STUDY PROTOCOL: THRIVE AND LARYNGOLOGIC SURGERY

The Safety and Efficacy of the Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) for Short Laryngologic Surgical Procedures

Study Protocol

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STUDY OBJECTIVES

1. DETERMINING THE SAFETY AND EFFICACY OF THRIVE FOR SHORT LARYNGOLOGIC SURGERY.

THRIVE should improve operating conditions, decrease surgical time, and potentially lead to better patient outcomes. The safety of THRIVE for short laryngologic surgery has not been formally investigated, and will be explored in this study. 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 has not been directly investigated, but is suggested to be between 1.1 and 1.8 mm Hg per minute. It is expected that the short duration of laryngologic procedures explored in this study (not exceeding 30 min) will not lead to substantial rise of $PaCO_2$. The $PaCO_2$ rise to 75 mm Hg is considered a safe level for moderate hypercapnia in patients without significant comorbidities (see Exclusion Criteria).

2. DETERMINING POSSIBLE BENEFICIAL EFFECT OF THRIVE ON IMMEDIATE POSTOPERATIVE RECOVERY in PACU, QUALITY OF POSTOPERATIVE RECOVERY (QoR15), OPIOD CONSUMTION, AND VOICE HANDICAP INDEX (VHI-10).

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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 above 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

1. Patients will be randomly assigned to either THRIVE or ETT (control group). Patient with supraglottic jet ventilation will also be included in ETT group, if JV requested by surgeon.
2. Anesthetic management is standardized for both groups.
3. Study end-points:
    A. THRIVE GROUP
        i. Total apnea time
    B. BOTH GROUPS
        i. Demographic, ASA class and airway exam data
        ii. Anesthesia duration: from induction to awake (opening eyes to command)
        iii. Surgical duration: from picking up suspension laryngoscope to laryngoscope withdrawal
        iv. Apnea time: from induction to spontaneous ventilation
        v. Extubation time: from surgery stop to opening eyes to commands
        vi. Time to suspension: from picking up suspension laryngoscope to full suspension
        vii. Number of required repositions/adjustments of suspension laryngoscope during surgery
        viii. Lowest SpO_2
        ix. Hemodynamic & Sedline profile
        x. Total doses of anesthetic drugs used intraop, including vasopressors, etc.
        xi. Intraop complications
        xii. PACU recovery profile:
            - Time to AO x 4: from arrival to PACU
            - Time to PACU phase 2-ready: from arrival to PACU
            - Pain and PAS scores
            - IV and PO opioid requirements
            - PO non-opioid requirements (PO Tylenol)

- Shivering: incidence; IV Demerol requirements
- PONV profile (nausea and vomiting incidence); IV Zofran/Phenergan requirements

xiii. Immediate postop complications

xiv. Functional home recovery profile after surgery during first postop week

- Pain scores
- PO opioid requirements
- PO non-opioid (Tylenol) requirements
- QoR15
- Return to daily activities
- Return to work

xv. VHI-10 (Voice Handicap Index)

- Preop vs 1 month after surgery

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OPERATING ROOM PREPARATION

1. All drugs, airway supplies, eye tape, per routine.
2. 5.0 MLT ETT.
3. Precut large Tegaderm for securing ETT to the chin in left corner of mouth.
4. Video laryngoscopy system: either a Glidescope or Storz CMAC system.
5. Monsoon JV with connection tubing for suspension laryngoscope, and full humidification set up.
6. 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
7. 20 ml NS syringe in-line for chasing the induction and IVP drugs intraop. **Please minimize IVF beyond 10 ml/kg total (5 ml/kg prior to induction, and 5 ml/kg as required intraoperatively), due to high incidence of urinary retention in male patients.**
8. Working PNS with pads (make sure the battery is fresh).
9. 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.
• Randomize the patient to either THRIVE or CONTROL group (5.0 MLT or supraglottic jet). Note: patient is blinded to the modality used.
• Obtain preop VAS pain score, QoR15 and VHI.
• Patient's folder contains: a copy of consent, postop diaries, QoR15, VHI, all stamped with patient's stickers, and 3 return, pre-stamped envelopes. Enter DOS and subject # in diaries, QoR15, VHI.
• Study folder contains: consent, preop QoR15, VHI, intraop and PACU data collection sheets, all stamped with patient's stickers. Place patient's sticker on study folder.
• 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.</td></tr>
<tr><td rowspan="4"><u>PRE-INDUCTION: 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, Sedline, and peripheral nerve stimulator (TOF ulnar nerve)</td></tr>
<tr><td>• Pre-O_2 with THRIVE (FiO_2 1.0) at 40 (30) l/min for 5 min.
• Maintain patient's head is elevated 30-40° (table in BACK UP position, <u>not</u> reverse Trendelenburg).</td><td>Preoxygenate for 5 min or until FeO_2 > 0.9.</td></tr>
<tr><td colspan="2">• 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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INDUCTION	• **IV Remifentanil 1 mcg/kg, Propofol 2mg/kg IV, Rocuronium 0.6 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 Sedline readings.	
	• Turn THRIVE to 70 l/min; mask ventilation if required. • Maintain jaw thrust, with oral airway as necessary, for 3 min, before surgeon starts suspension laryngoscopy. Continue, as necessary until patient is in full suspension. • Suspension laryngoscopy by surgeon in 3 min.	• Mask ventilation. • Intubate when TOF is 0, with 5.0 MLT tube and video laryngoscopy (Glidescope or Storz CMAC), secure ETT to chin in left corner of the mouth. • **If Jet is used**, suspend when TOF is 0.

MAINTENANCE	• TIVA + THRIVE (FiO_2 1.0) at 70 l/min.
	• **NBP q 5 min, unless indicated more frequently.**
	• **If SpO_2 < 90%, or ventricular arrhythmias**, discuss with surgeon converting to the following options:
	  ○ Supraglottic or Infraglottic HFJV
	  ○ 5.0 MLT
	  ○ 5.0 MLT with intermittent apnea technique
	• **If surgical duration more than 30 min, institute supraglottic HFJV per THRIVE protocol, for at least 10 min. See jet settings in THRIVE protocol.**
		• TIVA + O_2:Air; FiO_2 = 0.5
		• **NBP q 5 min, unless indicated more frequently.**
		• 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)
		• **For Jet, see settings in THRIVE protocol.**

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MAINTENANCE (cont.)	• Sedline-guided TIVA with Propofol/Remifentanil to maintain Sedline 25-50. • **Maintain main IV at TKO. All IV bolus drugs are chased by 15 ml of NS using in-line 20 ml syringe.** • **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. • **No IV Tylenol** • **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 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 Sedline readings ○ Fentanyl 0.5 mcg/kg IV bolus, total dose limit 1 mcg/kg, **only** if perceived need for additional analgesia after Remifentanil had been maxed out at 0.3 mcg/kg • **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
EMERGENCE	• **No IV Tylenol**

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<tr><td></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 and disconnect TIVA line upon completion of surgery.
• Transport to PACU: FMO_2 at 6 l/min.</td></tr>
<tr><td></td><td>• Maintain THRIVE at 70 l/min with jaw thrust ± oral airway as required, until return of spontaneous ventilation and consciousness.</td><td>• Extubate per routine.</td></tr>
<tr><td>STANDARDIZED POSTOP ORDERS</td><td colspan="2">• Mild pain (1-3): Oxycodone 5 mg PO, may repeat x 1.
• Moderate pain (4-6): Fentanyl 25 mcg IV q 5 min, for a total dose 3 mcg/kg.
• Severe pain (7-10): Fentanyl 50 mcg IV q 5 min, for a total dose 3 mcg/kg.
• Adjuvant analgesics: Tylenol 500 mg, 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: Oriented x 4; Pain scores q 15 min; PAS scores q 30 min; Phase 2 ready.</td></tr>
</table>

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THRIVE PROTOCOL	
PREOP	• Randomize patient to THRIVE or CONTROL group. A control group is usually either a 5.0 MLT ETT or a Supraglottic HFJV.
PREINDUCTION	• Pre-O_2 with THRIVE (FiO_2 1.0) at 40 (30) l/min for 5 min. • Make sure the patient's head is elevated 30-40° (table in BACK UP position, **not** reverse Trendelenburg).
INDUCTION	• THRIVE @ 70 l/min. • Maintain jaw thrust, with oral airway as necessary, for 3 min before surgeon starts suspension laryngoscopy. Continue jaw thrust as necessary, until patient is in full suspension.

MAINTENANCE	• Maintain THRIVE @ 70 l/min.
	• **If surgery prolonged (over 30 min), institute supraglottic HFJV for at least 10 min before switching back to THRIVE. Repeat as necessary.**
	  ○ **HFJV settings:**
	  ▪ **Frequency: 150 cpm**
	  ▪ **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)
	• **5.0 MLT can be placed by surgeon either instead of, or in conjunction with jet.**

EMERGENCE	• Maintain THRIVE at 70 l/min with jaw thrust ± oral airway as required, until return of spontaneous ventilation and consciousness. Mask (SGA) ventilation, as necessary.