Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) Use in Pediatric Populations: A Randomized, Prospective Multi-Collaborative Trial

Study Protocol / Statistical Analysis Plan

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Sample Size:

500 total across 6 sites

Study Population:

Patients under the age of 18 years undergoing airway examinations or airway procedures with or without laryngoscopic suspension under general anesthesia.

Study Design and Purpose:

This study is a national multi-center project seeking to evaluate the efficacy of high flow nasal cannula (HFNC) compared to standard of care (SOC) without HFNC when delivered as part of an anesthetic plan in individuals undergoing microdirect laryngoscopy and bronchoscopy (MDLB). The centers include the primary site - Lucile Packard Children's Hospital (Stanford University, Palo Alto, CA), Cincinnati Children's hospital (Cincinnati, OH), Lurie Children's Hospital (Chicago, IL), UC Davis Children's Hospital (Davis, CA).

This is a prospective, randomized study which includes a two-parallel group design with one active intervention and a control group receiving standard airway management without the active intervention. Participants will be randomized to one of two groups at a 1:1 ratio: HFNC or SOC using a simple randomization procedure generated by REDCap. A total of 100 patients per site (for a total of 500 patients) is the target enrollment.

The purpose of the study is to determine if patients undergoing MDLB have less oxygen desaturations compared to those utilizing standard of care as measured by oxygen desaturation index. The secondary endpoints will determine if children receiving HFNC will have less desaturations below 90% and fewer surgical interruptions without an increase in adverse events.

Study Duration:

We estimate that the entire study will require 4 years, including patient recruitment, data collection, analysis, and report writing.

Specific Aims and endpoints:

Pediatric patients undergoing microdirect laryngoscopy and bronchoscopy (MDLB) pose anesthetic challenges of maintaining adequate oxygenation and ventilation while providing a motionless surgical field without an endotracheal tube. Given this challenge, we propose a prospective, randomized controlled trial to evaluate the use of high flow nasal cannula (HFNC) as transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in pediatric patients undergoing MDLBs.

Research Questions:

1. Can the use of HFNC during MDLB result in reduced oxygen desaturations as measured by the oxygen desaturation index (ODI) as compared to standard of care (SOC)?

2. Does the use of HFNC during MDLB result in a reduced number of oxygen desaturations below 90% during the procedure?

3. Does the use of HFNC during MDLB resulted in a reduced number of surgical interruptions?

AIM 1:

To prospectively determine if treatment with HFNC during MDLB reduces oxygen desaturations as measured by oxygen desaturation index (ODI) as compared to SOC in pediatric patients under general anesthesia. We hypothesize that participants receiving HFNC will demonstrate statistically improved ODI over participants receiving SOC. ODI is defined as a 4% decrease in saturation from a 120 second rolling mean for greater than 10 seconds.

AIM 2:

To determine if treatment with HFNC during MDLB results in a reduction in the number of desaturations below 90% and a reduction in the number of surgical interruptions as compared to standard of care in pediatric patients under general anesthesia. We hypothesize that participants receiving HFNC catheters will demonstrate statistically fewer desaturations over participants receiving SOC. Desaturations will be controlled by duration of procedure.

Abstract:

Maintenance of adequate oxygenation during microdirect laryngoscopy and bronchoscopy (MDLB) is challenging as the anesthesia provider is unable to place an endotracheal tube that would obstruct the surgeon's operative field. This challenge is exacerbated in infants and young children due to their increased oxygen consumption and decreased functional residual capacity as compared to adults, resulting in a faster rate of desaturation. Moreover, given the increasing complexity of the patients with whom we work, these cases are increasingly more challenging. Several techniques have been described to optimize oxygenation and ventilation in these patients but each of these techniques has downfalls. The intermittent positive pressure technique, while successful in intermittently ventilating the patient, is associated with risk of trauma from multiple reintubations and does not provide adequate ventilation and oxygen during periods of apnea. The spontaneous respiration technique, while generally can maintain adequate oxygenation and ventilation, may not be always adequate and may lead to surgical interruptions from inadequate depth of anesthesia. Lastly, the jet ventilation technique carries a significant risk of barotrauma. In addition, none of these methods provide adequate and consistent monitoring of end-tidal carbon dioxide.

High flow nasal cannula (HFNC) as transnasal humidified rapid insufflation ventilatory exchange (THRIVE) has been described as a successful method to deliver humidified oxygen and provide adequate

ventilation as an alternative to invasive airways in several populations. THRIVE has been used during adult procedures and to prolong apneic oxygenation in pediatrics. We introduce THRIVE as method for airway management in pediatric patients undergoing MDLB.

The purpose of this multi-site, prospective, randomized controlled trial is to determine if patients undergoing MDLB have less desaturations compared to those utilizing SOC, as measured by oxygen desaturation index (ODI). The secondary aims will determine if children utilizing HFNC will have less desaturations below 90% and fewer surgical interruptions without an increase in adverse events. When novel intraoperative techniques, such as HFNC, are integrated into practice, their contribution to potentially reducing postoperative morbidity should be studied, as pediatric anesthesiologists redefine their role in the care continuum. Utilization of HFNC in this high risk patient population has the potential to radically transform management and improve outcomes.

Key words: High flow nasal cannula (HFNC), transnasal humidified rapid-insufflation ventilatory exchange (THRIVE), oxygenation, ventilation, microlaryngoscopy and bronchoscopy

Background:

Infants and children undergoing microdirect laryngoscopy and bronchoscopy (MDLB) pose a challenge to anesthesia providers. Maintaining adequate oxygenation and ventilation in a spontaneously breathing patient without an endotracheal tube while the surgeons work in the airway often results in desaturation and/or the need to interrupt the procedure to oxygenate and ventilate the patient. This challenge is exacerbated in infants and very young children secondary to more rapid desaturation due to smaller functional residual capacity, a higher metabolic demand resulting in higher carbon dioxide generation and a greater tendency for airway collapse.[1] While several techniques are utilized to help prevent desaturation and improve ventilation, these techniques are not without issue. Intermittent positive pressure ventilation administered via endotracheal tube results in multiple intubations, increasing the risk for trauma and apnea, with apnea leading to increased difficulty in smoothly continuing the procedure. While allowing the patient to maintain spontaneous respiration is idea, surgical interruption can occur as the anesthesia provider may be unable to maintain an adequate depth of anesthesia. Lastly, while jet ventilation is commonly used in adults for such procedures, the risk of barotrauma makes it less idea in the pediatric population. Furthermore, none of these methods provide consistent carbon dioxide monitoring.

High flow nasal cannula (HFNC) delivered using the Optiflow THRIVE system (Fisher & Paykel Healthcare, Irvine, CA, USA) has been described as a safe, successful method to deliver humidified oxygen to pediatric patients.[1-4] THRIVE has been used during adult procedures successfully and to prolong apneic oxygenation in pediatric patients.[1-4] In addition, a small study published by Humphreys and colleagues in 2017 demonstrated that THRIVE can be used safely as an oxygen delivery system in anesthesia for spontaneously breathing patients during spontaneous ventilation for airway procedures.[2]

The purpose of this study is to further assess the use of THRIVE in pediatric patients undergoing MDLBs in a multi-center, randomized, prospective clinical trial to further understand the role of this oxygen

delivery system in pediatric anesthesia management. When a novel technology such as HFNC is integrated into practice, larger studies are important to better understand its role in patient care and to determine if it has the ability to transform management and improve outcomes.

Preliminary Results

HFNC has been studied in pediatrics during MDLB at a single institution (Stanford University). After IRB approval, patients were randomized to control or THRIVE. Controls received 100% oxygen via the side port of a Parson's laryngoscope to insufflate the oropharynx at 6-10 L/min, titrated by the anesthesiologist. THRIVE patients received 100% oxygen via HFNC at 2L/kg/min using an Optiflow machine. Inclusion criteria were all patients from birth to 18 years old. Exclusion criteria included papillomatosis, tracheostomy, or unrepaired heart disease.

The primary aim was surgical interruptions. *A priori* power calculation based on 15 pilot surgeries demonstrated the frequency of interruptions in the control to be 0.93 and 0.33 in THRIVE. Assuming a Poisson regression, 80% power, and 95% confidence interval, 27 patients in each group (54 total) were needed to demonstrate a significant difference. To account for incomplete data and dropouts, an additional 20 patients (74 total) were targeted for consent. The secondary aims were to compare differences in oxygen desaturation index (ODI), desaturations below 90%, transcutaneous carbon dioxide (tCO2), and adverse events.

Demographics and postoperative diagnoses in control and THRIVE were collected. Interruptions were defined as the need to pause surgery to provide airway support, such as mask ventilation or intermittent intubation. Pulse oximetry was recorded by second in the electronic medical record. ODI was defined as a 4% decrease in saturation from a 120 second rolling mean for greater than 10 seconds. TCO2 was recorded at procedure start and end. Adverse events (nausea, vomiting, sinus pain, throat pain, epistaxis) were recorded prior to discharge.

Outcomes were calculated using negative binomial regression with case duration as an offset in the unadjusted and adjusted models, with the exception of tCO2. Models were adjusted for postoperative diagnoses. 210 patients were screened and 67 (control = 36, THRIVE = 31) were included in the final analyses. There were no demographic group differences. P values are reported as (unadjusted value, adjusted value), respectively. There were no significant differences in surgical interruptions, tCO2, or adverse events. There were significant differences in ODI between groups (p=0.003, 0.005) and number of oxygen desaturations below 90% in the unadjusted model (p=0.039,0.082).

This was the first prospective study examining THRIVE's effectiveness during pediatric MDLBs. Although there were no significant differences in surgical interruptions, there were significant differences in ODI and oxygen desaturations when not adjusting for postsurgical diagnoses. Although THRIVE has been reported to potentially contribute to ventilation, these results do not support a difference. The table below summarizes these findings.

			THRIVE vs. control	
			β	**p-value**
Primary outcome	**Number of Interruptions**	Unadjusted	-0.70	0.13
		Adjusted for post-surgical diagnosis	-0.41	0.37
Secondary outcomes	**ODI**	Unadjusted	-1.78	**0.003**
		Adjusted for post-surgical diagnosis	-1.74	**0.005**
	Desaturations below 90%	Unadjusted	-1.25	**0.039**
		Adjusted for post-surgical diagnosis	-1.08	0.082
	Adverse Events	Unadjusted	-0.23	0.72
		Adjusted for post-surgical diagnosis	-0.33	0.64
	Final CO2*	Unadjusted	-1.93	0.55
		Adjusted for post-surgical diagnosis	-1.04	0.75

* = linear regression result, with case duration included as a covariate in both unadjusted and adjusted models

Summary

Pediatric patients undergoing MDLB pose anesthetic challenges of maintaining adequate oxygenation and ventilation while providing motionless a motionless surgical field without an endotracheal tube. Given this challenge, we propose a prospective, multi-site, randomized controlled trial to evaluate HFNC as THRIVE in pediatric patients undergoing MDLB.

Potential benefits:

Individual study participants may not derive direct benefit from participation in this study as we are studying whether the use of HFNC during MDLB can decrease the risk of oxygen desaturation. However, if proven successful, these patients may benefit from having decreased rates of oxygen desaturation to below 90% during the procedure as well as decreased number of surgical interruptions. Results from this study may yield new information which will contribute to a better understanding of the use of HFNC during ENT procedures resulting in possible changes in clinical management of subsequent patients.

Potential risks, discomforts, inconveniences:

Based upon preliminary data, HFNC has been utilized in over 100 patients intraoperatively during MDLB, including those under 2 kg without adverse effects. There have been limited reports of serious adverse events during its widespread and pervasive use in neonatal and pediatric intensive care units across the country including pneumothorax and pneumodiastinum, potentially associated with improperly sized nasal cannula. We will monitor patients for any adverse events during this study. In addition, participation in the study will not impact their clinical management as both groups of patients will receive the same level of anesthetic care as non-enrolled patients. Risks specific to this research are expected to be minimal. Adverse events will be defined using standard criteria. The researchers shall monitor the child while the HFNC is applied and review the child or the child's record 1 week later. Serious adverse events, although unanticipated, will be addressed as follows.

Any physical or clinical change or illness not expected after surgery will be recorded on the medical record chart and adverse event case report form. Recordings will include date of onset, duration, and the relationship to HFNC. The severity and pattern of the event, and any action taken by the study physician and/or outcome will also be recorded. In case of an adverse event thought to reflect HFNC, appropriate evaluation and management will occur. This may include a reduction in HFNC flow, temporary discontinuation of the HFNC, or early termination from the trial.

Patients who experience adverse events will be monitored clinically until the event is either satisfactorily resolved or stabilized, as determined by the physician investigators. Actions taken and follow-up results will be recorded in the participant's medical record chart and adverse event case report form. Patients who are discontinued from the study as a result of an adverse event will be followed with appropriate clinical assessments and laboratory tests until resolution.

The principal investigator or a designee will report by telephone to the IRB all serious adverse events, whether or not they are deemed study-related, within 24 hours. A written report, including a full description of the event and any sequelae, will follow as required. An adverse experience is defined as serious if it meets any of the following criteria: (1) fatal, (2) life threatening (at immediate risk of death due to event), (3) significantly or permanently disabling, (4) requiring or prolonging in-patient hospitalization, (5) causing a congenital anomaly, or (6) considered to be a serious adverse event by the physician investigators.

Recruitment plan:

Children will be identified from the operating room schedule or, for unscheduled, add-on cases, the coordinating anesthesiologist will contact the study team. A member of the local study team will approach the families pre-operatively to explain the project and obtain consent. Once consent is obtained, patients will be randomized into either the usual care (control) or THRIVE (treatment) arm.

Device Description:

Physiological data (oxygen saturation and heart rate) will be captured real-time using the Masimo Rad-97 Pulse Co-Oximeter (Masimo Corporation, Irvine, CA, USA). This device is FDA approved and used routinely in patient care, including in pediatric and neonatal populations. There is no evidence of harmful effects on human tissues by the utilization of this device. The device will be inspected by Biomedical Engineering at each site and will undergone the necessary safety tests required of all clinical equipment to be used in the hospital. The device will be accessed only by study staff members and the biomedical engineers supervising the device. It will be kept in a locked research office when not in use, accessible only to study staff. The investigators have received appropriate training with the equipment since this device is not in routine use in our hospital.

HFNC will be provided to treatment arm patients using the Optiflow THRIVE system (Fisher & Paykel Healthcare, Irvine, CA, USA). This device is routinely utilized in pediatric and neonatal intensive care units internationally to provide high flow oxygenation. This device will be inspected by Biomedical Engineering and will undergone the necessary safety tests required of all clinical equipment to be used at the hospital. The device will be accessed only by study staff members and the biomedical engineers supervising the device. It will be kept in a locked research office when not in use, accessible only to study staff. The investigators have received appropriate training with the equipment.

Risk/Benefit Analysis:

Those enrolled in the intervention arm will be exposed to greater than minimal risk. Potential benefits to the intervention arm include improved oxygenation and ventilation, improved surgical operating conditions, prevention of oxygen desaturation, prevention of complications related to apnea or oxygen desaturations, prevention of atelectasis and any subsequent complications. Potential serious risk such as pneumothorax or pneumocephalus are exceedingly rare and will be minimized by careful observation of the patients during the duration of high-flow cannula application. Potential risks such as headache, sinus or nasal mucosal irritation, aspiration, and gastric insufflation are also low risk with less associated morbidity, but the researchers feel the potential benefits outweigh these risks. The potential risks and benefits will be provided to the parents or guardians when obtaining written consent prior to the procedure.

Methods:

This prospective, randomized, controlled trial is a multi-center collaborative project including the primary site - Lucile Packard Children's Hospital (Stanford University, Palo Alto, CA), Cincinnati Children's hospital (Cincinnati, OH), Lurie Children's Hospital (Chicago, IL), University of Virginia Children's Hospital

(Charlottesville, VA), Massachusetts Eye and Ear Infirmary (Harvard University, Boston, MA), and Boston Children's Hospital (Harvard University, Boston, MA).

The primary outcome measure will be oxygen desaturation index (ODI), as defined by a 4% decrease in saturation from a 120 second rolling mean for greater than 10 seconds. Secondary endpoints include the relative number of desaturations below 90% lasting greater than2 seconds as a function of overall case duration and the number of surgical interruptions, as defined by any time the procedure is temporarily halted due to suboptimal airway conditions.

Preoperatively, medical history will be collected along with baseline physiological data (blood pressure, heart rate, age, weight, gender, medical conditions, medications and allergies). The Masimo pulse oximeter will be applied to the patient where appropriate prior to induction of anesthesia to obtain baseline oxygen saturation and heart rate and will remain on the patient until the patient has emerged from anesthesia. The THRIVE system will be placed on patients randomized to the treatment arm following induction of anesthesia and prior to initiation of the procedure. It will be removed following completion of the procedure and prior to emergence from anesthesia. Although this may pose a challenge in an active infant, the team will do its best to obtain baseline data prior to induction of anesthesia.

Physiological data (pulse oximeter and heart rate) will be collected real-time using the Masimo device. The heart rate and oxygen saturation will be continuously recorded by the Masimo device and data will be extracted to a research laptop via USB transfer following completion of case. The anesthesia monitors will record into EPIC anesthesia every 3 minutes according to anesthesia standard of care: (i) (non-invasively-measured) systolic/diastolic/mean arterial pressures; (ii) SaO_2; (iii) heart rate; (iv) end tidal CO_2; (v) end tidal volatile concentration and all drugs given; (vi) ventilator settings (vii) temperature. These vital signs will be recorded as is standard of care, but not collected by the study investigators, who will only gather the heart rate and oxygen saturation in two second intervals from the Masimo.

The following data will also be collected: (i) medical history; (ii) type and duration of anesthesia and surgery; (iii) any critical or adverse events.

Apart from placing the Masimo and THRIVE devices, the patients will receive standard care for anesthesia and surgery. A study personnel will remain in the operating room as an observer throughout the procedure. The personnel will record procedure start and end times, method of supplemental oxygen in the control group, and the number of surgical interruptions, defined by the need for the surgeon to cease the examination or operation due to suboptimal patient conditions such as desaturations. During procedure interruptions, the observer will record what, if any, airway intervention occurred, such as jaw thrust, bag mask ventilation, or intermittent intubation. Following recovery from anesthesia, a questionnaire regarding adverse events will be provided to applicable patients or their parents/guardians/representatives.

The THRIVE flow rate regimen will be 2 L/kg/min, maximum 70 L/min as previously described.[1-3] The oxygen concentration will be titrated based on the surgical conditions and requirements (21 to 100% oxygen).

Method of Obtaining Informed Consent:

Children will be identified from the operating room schedule. Parents will be provided with oral and written information about the research project. The anesthesiologist for the patient will be approached and written consent from the parents will be obtained prior to recruitment into the study. The surgeon will be notified and given oral information about the study prior to the start of the case. If the THRIVE nasal cannula interferes with the safe conduct of surgery or anesthesia, then the device shall be removed. While the child is under anesthesia, the parents will not have the opportunity to withdraw. Parents may withdraw their child after surgery. If they withdraw from the study, we shall ask if they will allow us to use the collected data even if the child has withdrawn. If not, then the data will be deleted.

Inclusion Criteria:

Patients meeting the following criteria will be enrolled:

- Patients between the ages of 2 months and 18 years;
- Patients willing and able to provide assent/parental consent to participate in the study in English;
- Patients undergoing airway examinations or airway procedures with or without laryngoscopic suspension with the goal of maintaining spontaneous respiration.

Exclusion Criteria:

Patients will be excluded if they meet any of the following criteria:

- Patients who are pregnant;
- Patients with congenital cyanotic heart disease;
- Patients with history of airway papillomatosis;
- Patients with an absence of a parent or legal guardian who are therefore unable to provide appropriate consent for study participation;
- Anatomical or surgical contraindications to the placement of HFNC (including but not limited to epistaxis, basilar skull fractures or abnormalities, facial fractures or abnormalities, nasal surgery or obstruction, nasal fractures, nasal vascular abnormalities);
- Presence of tracheostomy;
- Patients presenting for emergent surgery for which application of the HFNC may delay surgery or may result in increased risk of aspiration;
- Patients who are intubated.

Statistical Methods:

Randomization: This is a prospective, randomized, multi-center, non-blinded study.

Data Storage: Data confidentiality will be maintained by data being stored in a password protected computer and hard copies of patient information stored in a locked office. Data will be transmitted to a password-protected computer for further analysis. REDCap will be utilized to store de-identified data.

Statistical analysis: This is a prospective, randomized study.

Sample size determination: A power calculation was done by simulation. Using data from a prior pilot study, the data was found to be a negative binomial distribution so a negative binomial regression was used. The simulation assumed a mean for the control group of 0.119 events / minute, a theta of 0.3609 (both from the pilot study), an average case duration of 30 minutes, and an effect size of 20% between the control and the experimental group. 10,000 simulations were done and a sample size of 500 (300 per group) was determined to provide an 82% power. The analysis was undertaken using R version 3.5.3 (Vienna, Austria), Rstudio version 1.1.456 (Boston, MA), and the MASS package version 7.3-51.4 (New York City, NY)

Blood draws: No blood draws are required for this study.

Special considerations: Study subjects will NOT be exposed to any radiation and will NOT be exposed to any investigational drugs; genetic studies, discarded tissues, tissue banks, and institutional biohazard committee do NOT apply to this study. Study subjects will have a non-invasive, non-radiation producing imaging study.

Gender and minority inclusion: It is expected that the demographics of participants will reflect the overall gender and ethnic characteristics of the current clinical population.

Randomization method: The method of randomization is simple randomization. Prior to study initiation, the study statistician will provide the randomization schedule through REDCap. At study conclusion, descriptive analyses will be conducted prior to hypothesis testing to evaluate the success of the randomization procedure in equally distributing patient characteristics (such as age, gender, past medical history, type of procedure, type of supplemental oxygen, etc.).

Retention of patients: Retention of patients is a consideration in every study and random attrition may reduce statistical power. Systematic attrition threatens the external validity of the results (such as if a subgroup of participants tend to discontinue the study, generalizability may be compromised). Differential attrition may reduce validity when comparing conditions if baseline variables correlate with outcome. Retention will be analyzed with chi-square and life table methodology and is anticipated to be low. We will examine closely the enrollment of targeted patients at month 6 and 12. If, at these time points, we discover that the recruitment is below anticipated volume, we will immediately contact our colleagues at other sites. CHOP is the most likely additional sites given preliminary interests that have been expressed from anesthesiologists there.

Payment:

There is NO financial benefit or reimbursement for participation in the study.

References:

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