring. No NBP monitoring, unless A-line malfunction.
• BIS-guided TIVA with Propofol/Remifentanil to maintain BIS 40-60.
• Maintain main IV at TKO. All IV bolus drugs are chased by 15 ml of NS using in-line 20 ml syringe.</td></tr>
</table>

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MAINTENANCE (cont.)	• **TIVA dosing:** ○ TIVA is carried in by Alaris NS carrier at 50 ml/hr. ○ For normal weight patients, dose Prop/Remi infusions per total body weight. ○ For obese patients (BMI ≥ 30), dose Prop/Remi infusions per lean body weight (LBW). **Simplified LBW formula: LBW = IBW x 1.2; IBW = 22 x Ht(m)^2**. ○ **Starting dose:** Propofol 120 mcg/kg/min, Remifentanil 0.1 mcg/kg/min. ○ **Titratable range:** Propofol 80-150 mcg/kg/min, Remifentanil 0.05-0.3 mcg/kg/min. **Optimize Remifentanil dose first**. ○ Rocuronium boluses 0.15 mg/kg, to maintain 0-1/4 TOF at ulnar nerve. • **Treating hypertensive responses (MAP > 20 mmHg from preoperative baseline):** ○ Remifentanil 0.5 mcg/kg and Propofol 0.5 mg/kg boluses q 2 min, as required per hemodynamic responses and BIS/Sedline readings ○ Labetalol 0.07 mg/kg boluses q 10 min up to a total dose of 1 mg/kg, as required per hemodynamic responses and BIS/Sedline readings ○ Fentanyl 0.5 mcg/kg IV bolus, total dose limit 1 mcg/kg, **only** if perceived need for additional analgesia after Remifentanil infusion had been maxed out at 0.3 mcg/kg/min • **Treating hypotensive responses (MAP < 20 mmHg from preoperative baseline):** ○ Crystalloid loading 5 ml/kg x 1 ○ Ephedrine 5 mg IV if HR < 60 bpm, or Phenylephrine 100 mcg IV if HR > 60 bpm. Repeat x 2 in escalating doses if no response: Ephedrine (10 mg, 20 mg q 1 min), or Phenylephrine (200 mcg, 400 mcg q 1 min). ○ Vasopressin 1 unit IVP if no response to Ephedrine/ Phenylephrine, repeat x 2 prn. ○ Phenylephrine drip, start at 0.3 mcg/kg/min, increase in 50% increments • **Obtain tracheal FiO_2 before withdrawal of suspension laryngoscope, per THRIVE protocol.**

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<tr><td rowspan="2">EMERGENCE</td><td colspan="2">• Zofran 4 mg IV.
• Reverse NMB with Suggamadex, as following: 2 mg/kg for TOF 1-2/4; 4 mg/kg for TOF 0/4, with postetanic count of 1-2. Administer additional Suggamadex 2 mg/kg, if 4 mg/kg not fully effective.
• Discontinue TIVA upon completion of surgery.
• Transport to PACU: FMO_2 at 6 l/min.</td></tr>
<tr><td>• Maintain THRIVE at 70 l/min with jaw thrust ± oral airway as required, until return of spontaneous ventilation and consciousness. Mask ventilation, if required.
• Obtain ABG and Troponin I level #2, once patient resumes spontaneous ventilation, per THRIVE protocol.</td><td>• Extubate per routine.</td></tr>
<tr><td>STANDARDIZE POSTOP ORDERS</td><td colspan="2">• IV Fentanyl 25 mcg boluses q 5 min prn VAS ≥ 4, total dose 250 mcg.
• PO Hydrocodone-acetaminophen (NORCO) 5-325 mg, 1 tab prn VAS ≥ 4, may repeat x 1.
• If allergic to NORCO, Oxycodone-acetaminophen (PERCOCET) 5-325 mg, 1 tab prn VAS ≥ 4, may repeat x 1.
• IV Demerol 12.5 mg for shivering only, may repeat x 1.
• Treatment of PONV:
○ Zofran 8 mg IV x 1
○ If no effect, and no contraindications, add IV Promethazine 12.5 mg x 1</td></tr>
<tr><td>PACU DATA COLLECTION</td><td colspan="2">• Obtain PACU data collection sheet.
• Discontinue A-line once the last ABG and Troponin I are drawn 1 hr after resumption of spontaneous ventilation, per THRIVE protocol.</td></tr>
<tr><td>EDWARDS DATA COLLECTION</td><td colspan="2">• Download Edwards data to flash drive, selecting 20 sec download interval, before starting next case.</td></tr>
</table>

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THRIVE PROTOCOL	
PREOP	• **Obtain baseline ABG and i-STAT Troponin I #1.**
PREINDUCTION	• **Pre-O_2 with THRIVE (FiO_2 1.0) at 40 l/min for 5 min.** • Maintain patient's head is elevated 30-40° (table in BACK UP position, **not** reverse Trendelenburg). • Connect OR monitors and Edwards system. • **Obtain ABG after 5 min of THRIVE @ 40 l/min.**
INDUCTION	• THRIVE @ 70 l/min. • Maintain jaw thrust, with oral airway as necessary, for 1 min before surgeon starts suspension laryngoscopy.
MAINTENANCE	• Maintain THRIVE @ 70 l/min. • **Obtain tracheal FiO_2 once patient is suspended, before the start of surgery.** • **Assure fully moistened pledgets, and no cotton material/other fuel left in airway before firing the laser.** • **ABG q 10 min post-induction, until patient resumes spontaneous ventilation.** • **Once $PaCO_2$ > 75 mmHg, randomize patients to low-frequency (20 cpm) or high-frequency (150 cpm) supraglottic jet ventilation** ○ Settings for either JV modality: ▪ **DP (driving pressure, psi) = total body weight x 0.4 (do not exceed 45 psi)** ▪ FiO_2 1.0, Inspiratory time 40%, Humidity level: maximum (8) ○ **Continue JV, checking ABG q 10 min, until $PaCO_2$ reaches ≤ 65 mmHg, at which point resume THRIVE** ○ Repeat JV per above, as necessary for $PaCO_2$ > 75 mmHg. **Crossover each patient to an alternative JV frequency for repeated JV rounds.** • Obtain tracheal FiO_2 once surgery completed, before withdrawal of suspension laryngoscope.
EMERGENCE	• Maintain THRIVE at 70 l/min with jaw thrust ± oral airway as required, until return of spontaneous ventilation and consciousness. Mask ventilation, as necessary. • **Obtain ABG and i-STAT Troponin I #2 once patient resumes spontaneous ventilation.**
PACU	• **Obtain ABG and i-STAT Troponin I #3 one hr after resumption of spontaneous ventilation. Remove A-line.**