

The effect of povidone-iodine ophthalmic surgical prep solution on respiration in children undergoing strabismus surgery with general anesthesia.

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PROTOCOL TITLE:

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1.0 Objectives / Specific Aims

The objective of this study is to determine whether the application of povidone-iodine ophthalmic solution onto the ocular surface causes a change in respiration in children undergoing strabismus surgery with general anesthesia.

Hypothesis: The application of povidone-iodine ophthalmic solution to the ocular surface causes a change in respiration in children during general anesthesia prior to strabismus surgery.

2.0 Background

Primitive neural reflexes are often unmasked during anesthesia. This is most likely due to an imbalance in the effect of anesthetics on inhibitory and excitatory neurons. The oculo cardiac reflex (OCR) is a well-known reflex that occurs when traction is applied to an extra-ocular muscle. The afferent limb of the reflex is mediated by sensory branches of the trigeminal nerve and the efferent limb is mediated by the vagus nerve. Stimulation of a branch of the trigeminal nerve causes an increase in vagal activity that can cause a variety of changes in heart rate and rhythm. Although the OCR has been reported to cause atrioventricular block, premature ventricular contractions (PVCs), ventricular tachycardia, and sinus arrest, bradycardia is the most consistently reported finding during anesthesia. The OCR has been known to occur with strabismus surgery for many decades and is correlated with traction on the extraocular muscles.^{1,2} If the decrease in heart rate is significant enough to cause a decrease in cardiac output and/or blood pressure, the intravenous administration of glycopyrrolate or atropine effectively increases the heart rate in most patients. Less well-known triggers of the trigemino-vagal reflex during anesthesia involve noxious stimuli to the mandible or skull base.³⁻⁵ Changes in respiratory pattern (e.g. apnea, dachypnea, and bradypnea) have not been described with the OCR that occurs during anesthesia.

The diving reflex that occurs in diving birds and mammals is characterized by cessation of respiration, decrease in heart rate, and diversion of blood flow to critical organs (brain, heart, kidneys) from less critical tissue beds.⁶ The diving reflex is initiated in these animals when the head and face are submerged resulting in stimulation of the trigeminal nerve. A diving-type reflex has been described in humans, most notably in near-drowning victims. Activation of this reflex may explain the survival of humans, especially children,

submerged in cold water for 30 to 40 minutes. The diving reflex has also been implicated in the pathophysiology of sudden infant death syndrome (SIDS).⁷ Despite the similarity of the OCR and the diving reflex, the relationship between the two is unknown.^{8,9}

In 2015, an observational study was published that described apnea after the application of povidone-iodine ophthalmic solution on respiration. All of those children were breathing sevoflurane spontaneously via a laryngeal mask airway (LMA). Why this was not observed previously is not clear. Prior to the introduction of the LMA into clinical practice, most children undergoing strabismus surgery underwent tracheal intubation and were managed with controlled or assisted ventilation. A brief period of apnea or changes in respiration were, consequently, not obvious. For the vast majority of children undergoing strabismus surgery throughout the United States (including at MUSC), standard airway management during anesthesia practice is with an LMA. The predominant inhaled anesthetic administered is sevoflurane.

Povidone-iodine solution has become the standard for disinfection of the eye prior to surgery.^{11, 12} Povidone-iodine solution has been typically formulated as a 10% solution. For surgical eye preparations, the 10% solution is diluted to produce a 5% solution. Recently, a specially formulated 5% Betadine[®] ophthalmic solution (manufactured for Alcon Laboratories, Fort Worth, Texas by Catalent Pharma Solutions, LLC, Woodstock, IL) was introduced and has become a standard for surgical eye preparation. Ophthalmic balanced salt solution (BSS) is an isotonic solution specifically formulated for irrigation of eye tissues. BSS is used in nearly all eye surgeries for irrigation. These solutions are both FDA approved.

The objective of this study is to try to begin delineating the physiology of a potential reflex change in respiratory pattern initiated by a mechanical or chemical stimulus. This study is the first step in the study of this reflex. The results of this study will be used to develop further studies aimed at complete definition of this reflex.

3.0 Intervention to be studied

The effect of the application of povidone-iodine ophthalmic solution on the ocular surface on respiration will be compared to the effect on respiration of the application of the application of ophthalmic BSS on the ocular surface during general anesthesia. Both of these solutions are FDA approved for use in this manner and this intervention will begin once a steady state of anesthesia is achieved by means of the standard of care. After the

induction of general anesthesia and at the time the patient is ready for surgical preparation of the eyes, subjects will first have their average peak to peak interval for respiration measured at a steady state of anesthesia, using capnography. This will give us a baseline for measuring a change in respiratory rate. They will then have one of two solutions applied to the ocular surface of each eye. It is this application of eye solution that is the main study intervention. The solution to be used is determined by randomization upon enrollment and will either be 3 drops of povidone-iodine ophthalmic solution in each eye (Group A) or 3 drops of BSS in each eye (Group B). The eye solution intervention period will take less than 5 minutes and will cause either only a slight delay or no delay in the surgical time. The only other intervention is the collection of data after induction (but just prior to IV insertion), as well as before and after the drops of eye solution are delivered.

4.0 Study Endpoints (if applicable)

The effect on respiration will be recorded upon application of either the 3 drops of povidone-iodine ophthalmic solution or 3 drops of BSS in each eye. The presence of any respiratory effect – specifically a change in respiratory rate – will be the primary endpoint for this study. Changes in respiratory pattern will be detected and measured by observation of the capnograph, which measures breath by breath CO₂.^{13, 14} The capnograph is a standard monitor employed during the standard administration of general anesthesia.¹⁵

5.0 Inclusion and Exclusion Criteria/ Study Population

Operating room schedules will be screened the day prior to surgery and eligible candidates (their families) will be invited to participate in the study on the morning of surgery in the preoperative holding area. The primary reason for including children is that strabismus is normally corrected during childhood and strabismus surgery is of importance because, as was mentioned previously, the oculo cardiac reflex has been known to occur with strabismus surgery.

Inclusion Criteria

- *Children 17 years and less*
- *Scheduled for strabismus surgery*
- *Anesthesia plan includes inhalational induction with sevoflurane and the use of a laryngeal mask airway (LMA) with spontaneous ventilation, per the attending anesthesiologist.*

Exclusion Criteria

- *History of an adverse reaction to iodine*
- *History of any thyroid disease*
- *Patients who require tracheal intubation, as determined by the attending anesthesiologist; e.g. craniofacial anomalies.*
- *Patients with a contraindication to sevoflurane, such as malignant hyperthermia or severe left ventricular dysfunction.*
- *Inability or unwillingness of the subject or legal guardian/ representative to give informed consent.*

6.0 Number of Subjects

We will enroll approximately 110 patients in this study to include 55 patients for each randomized ‘treatment’ group. Please refer to section 12.0 for the justification behind this enrollment number.

7.0 Setting

This study will be conducted solely in the perioperative areas of MUSC.

8.0 Recruitment Methods

The surgical schedule will be reviewed by a member of the study team on the day prior to surgery to identify patients undergoing strabismus surgery. A chart review will be performed to ensure that they fall under proper inclusion criteria. Furthermore, the study team will contact the attending anesthesiologist who will be working the potential study candidate’s case to make sure the anesthesia plan does not exclude the patient from the study. Patients will be approached on the morning of surgery in the preoperative holding area of MUSC by a study team member and the consent process will proceed.

9.0 Consent Process

Upon approaching the patient in the perioperative holding area of MUSC, the study will be thoroughly explained to the patient (if old enough to comprehend), as well as the family of the patient. The consent and HIPAA forms will be presented and explained and the family will be given the opportunity and time to read through the forms. Any questions they might have about the study or either of the forms will be answered by the study member and/or the attending anesthesiologist. The parents or guardian(s) will then be asked to sign the consent form, as the patients will be under the age of 18. If they patient

is over the age of 12, they will also be asked to give assent for study participation and the proper form for this will be presented to them and explained prior to obtaining their signature.

10.0 Study Design / Methods

Once it is confirmed that the attending anesthesiologist has both examined the patient and decided on an anesthesia plan that aligns with our inclusion criteria, the patient and their family will be consented. If the patient is included in the study, the study member will randomize the patient to one of two groups: Group A - povidone-iodine ophthalmic solution, or Group B - ophthalmic balanced salt solution. This randomization will be determined using a simple randomization scheme provided by the study's statistician. All decisions regarding anesthesia care, including the indication for preoperative pharmacologic anxiolysis, will be made by the attending pediatric anesthesiologist. The case will then progress as it would without study involvement and the patient would be brought into the operating room and anesthesia would be administered. The standard of care course of anesthesia includes:

- Inhalation induction with oxygen in sevoflurane
- Insertion of a peripheral intravenous catheter after induction of anesthesia
- After a suitable depth of anesthesia is achieved, a laryngeal mask airway of an appropriate size will be inserted and secured

The only deviation from standard of care during the above process is the collection of data after induction, just prior to IV insertion. These data points are heart rate (HR), blood pressure (BP), respiratory rate (RR), arterial oxygen saturation (SaO₂), end tidal CO₂ (ETCO₂), inspiratory sevoflurane (InspSevo), and expiratory sevoflurane (ExpSevo). This data will be collected by a study member in real, intraoperative time. The collection of data will not affect the progression of standard anesthesia practice, as the data collector will not be involved in the clinical care of the patient. Once the airway is secured and the patient has reached a steady state of anesthesia, the main study intervention will then commence. We first would like to obtain the patient's average peak to peak interval for respiration at this steady state of anesthesia, as measured from the capnography. To do this, the research member in the room for data collection will use the iPhone stopwatch application and its 'lap button' feature to collect the respiration peak intervals (in seconds)

for 5 breaths. Specifically, at the patient's peak inspiration (as seen on the capnography), the study member will start the stopwatch and proceed to hit the 'lap' button for the next 5 consecutive inspiration peaks. These data intervals will be recorded on the data sheet after the 5 breaths are over, as the intervals are conveniently stored and numbered below the stopwatch in the app. We will do this to establish an average baseline respiratory rate for each individual patient. Next, patients who are randomized to Group A will receive three drops of povidone-iodine ophthalmic solution in each eye, with the right eye to receive the drops first. Group B will receive three drops in each eye of ophthalmic balanced salt solution. Similarly, the right eye will receive the drops first; the reason being that we know that there are differences in sympathetic stimulation on the right side of the face vs left (e.g. termination of supraventricular tachycardia) and although we don't know if this effects OCR, we chose to standardize right eye first. The eye drops will be administered by the study anesthesiologist. After application of either solution to the eyes of the patient, any change in ventilation can be detected and timed by observation of the capnography (end-tidal carbon dioxide) and direct observation of the chest wall with use of the iPhone stopwatch feature again. The capnograph is a standard monitor of respiration used during the administration of general anesthesia. Data collected at this time will include whether or not there was a change in respiration, what this change in respiration was, if assisted ventilation was required, how long assisted ventilation was required (if applicable), HR, BP, RR, SaO₂, ETCO₂, InspSevo, and ExpSevo. This study intervention and data collection will take less than 5 minutes and the surgical team will then progress with the case as they normally would.

Other data to be collected is as follows:

- Attending anesthesiologist and CRNA
- Age
- Weight
- Sex
- Co-existing diseases
- If the patient was a pre-term birth and if yes, the estimated gestational age at birth
- If premedication was given and if yes, what medication and dose
- If N₂O was used during inhalational induction

12.0 Data Management

Descriptive statistics by treatment group will be evaluated for all demographic and procedural characteristics. The goal of the study is to determine if there is a significant difference in the change in respiratory response immediately following administration of saline or povidone-iodine solution in patients undergoing strabismus surgery. The primary outcome is the difference between the peak to peak interval time from the capnograph measured before saline or povidone-iodine administration versus after administration. Pre-exposure peak to peak interval will be measured as the average time between peaks for five breaths prior to administration. Post-exposure peak to peak interval will only be evaluated as the time between the two peaks at saline or povidone-iodine administration. Differences in the change in peak to peak interval time between the saline and povidone-iodine exposure groups will be evaluated using a linear regression approach. The model will include a treatment effect and will additionally control for patient age, history of prematurity, and use of any pre-medication to account for other factors thought to be associated with respiratory rate. We anticipate no change in peak to peak interval time in the saline group with variability of ± 4 seconds. A sample size of 50 patients per treatment group (100 patients total) provides $>80\%$ power to detect an increase in change in peak to peak interval of 2.5 seconds in the povidone-iodine group compared to the saline group assuming equal variance between the two groups using a 2-sided test with significance level set at $\alpha = 0.05$. If the variability of the povidone-iodine group is larger, for example a variability of 8 seconds, compared to 4 seconds in the saline groups we still have 80% power to detect an increase in the povidone-iodine group of approximately 4 seconds.

Several steps will be taken to ensure that the data collected for this study remains secure for the sake of the confidentiality of the patients enrolled. All study members are CITI certified and the anesthesia research staff have received Core Clinical Research Training (CCRT). Any data collected on the physical data sheet will not contain identifiers, but will rather contain the study ID number which is connected with patient identifiers on the study enrollment log saved on the secure research server. All data sheets are kept in a locked cabinet in the locked research office and all electronic data is stored in the study's secure REDcap database. All data will remain in the confines of MUSC and will be brought down for storage in the research office promptly after data collection.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

The Department of Anesthesia's Data Safety and Monitoring Board (DSMB) will review this study biannually. Any adverse events will be reported to the DSMB and IRB per policies in place. The members of the DSMB for the Department of Anesthesia and Perioperative Medicine are Drs. Jerry Reves, John Waller, and Fred Guidry. These physicians are professors at MUSC who have engaged in clinical research throughout their careers.

14.0 Withdrawal of Subjects (if applicable)

Subjects will be withdrawn from the study if any changes need to be made to the anesthesia plan that do not align with the inclusion/ exclusion criteria of the study; e.g. if any airway intervention other than an LMA is required at the start of surgery.

15.0 Risks to Subjects

The risks to the subjects are minimal. The anesthetics will be standard of care and the BSS and povidone-iodine ophthalmic solutions are commonly used eye surgery solutions that are safe for the application to the ocular surface in the manner in which we propose, as deemed by the FDA. These solutions are routinely used during strabismus surgery. As stated previously, the duration of the study intervention is very brief (seconds, to 4 minutes) and will cause minimal, if any, delay in the surgical procedure. If apnea becomes significant (e.g. arterial oxygenation saturation less than 94%, as measured by pulse oximetry), assisted or controlled ventilation is very easily provided via the LMA to counteract the apnea.

There is a risk of loss of confidentiality, but the anesthesia research team has safeguards in place for keeping patient health information secure and only accessed when absolutely necessary. All data will be stored on a secure server and consent and data forms will be held in a locked cabinet in a locked research office.

Though it is a randomized study, there is not a risk of randomization because neither of the possible groups poses any additional risk to the participants.

16.0 Potential Benefits to Subjects or Others

There is no direct benefit to participants by being enrolled in this research study, but the information gained from completing this study may enable pediatric anesthesiologists to predict when respiratory changes may occur during the course of strabismus surgery. Subsequent studies, based on the findings of this study may determine whether pretreatment with glycopyrrolate or atropine may attenuate or prevent changes in respiration.

17.0 Sharing of Results with Subjects

There are no plans to share the results with the subjects or their families. If, however, the patient or family requests such information, it shall be provided after completion of the study.

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