HRPO Protocol

1) Protocol Title (Version Date 21 Oct 2015)

Effect of peri-intubation apneic oxygenation via nasal cannula on pediatric patients' oxygen saturations during airway management.

Brief title: Apneic Oxygenation during Airway management in pediatric patients.

2) IRB Review History

The HRRC reviewed this study on 2/10/2015, and after requested modifications were completed, the HRRC approved it on 4/17/2015. A modification to add research assistants was reviewed and approved by the HRRC on 5/19/2015. Post-approval monitoring was conducted by the HRPO on 10/21/2015.

3) Objectives

We hypothesize that apneic oxygenation via nasal cannula during airway placement improves oxygen saturation in pediatric patients. Patients who receive this treatment will be compared to patients managed under the current standard of care, which does not include apneic oxygenation during anesthetic induction and airway management.

The primary outcome is the elapsed time between anesthetic induction and pulse oximetry (SPO_2) falling to 95%, if it happens at all.

The secondary outcomes are as follows:

- whether the 95% threshold is met at all

- whether intervention by attending or temporary mask ventilation is required

- whether pulse oximetry falls to 90%

- the lowest observed pulse oximetry during airway placement

4) Background

This observational study aims to investigate the effect of a planned practice change; instituting oxygenation via nasal cannula during induction of anesthesia. The use of a nasal cannula during the peri-intubation period is of minimal risk and is not considered a standard of care in pediatric anesthesia. Some providers use it in certain clinical situations, but it is not broadly used and has virtually no pediatric literature to support or refute its use.

At our institution, intubation of pediatric patients by inexperienced (learner) providers under expert supervision is routine. The attending

physician intervenes if necessary before the patient experiences excessive loss of oxygenation.

There has been increasing discussion of nasal cannula apneic oxygenation in the adult anesthesia and emergency medicine literature, but there is a paucity of pediatric literature to support or refute its use in the pediatric population. Weingart and Levitan 2012, discuss how Apneic oxygenation is based on the physiology of the lungs absorbing a greater volume of oxygen, 250 ml/min in an adult, than the volume of carbon dioxide, 8-20 mL/min, that is released by the lungs as the majority of carbon dioxide is buffered in the blood stream during apnea. With the imbalanced volumes of absorption and release of gasses in the lungs there is a lower than atmospheric pressure in the lungs, creating a passive movement of gases from pharynx to alveoli. If the gas in the pharynx has a significantly higher percentage of oxygen instead of room air at 21% oxygen, a higher amount of oxygen can be passively delivered to the lungs for absorption prolonging the time to hemoglobin desaturation.

Taha et al 2006, concluded the use of nasal cannula insufflation after preoxygenation can delay the onset of hemoglobin desaturation for a prolonged period of time during the subsequent apneic period in adults. Ramachandran et al 2009, demonstrated the ability to prolong oxygen saturations >95% and increase the lowest saturation level with use of a nasal cannula at 5 L/min during simulated difficult intubations in adult obese males. Weingart and Levitan 2012, recommend that nasal cannula apneic oxygenation can extend the safe apnea period after the use of sedatives and muscle relaxants in adults. With a variety of search terms only three relevant articles were found in pediatric anesthesia literature. Bhagwan 2013, in Pediatric Anesthesia, commented about Levitan's NoDesat article in EPmonthy 2012, endorsing how her use of the nasal cannula adjunct in the peri-intubation period has led to fewer desaturations and bradycardic episodes in infant intubations by resident physicians. Her opinions were based on her experiences, but no data was gathered or presented to support the claims in a form representing a true study. T.M. Cook 1998, wrote a paper discussing blood gas results during pediatric apneic oxygenation in intubated pediatric patients undergoing undergoing cardiac catheterization. The findings demonstrated that apneic oxygenation was likely safe for up to 10 minutes before hypoxia would occur. An earlier study by Kernisan et al 1987, also studied apneic oxygenation in pediatric patients. Patients were intubated and not ventilated and they found desaturation via pulse oximetry did not occur in patients at 3 minutes.

Physiologically, children have a higher oxygen consumption than adults, 5-10 mL/kg/min, compared to adults, 3mL/kg/min. This high metabolic rate leaves pediatric patients at higher risk for hemoglobin desaturation in the peri-intubation period. In a Hospital setting there can be prolonged time periods as airway devices are placed in certain patients. The current

adult literature indicates that peri-intubation nasal cannula oxygenation can decrease the occurrence of hemoglobin desaturation during prolonged intubations. There is some pediatric literature supporting the physiologic safety of apneic oxygenation for a brief period of time after endotracheal intubation. Our adaptation of using a nasal cannula in the peri-intubation period would be new to the pediatric literature and would hopefully further elucidate the potential effects during the peri-intubation period and investigate whether this benefit also extends to pediatric patients. There are anatomical differences in the pediatric airway compared to adults which may make the use of nasal cannula apneic oxygenation less beneficial in the pediatric population.

This minimal risk study would add to the literature extending this concept to the pediatric patient population. If the same results were to be found as in the adult patient population there is the potential for an improved less stressful pediatric intubation learning environment and improved patient care with fewer and less severe desaturations during the peri-intubation period.

5) Inclusion and Exclusion Criteria

The study population would be infants and children with adjusted gestational age of 40 weeks or greater to 8 years of age, scheduled for surgery at UNM. Patients to be excluded would be premature infants with adjusted gestational age of less than 40 weeks, those undergoing mask ventilation, and patients with ASA class 4-6. Enrollment would occur for up to six months after HRRC approval and study commencement.

6) Number of Subjects (Recruitment Target)

A sample size estimate based on prior studies of apneic oxygenation in adults indicates that approximately 400 subjects would be appropriate for this study, 200 in the baseline group without nasal cannula adjunct and 200 patients with implementation of nasal cannula adjunct during the peri-intubation period.

A power analysis (based on formulae in *Statistics in Medicine* 1982; 1:121-9) indicated that if the baseline rate of reaching 95% SPO2 is 15% of patients and this procedure reduces that rate by half, 80% power at α=0.05 is reached for a one-tailed logrank test with a total of 371 patients. Rounding up to 400 patients to accommodate incomplete datasheets would provide power of 94%.

Based on enrollment rate to date, we estimate that enrollment of 400 patients will take approximately one year. Because the planned evaluation of routine use of nasal cannula adjunct oxygenation is occurring independent of enrollment counts to the baseline study condition, data

may be gathered on more than 200 patients in that group. In order to permit analysis without loss of power, we may need to enroll a higher total sample size in order to achieve an equal sample size in the group with the cannula. To accommodate this reality, we may enroll a maximum of 500 patients in the entire study.

This period will also permit education of all relevant providers and staff on the use of peri-intubation nasal cannula oxygenation.

7) Recruitment Methods

Investigators will recruit participants from among their own patients. All patients who meet the inclusion/exclusion criteria will be enrolled. We are requesting waiver of consent.

8) Study Timelines

- Duration of individual patient participation: Patients will participate from the time when they are brought into the OR preoperative suite and it is determined they will have an endotrachaeal tube (ET) or laryngeal mask airway (LMA) placed. The study observation period will end once the airway has been secured.
- The duration anticipated to enroll all study subjects will be sufficient time to enroll the target sample of patients.
- An interim analysis will be conducted halfway through enrollment of the with-cannula group.
- The estimated primary analysis will be done by December 2016.

9) Study Endpoints

As this study is of minimal intervention and minimal risk, we do not anticipate early study termination for research-induced adverse outcomes. The planned intervention may be suspended or canceled after the interim analysis if it is ineffective, or if we reach statistical significance on the primary outcome halfway through collecting our estimated number of patients. "Ineffectiveness" is defined here as a failure to identify one-tailed superiority of the with-cannula group with $p<0.20$ on *any* of the outcomes (primary or secondary) at the interim analysis.

10) Research Setting

Data will be collected at the UNM hospital pediatric surgical suites.

11) Study Methods

This is a prospective observational study. Prospectively-recorded data are necessary because data on the outcomes of interest are not available in the medical record.

Participants will be enrolled in the study once they have entered the pre-operative area and they are determined by the attending anesthesiologist to

that they are an eligible study participant. Participants enrolled in the first three months of the study will be assigned to the baseline condition as described below. Participants enrolled in the second phase of the study will be assigned to the with-cannula condition described below.

A patient sticker will be added to the data collection form. Basic demographic information and vitals will be recorded before premedication is administered as is standard at entry to the pre-operative area. Timing devices of the same make and model will be used consistently between all study cases.

For the **baseline group** of this observational study, all intubation procedures will be performed as per usual practice. Patients will receive premedication as determined by anesthesiologist/resident/midlevel, and the type and dose will be recorded.

Once patients are brought to the operating room suite and vital signs are being monitored, patients will be preoxygenated via mask per standard of care, with an expired oxygenation concentration minimum of 0.75. Vitals will be recorded at the moment prior to removal of the face mask at the end of the preoxygenation period. Anesthetic induction will then be performed with agents and dosages as per the provider's clinical judgment.

Airway management consisting of oral endotracheal intubation or laryngeal mask airway insertion will take place. As per usual practice, an attending physician who is expert in pediatric airway management will supervise the procedure and intervene before the patient experiences excessive oxygen desaturation. The lowest oxygen saturation and the time to either successful intubation or intervention by an attending physician will be recorded.

For the **with-cannula group**, all of the above steps will be maintained. The sole difference will be nasal cannula placement after induction. It will be set to deliver 5L of oxygen per minute.

Airway management consisting of oral endotracheal intubation or laryngeal mask airway insertion will take place. As per usual practice, an attending physician who is expert in pediatric airway management will supervise the procedure and intervene before the patient experiences excessive oxygen desaturation. The lowest oxygen saturation and the time to either successful intubation or intervention by an attending physician will be recorded. Apneic oxygenation will not be used as a long-term oxygenation strategy. No patient will be allowed to cross any particular SPO_2 threshold solely for research reasons.

All intubation procedures in both study groups will proceed as per usual practice. The goal of all intubation procedures has always been and remains the maintenance of adequate oxygen saturation.

12) List of Appendices

Data collection form

13) Data and Specimen Banking

Deidentified data will be retained indefinitely in electronic format after study completion. This retention will be only for possible use in preparation for future studies involving one or more of the investigators on this study, such as to inform power analyses. While future studies are not currently planned, they may include investigations of the optimal use of and indications for pediatric apneic oxygenation, for example. All retained data will be stripped of all 18 HIPAA identifiers and stored on UNMHSC password-protected servers. The paper data collection forms and link to identity will not be retained, but will be shredded upon study completion.

14) Data Management

Only study investigators will have access to study data. Study participants will be assigned a study number, and this number will be used in all data analyses. The data will be entered into an electronic database that will be stored on UNMHSC password-protected servers. The electronic data will only have study participant numbers and no identifiers that could link specific patients to the data. All data forms that bear identifiers will be securely destroyed (shredded) upon application to HRRC for study closure, so that only deidentified data remain when that application is made.

As noted above, data to be gathered include basic demographic data, data about the anesthetic induction procedure, and data about the patient's O_2 saturation.

Routine demographic data will be analyzed with t-tests and Wilcoxon rank-sum tests, as appropriate depending on normality of data distributions. Categorical data will be analyzed with appropriate analyses, such as chi-square, Fisher's exact, risk ratio, and/or odds ratio.

The primary outcome of time to cross the 95% saturation threshold will be analyzed with Kaplan-Meier curves and survival analysis with "censoring" for cases in which the threshold was not crossed because of either successful intubation or intervention by the attending physician.

Secondary outcomes with continuous data (e.g. the lowest observed O_2 saturation) will be analyzed with standard t-tests or Wilcoxon rank-sum tests, as appropriate depending on normality of data distributions. Secondary outcomes with binary data (e.g. whether intervention by the attending physician is required) will be analyzed with chi-square or Fisher's Exact tests as appropriate depending on cell counts.

15) Provisions to Monitor the Data to Ensure the Safety of Subjects

NA; this is a minimal-risk study. Patients will receive either usual care or usual care with additional oxygen.

16) Withdrawal of Subjects

As we are requesting waiver of consent and HIPAA authorization, there will not be withdrawals from the study.

17) Risks to Subjects

This study has minimal anticipated risk beyond the standard medical treatment which they are already consented to undergo for reasons outside of the study. The control group is simply an observation of the current standard of care, documentation of vitals at specific times, and airway management success.

The with-cannula part of the study has minimal risk and an unknown likelihood of delivering a very small benefit (see Benefits, section 18) to the patients. It is routinely used in other clinical settings. Some pediatric patients wear a nasal cannula chronically in the home environment without significant complications. Other children may wear a nasal cannula for days on an inpatient medical service. Nasal cannula placement has a very low probability of causing harm to the nares, eyes or to interfere with the ET or LMA placement process.

The risk of a breach of confidentiality is minimal, as no data that are usually considered "sensitive" will be gathered and all identifiable data will be destroyed upon study completion.

18) Potential Benefits to Subjects

Subjects in the with-cannula group may have a small potential benefit during the study as they may experience improved oxygenation during the ET or LMA placement period, but it is not known whether the planned intervention is effective at all. This hypothetical benefit is low for the individual patient, as it springs from any improvement in oxygenation that may result. This benefit is expected to be low for several reasons: 1) even in the no-cannula group (current practice), an attending physician who is expert in pediatric airway management is always ready to intervene before the patient's oxygen saturation reaches dangerous levels: therefore any temporary reduction in blood O_2 saturation that may be avoided in the with-cannula group is mild; 2)the rates of mild SpO_2 reduction during intubation are already very low, and 3) rates of complications from any brief mild SpO_2 reduction are extremely low.

19) Vulnerable Populations

The research will involve children from the age of birth to the age of 8 years. Permission will not be sought from the parents or assent from the children as this study is of a minimal intervention and of minimal risk to the participants. The planned transition to use of routine oxygen cannulation during intubation will not modify the participants' degree of risk to a level above that of standard medical treatment. The standard of care will simply be observed with the participants in the baseline group, and during the implementation of the peri-intubation adjunct nasal cannula (a device considered standard care in various other clinical settings and that poses no foreseeable significant risk to the patient) the same readily available data will be collected for comparison.

20) Multi-Site Research

NA.

21) Community-Based Participatory Research/Field Research

NA.

22) Sharing of Results with Subjects/Incidental Findings

Study participation periods will be so brief that results analyzed after the fact would have no positive or negative effect for the patient.

23) Resources Available

This project will be completed at the UNM Children's Hospital, which serves a large pediatric surgical population. The investigators include:

Codruta Soneru, M.D., Assistant Professor, Faculty Physician, UNM Department of Anesthesia and Critical Care

Ricardo Falcon, M.D., Associate Professor, Faculty Physician, UNM Department of Anesthesia and Critical Care

Jimmy Windsor, M.D., Associate Professor, Faculty Physician, UNM Department of Anesthesia and Critical Care

Darren Braude, M.D., MPH, EMT-P, Professor, Faculty Physician, UNM Department of Emergency Medicine

Hans Hurt, M.D., Resident Physician, UNM Department of Emergency Medicine

Timothy Petersen, Ph.D., Research Coordinator, UNM Department of Anesthesia and Critical Care

UNMCH has all of the required supplies, equipment, facilities, and staff to perform pediatric surgery and provide intubation of pediatric patients.

24) Prior Approvals/Attachments Requiring Signatures

The departmental review form is included with this submission.

This study has been registered with clinicaltrials.gov, and assigned record number NCT02437864.

25) Confidentiality

See section 12. The link to identifiers will only be maintained for the duration of this research study. Only investigators will have access to identifiable study data. The link to identifiers will be destroyed upon application to HRRC for study closure.

26) Provisions to Protect the Privacy of Subjects

The transition to routine oxygen cannulation during intubation is planned regardless of this project. This project therefore does not modify patient experience in any way, and there is no research-related contact between investigators and patients or parents.

27) Compensation for Research-Related Injury

NA. As this is an observation of the standard of care there is no potential for research specific related injuries.

28) Economic Burden to Subjects

There will be no economic burden to the study participants or to a 3rd party payer. The cost of the pediatric nasal cannula (NC) is included in the hospital facility fee and will not be billed extra to the subjects. The potential cost of the nasal cannulas for the intervention group is negligible as it is standard of care to have a NC or face mask available for patients during their post operative time to provide oxygen supplementation as the anesthetic wears off, and the NC used during the peri-intubation period can still be used for that patient after extubation.

29) Consent Process (including waiver request for HIPAA, waiver of HIPAA for recruitment only, Waiver of Informed Consent, and Alteration of Informed Consent)

Waiver or Alteration of Informed Consent:

We are requesting waiver of consent for this study. This research is not FDA-regulated, and does not involve non-viable neonates. As noted above, this project presents minimal risk to participants. Similarly, the available literature does not clearly indicate whether the planned intervention offers any benefit to patients at all. Patients' experience and clinical care will not be modified by to a level outside of standard medical care in this study. The use of a nasal cannula is standard care in multiple clinical settings and will simply be monitored in another aspect of clinical care. The risk of breach of confidentiality presented by the recordkeeping in this study is similar to that of normal practice, because normal practice involves the production and maintenance of both routine medical records and supplemental Quality Assurance datasets. The information to be recorded is not particularly sensitive, and will not pose risks to participant employability or insurability.

Similarly, waiver of consent for this study will not adversely affect the rights and welfare of the subjects. This study consists of recording routine clinical data during routine medical care. These data are already recorded for both patient-care and healthcare operations purposes.

This study could not practicably be carried out without the waiver because the validity of observational studies depends on data capture as close to 100% as possible. Anything else introduces the possibility of bias, which would invalidate the results. Parents of children of certain ages, or with certain types of medical conditions, may be more or less likely than others to provide consent. Since this study does not modify patient care beyond minimal risk, it would not be appropriate to provide participants with extraneous information after participation.

Waiver of HIPAA authorization:

The PHI to be used for this study is described above, and includes basic demographic data, data about the anesthetic induction procedure, and data about the patient's O_2 saturation. Only the specific measurements made for the outcomes themselves are not already found in the medical record.

As noted above, the study data will be kept in a locked cabinet in Anesthesiology department offices. Identifiable data will only be available to study investigators, and will be maintained only to permit completion of data for any cases in which data collection was incomplete or unclear. The

identifiable datasheets will be destroyed upon application to HRRC for study closure. Deidentified data may be retained for use in the preliminary stages of future research, but identifiable PHI will not be reused or disclosed to any other person or entity, except as required by law, or for authorized oversight of the research study.

As noted above for waiver of consent, this research could not practicably be conducted without the waiver of HIPAA authorization because study validity depends on near-100% data collection. Attempting to obtain authorization would invite bias. Similarly, the study could not be conducted without access to and use of the PHI because it is a study of medical care. It would not be possible to evaluate the planned intervention without access to these data.

30) Drugs or Devices

Medical Devices:

This study records data on the clinically-indicated use of a nasal cannula for delivery of oxygen. An IDE application has not been submitted to the FDA. Nasal cannulas are FDA-approved for marketing, and they are being used in accordance with their labeling. The nasal cannulas to be used for this study will be supplied and maintained as per usual UNMHSC practice

References:

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