TITLE: Effect of Dexmedetomidine of Gastrointestinal Motility

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Boston Children's Hospital

CHeRP IRB Additional Protocol Information:

In addition to the CHeRP SmartForms, all protocols must include the following sections. If a section is not applicable for the current protocol please indicate why this is the case. Please note that a complete protocol consists of the CHeRP forms and the information provided in this form.*

TITLE: Effect of Dexmedetomidine of Gastrointestinal motility

A. Specific Aims/Objectives

Primary objective: To examine the effects of dexmedetomidine on intra-anal pressure and the dose response curve to balloon distention by comparing the baseline measurements with those after dexmedetomidine administration.

Dexmedetomidine is an alpha-2 agonist that is considered to be a smooth muscle relaxant. It's a potential use as a sedative for endoscopies has been considered. It is important to know whether or not it has effect on smooth muscle tone and would affect manometry studies in those patients who could receive it. We hypothesize that dexmedetomidine will have minimal effects in the dosing that we are administering.

B. Background and Significance

Anorectal manometry requires that the patient be able to respond to command and not receive any medications which could alter muscle tone or motility. These patients typically have the manometry performed without any adjuvant sedatives, anesthetics or medications. In the pediatric population, anorectal manometry can be psychologically challenging to parents and their child, particularly without adjuvant sedation or anesthesia. There are some exceptional circumstances which require sedation/anesthesia administration for these procedures, either because the children are young (< 5 years), they have behavioral issues (like autism) or because they have severe anxiety. In those patients with severe issues even general anesthesia may be needed. The risk of administering any medication to these patients is that they can alter motility and smooth muscle activity, consequently artificially altering the results of the anal manometry. It is important to know which medications can be administered without affecting anal muscle tone. Dexmedetomidine is a newer sedative and anxiolytic. It could be valuable for anxiolysis for anal manometry. Its effect on anal smooth muscle, however, has never been studied. It would be important to determine whether it spares smooth muscle function, as it would provide a viable option to provide sedation to children while still preserving their ability to respond to command.

Dexmedetomidine is one of the standard drugs administered for sedation in children who require sedation for diagnostic (gastroendoscopic upper and lower procedures) and radiologic diagnostic imaging studies (MRI, CT and Nuclear Medicine). Over 17,000 infants, children and developmentally compromised young adults have been sedated with dexmedetomidine at Boston Children's Hospital without a cardiac or respiratory arrest, or a need to provide positive pressure assisted ventilation.

C. Preliminary Studies

There are currently no preliminary studies available on the effects of dexmedetomidine gastrointestinal motility and manometry in children.

D. Design and Methods

(1) Study Design

This is a prospective, open label, interventional study.

(2) Patient Selection and Inclusion/Exclusion Criteria

Inclusion Criteria

- Ages 3-18 years who are scheduled to have an anorectal manometry followed by a gastrointestinal procedure in the Gastroenterology Procedure Unit (GPU)at Boston Children's Hospital
- Patients are cooperative to do the anorectal manometry without sedation (with the exception of pre-med midazolam)
- Anticipates to receive standard sedation with dexmedetomidine and propofol for a gastrointestinal procedure in the GPU
- Provides written consent to participate in the research study
- In females of reproductive age, pregnancy testing (carried out per routine clinical care by the anesthesia department) must be negative.

Exclusion Criteria

- Do not meet established sedation criteria
- Patients who require sedation prior to their anal manometry testing (with the exception of pre-med midazolam)
- History of allergy, intolerance, or reaction to dexmedetomidine
- Current, repaired or risk of Moya-Moya disease
- Recent stroke (cerebrovascular accident) within past 6 months
- Uncontrolled hypertension
- Concomitant use of opioids, beta antagonist, alpha 2 agonist or calcium channel blocker
- BMI greater than 30 or weight above 110th percentile
- Refuses insertion of intravenous catheter while awake
- Currently receiving pharmacologic agents for hypertension or cardiac disease
- Currently receiving or has received digoxin within the past 3 months
- Active, uncontrolled gastroesophageal reflux (an aspiration risk), requiring endotracheal intubation.
- Current (or within past 3 months) history of apnea requiring an apnea monitor
- Unstable cardiac status (life threatening arrhythmias, abnormal cardiac anatomy, significant cardiac dysfunction)
- Craniofacial anomaly, which could make it difficult to effectively establish a mask airway for positive pressure ventilation if needed

- Active, current respiratory issues that are different from the baseline status (pneumonia, exacerbation of asthma, bronchiolitis, respiratory syncytial virus).

Methods

As part of standard of care, patients will undergo the usual anal manometry study prior to any anesthetic or sedative administration. Pre-med midazolam may be administered at the discretion of the clinical care team. Once manometry measurements are completed, the anesthesiologist will administer a single dose of dexmedetomidine. The research team and clinical care team will observe and record any changes in manometry. After these measurements are collected, the anesthesiologist will continue standard anesthesia maintenance with propofol and dexmedetomidine per approved protocol for children undergoing gastrointestinal procedures requiring sedation.

As it is routine in these cases, subjects will have an intravenous catheter inserted pre-induction and standard of care anesthesia monitor (pulse oximetry, heart rate, ECG, NIBP, capnography via nasal cannula) applied and monitored prior to induction (in the GI suite).

Table 1. Data Elements to be Collected

Age
Height
Weight
Body Mass Index (BMI)
Sex
ASA status
NPO status
Current Medication list
Primary diagnosis
Coexisting diagnoses
Procedure(s) performed
Sedation start and end time
Time of dexemedetomidine administration
Ramsay sedation scale
UMSS sedation scale

Recruitment Methods

i. HOW, WHERE and WHEN will potential subjects be recruited?

All outpatients who are scheduled for anorectal manometry followed by upper or lower endoscopy will be screened for eligibility to participate in the study.

- Patients that are new to Dr. Nurko will learn about the study during their pre-procedure clinic visit with Dr. Nurko.
- Patients that have already seen Dr. Nurko in the past and do not have a pre-procedure appointment will be emailed or mailed information about the study (consent form, brochure, and cover letter). A member of the research team will then contact the

families via telephone to discuss the study in further detail and answer any questions families may have.

- Add-on patients will be approached by a member of the research team in pre-op holding.

All families will be given ample time to decide if they would like to participate in the study, if families need more time to make a decision the research team will coordinate a time to call the family back. The consent form will be signed by the parent or patient if the patient is older than 18 years of age (and assent given by the child where appropriate).

ii. WHAT recruitment methods and materials (e.g. posters, fliers) will be used?

The consent form along with an informational brochure containing a brief description of the study will be distributed via secure email or traditional mail in advance to subjects that do not have a pre-procedure clinic visit.

iii. WHO will be responsible for subject recruitment?

Subject recruitment will be and the responsibility of designated members of the research team working within Dr. Nurko and/or the Department of Anesthesiology.

(3) Description of Study Treatments or Exposures/Predictors

Intravenous catheters will be initiated as per standard clinical protocol in gastrointestinal endoscopy unit. Patients may also choose not to have any adjuvant local anesthesia prior to initiation of intravenous access. All patients will have baseline vital signs (already described) documented prior to induction. Those undergoing upper endoscopy will have 2 sprays of Cetacaine to posterior oropharynx prior to induction as part of standard clinical care. All patients will receive 4 L of supplemental oxygen by nasal cannula throughout the procedure.

Participation in this study involves an additional 15 minutes of manometry testing as well as 15 minutes of additional sedation in addition to what is clinically indicated.

Anorectal manometry

Patients will fast the night before. All patients receive the administration of a phosphate enema the night prior to the procedure. With the patient in the left lateral position, after lubrication the high resolution anorectal manometry probe will be gently inserted into the anal canal. It will slowly advance until the upper and lower borders of the high intra-anal-pressure zone are identified. The probe is held manually in place throughout the study.

Once the probe is in place, a resting period of at least 90 seconds is allowed until the patients are conformable and relaxed. The high-pressure zone is identified, and thirty seconds of resting pressures is obtained. To evaluate conscious sensation, the balloon is rapidly inflated and deflated with serial volumes of 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, and 180 ml. The balloon inflations are achieved with a 60 mL syringe that was connected to the probe via

stopcock that allows the administration of increasing balloon volumes. Threshold of sensation (minimum balloon volume that could be felt in 2 of 3 trials) is identified. The patients are then instructed to squeeze. Their ability to squeeze is determined and the squeeze pressure characteristics are recorded. To evaluate the recto-anal inhibitory reflex (RAIR) the balloon is again rapidly inflated and deflated with series of volumes mentioned previously and a full dose response curve is obtained.

After the baseline ARM is completed, the catheter will remain in place. The research team will confirm with the subject that they are still interested in participating in the additional 15 minutes of anal manometry testing. If subjects meet any of the following criteria, then the study will not proceed:

- Child verbalizes they no longer want to participate
- Child is visibly distressed after clinical manometry
- Parent expresses desire to not proceed
- Clinical care team does not agree to move forward

Once the subject has confirmed it is ok to proceed, dexmedetomidine will be administered as detailed below. The intra-anal pressure will be continuously measured through administration of DEX until 15 minutes following administration. This is the experimental portion of the present study.

Manometry associated with Lower endoscopy procedure:

Patients will undergo the usual anal manometry study, with no adjuvant medications, per routine practice currently in the gastrointestinal unit. Following completion of manometry, 0.5 mcg/kg DEX will be administered over 1 minute followed by an infusion of 0.15 mcg/kg/hr. Manometry measurements will be followed for 15 minutes in response to DEX. Following completion of research manometry, patients will resume the standard of care and receive propofol at the discretion of the anesthesiologist.

Manometry associated with Upper endoscopy procedure:

Patients presenting for upper gastrointestinal endoscopy with manometry, will receive a routine anesthetic with intravenous propofol (bolus and infusion) and endotracheal intubation (at the discretion of the anesthesiologist). Propofol will be administered and used for maintenance of the anesthetic.. If necessary for endotracheal intubation and to minimize aspiration risk, neuromuscular blockade will be administered. Following completion of the manometry, dexmedetomidine will be administered per above protocol (same as used for the anal manometry) for the remainder of the anesthetic. Manometry will be measured in response to dexmedetomidine and followed for 15 minutes.

No narcotics, no benzodiazepines and no dexamethasone will be administered during the anesthetic management for either group.

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(4) Definition of Primary and Secondary Outcomes/Endpoints

Primary outcome: To examine the effects of dexmedetomidine on intra-anal pressure and the dose response curve to balloon distention by comparing the baseline measurements with those after dexmedetomidine administration. The pressure measurements will be recorded by the

research team member who will be present, every 30 seconds starting from 5 minutes prior to DEX to 15 minutes following DEX administration.

(5) Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)

Manometry Data Collection for Analysis:

- Analysis of the high-resolution manometry will be done in a blind manner.
- The anal verge is defined as the most distal and the rectum as the most proximal part of the anal canal. The manometry probe allows a standard high-resolution visualization of the anal canal. The high-pressure zone (HPZ) of the anal canal at rest will be determined. Intra-anal pressure will be measured at each balloon inflation, and the percent anal relaxation at each inflation will be determined, and a dose response for the relaxation will be determined.

(6) Study Timeline (as applicable)

We plan to enroll 25 subjects for this study at Boston Children's Hospital. We anticipate that this study will take up to 1 year to complete.

E. Adverse Event Criteria and Reporting Procedures

All adverse events will be reported to the Radiology and Hospital Sedation Committee. These events will be reviewed by an Independent Committee set up by the Department of Anesthesia and will be reported to the IRB by this Committee as appropriate. According to the recommendations laid out in the Safety Reporting Requirements for INDs and BA/BE Studies guide, adverse events that are both serious and unexpected, associated with the use of the drug will be reported to the FDA. According to 21 CFR 312.32, an "adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect."

Subjects/parents may opt to remove themselves/their child from the study at any point in time.

F. Data Management Methods

Patient demographic, adverse events and motility data will be entered into an InForm database and then exported into the SAS system for statistical analysis (version 9.4, SAS Institute, Cary, NC).

G. Quality Control Method

To ensure that data will be of the highest quality and accuracy, research team personnel will routinely check and monitor data entry, missing data, and any inconsistencies.

H. Data Analysis Plan

Data will be analyzed after the completion of the study. The manometry measurements will be done blindly by one of the investigators.

Summary statistics for continuous variables and frequency counts for categorical variables will be calculated. Appropriate statistical testing will be performed where applicable.

I. Statistical Power and Sample Considerations

The study was powered and sample size calculated assuming a mean intra-anal pressure of 90 mmHg, with a mean reduction to 65 mmHg, and a standard deviation of 32. With a significance level of 0.05, it would require approximately 15 subjects to achieve power of 80.3%.

J. Study Organization

The principal investigator for this study is Dr. Keira Mason from the Department of Anesthesia, Perioperative and Pain Medicine at Boston Children's Hospital. The co-PI is Dr. Samuel Nurko, Director of the Center for Motility and Functional Gastrointestinal Disorders at BCH. Collaborators will be Drs. Chineyere Egbuta, Ray Park, Karen Boretsky and Cornelius Sullivan. The Pediatric Anesthesia Research Center will provide research staff support in the form of research nurses and/or research assistants.

K. Data and Safety Monitoring Plan

Dr. Mason, Dr. Nurko, and approved members of the research team will be responsible for all data and safety monitoring. An independent data monitor will also be part of this group. Data and safety monitoring will be reviewed every 3-6 months or more frequently if a specific problem is identified. Data and safety monitoring will be performed after every patient if a serious side effect has been noted and no more patients will be recruited, enrolled or studied until the cause been thoroughly investigated. If, after careful review by the data and safety monitor, there is a probability that the study might have caused or contributed to the serious reaction, then this will be reported to the IRB and the study halted until a risk/benefit assessment can be made.

L. Risks and Discomforts

The common side effects from dexmedetomidine are similar to other anesthetics, which include an increase or decrease in heart rate, an increase or decrease in blood pressure, a slower breathing rate and dry mouth. Serious, rare adverse events that have occurred with dexmedetomidine include anaphylaxis and sinus arrest (heart stops sending the electrical impulses that signal it to beat). Study patients will be monitored at all times by an anesthesiologist.

There are limited studies for administering dexmedetomidine to pediatric patients; however, these studies have shown dexmedetomidine to be a safe and effective agent with beneficial effects.

M. Potential Benefits

By receiving dexmedetomidine, there is the potential to reduce irritability that the participant may have while waking up, decrease the amount of pain medication that is needed, and decrease the amount of other sedation medications.

N. Privacy Provisions

Access to the electronic database will be restricted to IRB approved study staff and will be password protected. Study folders will be maintained by the study team and be stored in a lock cabinet within a locked office.

O. Confidentiality Provisions

The privacy of the study subjects will be maintained. Only the investigators and IRB approved members of the study team will know the identity of the subject whose data is being analyzed. Prior to analysis, all HIPAA identifiers will be removed. Data will be stored securely in a locked cabinet in a locked office. Research subject identifiers will be removed, linked or destroyed as soon as possible. The only document that contains a link to the identity of subjects will be kept securely in a locked cabinet in a locked office.

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