Title: The Synergistic Effect of Dexmedetomidine on Propofol for Sedation for Pediatric Endoscopy

PI: Keira Mason MD

NCT#: 02952222

Version Date: 05/25/2018

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: The Synergistic Effect of Dexmedetomidine on Propofol for Sedation for Pediatric Endoscopy

Propofol is a sedative that is currently being used for sedation of children for upper and lower endoscopic studies in Boston Children's Hospital. Dexmedetomidine is another sedative that is currently being used for sedation in BCH in the ICU and in radiology. Dexmedetomidine is a selective alpha-2 agonist, and one advantage in using dexmedetomidine is the lack of respiratory depression that is frequently seen in other sedatives.

It has been shown that with concomitant use, dexmedetomidine reduced the need for higher doses of anesthetics (Aantaa, 1990; Rao 2014), opioids (Gurbet, 2006; Pestieau, 2011), sedatives (Le Guen, 2014) and neuromuscular block agents (Memis, 2008). In adults, dexmedetomidine decreased propofol requirements for maintenance of optimum depth of anaesthesia during elective spine surgery (Sen, 2013).

In children, dexmedetomidine reduced the dose of analgesics (Al-Zaben, 2010). Dexmedetomidine also reduced propofol requirements during bispectral index-guided closed-loop anesthesia in adults (Le Guen, 2014).

This study will compare the propofol requirements of children who receive propofol with that of children who receive dexmedetomidine prior to propofol, for sedation for upper and lower endoscopic procedures.

This study will also compare adverse events and other markers of outcomes between the two groups. Adverse event capture will begin at the time of the first study-related procedure and continue through until the time at which a phone call will be attempted to the patient/parent in the first business day following the procedure. Adverse events are consider any untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related. These are summarized in section E.

A. Specific Aims/Objectives

Primary objective: To compare the propofol requirements (mg/kg) of children who receive intravenous propofol with pre-treatment of dexmedetomidine with those of children who do not receive dexmedetomidine.

Secondary objective: To compare the frequency of adverse events and the need for airway interventions during the sedation and the recovery period in patients who received dexmedetomidine prior to propofol versus patients who received propofol only

To compare propofol to dexmedetomidine with respect to:

-Time required to achieve sedation
- Need for supplemental sedation during the imaging study
- Time required to meet discharge criteria from recovery room
- Adverse events
- Need for unplanned airway interventions

- Duration of the sedation, need for supplemental doses of medication
- Emergence Delirium (PAED score)
- Return of BIS score to baseline (pre-sedation level) in recovery room

B. Background and Significance

Both propofol and dexmedetomidine may be used to achieve adequate sedation conditions. Propofol has been described to produce successful conditions for completion of the intended study in almost 99% of the patients. However, in a study that reviewed outcomes when using propofol for almost 50,000 pediatric procedures, propofol was associated with stridor, laryngospasm, airway obstruction, wheezing or central apnea at a rate of 1 in 65 sedations. The need for airway and ventilation interventions which include oral/nasal airway placement, positive pressure mask ventilation and tracheal intubation occurred at a rate of 1 in 70 sedations. Hemodynamic and respiratory fluctuations of a minimum of 30% fluctuations in heart rate, blood pressure or respiratory rate occurred at a rate of 1 in 165 sedations. Another recent study cited similar incidences of hemodynamic variability with propofol as well as inhalational anesthesia in the outpatient pediatric setting.

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

This study will determine if administration of dexmedetomidine with propofol administration will result in lower doses of the latter, which may mean safer outcomes in sedation for upper and lower endoscopic procedures.

C. Preliminary Studies

There are currently no preliminary studies available on the synergy of dexmedetomidine with propofol administration in comparison to propofol only for pediatric endoscopy.

D. Design and Methods

(1) Study Design

This is a prospective, open label, randomized study.

(2) Patient Selection and Inclusion/Exclusion Criteria

Inclusion Criteria

- Ages 7-18 years who are scheduled for upper or lower endoscopic procedures at Boston Children's Hospital and meets criteria to receive dexmedetomidine or propofol sedation for upper and lower endoscopic procedures
- 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
- Refuses administration of study medication prior to sedation
- History of allergy, intolerance, or reaction to dexmedetomidine or propofol or hypersensitivity
- 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
- Egg, soy or lecithin allergy
- 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
- 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

Patients in both endoscopy groups will be randomized to two equal treatment groups: those who will receive dexmedetomidine with propofol (DP) and those who will receive propofol only (P).

All groups will have an intravenous catheter inserted pre-induction, bi-spectral (BIS) monitor, 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
No premedication anxiolytics will be administered.

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 time
Sedation end time
Time in which patients meets discharge criteria

Table 2. Airway Management Interventions

Endotracheal tube
Jaw thrust
Laryngeal mask airway
Nasotracheal tube
Oral/Nasal-pharyngeal airway
O_2 mask increase in O_2 flow via nasal cannula
Bag- mask ventilation
Repositioning of head
Suction
Elevation of shoulders with a shoulder roll in order to achieve neck extension

Recruitment Methods

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

All outpatients who are scheduled for sedation for upper or lower endoscopy will be screened for eligibility to participate in the study. The consent form will be mailed to potential families of eligible patients for review up to 2 weeks prior to being contacted by telephone to discuss the study in further detail and answer any questions families may have. All families will then be given ample time to decide if they would like to participate in the study and verbal consent will be obtained at least 24 hours prior to the scheduled hospital visit. All families will also be given ample time to read the consent form on arrival to the department prior to giving written consent. 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) on the day of the scheduled study after any additional questions are answered. A follow-up phone call will also be attempted the first business day after the procedure to identify if any adverse events have taken place post discharge and also to answer any additional questions parents may have post study participation. If the family is not able to be reached, an additional phone call will be made within the first week following the procedure. If possible, a voicemail will be left. If not returned, a second call will be attempted within 1 week of the procedure. Parents will also be given a direct phone number to the research team in the event that they have any questions or concerns.

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

The consent form along with an informational brochure containing a brief description of the study will be distributed in advance to all potential study candidates.

iii. WHO will be responsible for subject recruitment?

Subject recruitment will be and the responsibility of designated members of the research team working within 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.

Patients who are randomized into the **Dexmedetomidine Group (DP)**

Patients in Group DP will receive 0.5 mcg/kg DEX administered over 1 minute followed by an infusion of 0.15 mcg/kg/hr. Following the 0.5 mcg/kg DEX bolus, propofol will be administered with the identical protocol (with same endpoint of BIS 40-50) of the P Group. Propofol infusion will be started at 200 mcg/kg/min and will be titrated throughout the procedure to maintain a BIS 40-50, up to a maximum of 350 mcg/kg/min. Propofol may be administered prn in 10-20 mg increments for any abrupt patient movement which may compromise the continuity of the procedure. Ondansetron (Zofran) 0.1 mg/kg IV will be administered after induction. The DEX infusion in the DP group will remain constant throughout the procedure, and will be discontinued at the termination of the procedure, simultaneous with the discontinuation of the propofol infusion. For both Group P and DP, the propofol infusion will remain until the termination of the procedure. At termination of procedure, monitors will remain and patient will be transported to recovery room for continuation of monitoring as indicated below.

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

Patients undergoing a lower endoscopy after a bowel prep, will receive a goal of 20 mL/kg saline prior to termination of procedure.

Patients who are randomized into the **Propofol Group** (Group P)
Patients in Group P will receive intravenous propofol in bolus increments (1.0 to 2.0 mg/kg bolus over one minute then 0.5 mg/kg bolus q 1 minute titrated to a BIS of 40-50). Ondansetron (Zofran) 0.1 mg/kg IV will be administered after induction. These patients will be maintained with a continuous intravenous infusion of propofol starting at 200 mcg/kg/min and will be

titrated to an endpoint of maintaining a BIS level of 40-50, up to a maximum of 350 mcg/kg/min. Propofol may be administered prn in 10-20 mg increments for any abrupt patient movement which may compromise the continuity of the procedure

If any member of the child's care team, at any time for any reason, believes the patient should be taken off the study, participating in the study will end immediately and the child's care will continue at the discretion of the anesthesiologist. Additionally, an inability to perform procedure because of inadequate sedation administered following this protocol will result in the child being withdrawn from the study. Additionally, if there is a need for pharmacologic intervention for respiratory or hemodynamic instability and the patient receives cardiovascular resuscitation with the AHA's Pediatric Advanced Life Support protocol, they will immediately be taken off the study and care will continue at the discretion of the anesthesiologist. If the unanticipated need for endotracheal intubation or an inhalation-based general anesthetic (which may be related to the procedure as well as to the sedation) arises, the child will be taken off the study and care will continue at the discretion of the anesthesiologist.

If any one patient experiences a sentinel event, as described in Figure 1, the study will immediately be stopped. Appropriate reports will be made to the IRB and FDA. If more than 5 patients in any one group require a bag mask valve, an oral/nasal airway or CPAP, the study will also be stopped and the FDA and IRB will be notified. In addition, if more than 5 patients require two or more weight-based IV fluid boluses following hemodynamic changes, the study will be stopped and the FDA and IRB will be notified.

(4) Definition of Primary and Secondary Outcomes/Endpoints

The primary outcomes will be: Dosage/consumption of propofol (mg/kg) in children who receive intravenous propofol with pre-treatment of dexmedetomidine to the consumption of children who do not receive dexmedetomidine.

The Secondary outcomes will be:
-Time required to achieve sedation
- Need for supplemental sedation during the imaging study
- Time required to meet discharge criteria from recovery room
- Incedence of adverse events (defined in Figure 1)
- Need for unplanned airway interventions
- Duration of the sedation, need for supplemental doses of medication
- Incidence of Emergence Delirium (PAED score)
- Time of BIS score to return baseline (pre-sedation level) in recovery room

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

- Data points as outlined in table 1.
- Ramsay Sedation Score (RSS)-at termination of initial dexmedetomidine or propofol bolus, on arrival to recovery room, and every fifteen minutes after arrival in recovery room until discharged home

- University of Michigan Sedation Score (UMSS)- at termination of initial dexmedetomidine or propofol bolus, on arrival to recovery room, and every fifteen minutes after arrival in recovery room until discharged home
- Time to meet baseline BIS (pre-sedation level) in the recovery room.
- Time to meet modified Aldrete discharge criteria (current standard)- measured in minutes from the time at which the infusion discontinued to the time at which the patient achieves a minimum Aldrete score of 9
- Occurrence of Failed Sedation: Defined as a Failure to sedate with designated protocols.
- The occurrence of any adverse events (Table 2) and the need for supplemental airway interventions (Table 3) will be documented
- Heart Rate (HR), Oxygen Saturation (O_2 sat), Respiratory Rate (RR), Non Invasive Blood Pressure Monitoring (NIBP) (systolic, diastolic and Mean Arterial Blood Pressure/MAP) will be measured and documented via computerized record keeping prior to receiving sedation, every 5 minutes after the initiation of the dexmedetomidine or propofol bolus and throughout the infusion period, then every 5 minutes in recovery room until the patient meets discharge criteria (modified Aldrete score of 9 or greater), after which these parameters will be measured at 15 minute intervals until the patient leaves the recovery room. Any deviation in blood pressure outside of the 20% accepted norms, will be treated with 20% 0.9 NS fluid boluses (to a maximum of two fluid boluses). Deviations in heart rate are not considered by the Hospital or Radiology Sedation Committee as adverse events and are not treated unless there is a concurrent instability in blood pressure, perfusion, electrocardiogram, pulse oximetry or capnography. The treatment of bradycardia in patients receiving dexmedetomidine with anticholinergics is discouraged because such treatment has previously resulted in extreme hypertension.
- Electrocardiogram will be monitored.
- An independent observer (designated member of the research team) will document adverse events and the need for airway interventions (Table 2 and 3).
- Hemodynamic and respiratory fluctuations will be identified from computerized documentation, (thus eliminating bias with respect to identifying fluctuations in blood pressure, heart rate and respiratory rate).
- PAED Score on arrival and q15min (or sooner if change of patient behavior) and immediately prior to discharge
- If the endoscopist remains blinded to the treatment at the end of the procedure, they will score the quality of sedation at the end of the case with the Adapted Dartmouth Operative Conditions Scale below (Chandran, 2017).

Table 1 Adapted Dartmouth Operative Conditions Scale

Pain/stress	(0) Eyes closed/calm expression	(1) Grimace/frown	(2) **Any vocalization** (Including any crying, sobbing, screaming)	
Movement	(0) Still	(1) Random little movement	(2) Major purposeful movement	(3) Thrashing/kicking **(Biting to be excluded when bite-guard is in place—intraprocedure)**
Consciousness	(0) Eyes open	(−1) Ptosis/uncoordinated/ drowsy	(−2) Eyes closed	
Sedation side effects	(−1) SpO_2 < 92%	(−1) Noise with respiration	(−1) Respiratory pauses >10 s	(−1) BP decreases >50% from baseline

The minor changes made to the original Dartmouth Operative Conditions Scale have been highlighted in bold. The scores given to each item is mentioned within brackets.

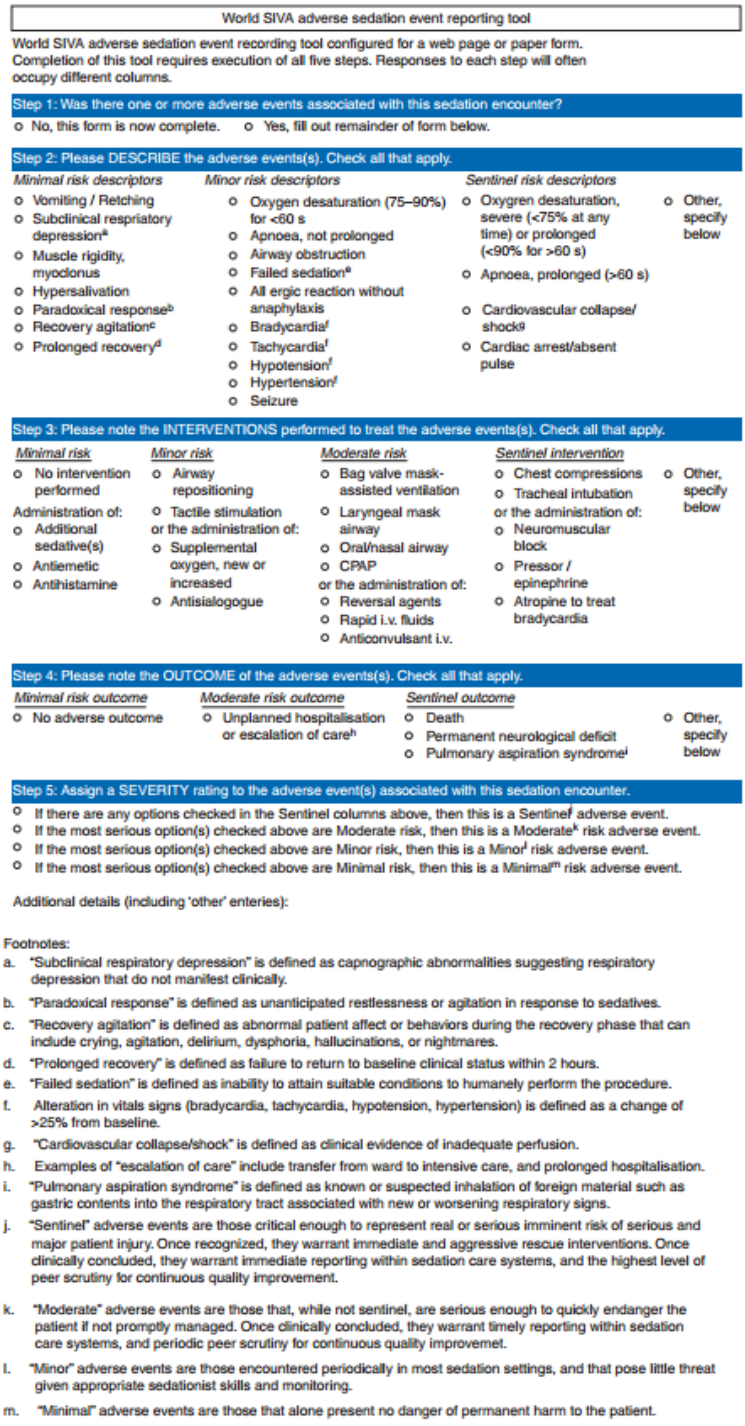
(6) Study Timeline (as applicable)

We plan to enroll 70 subjects for this study at Boston Children's Hospital. We anticipate that this study will take up to 2 years to complete. An interim analysis will be performed after 35 patients have been enrolled to review data and safety elements of the study and also to determine if patients have any obvious improvement in the DP group with a view to terminating the study early.

E. Adverse Event Criteria and Reporting Procedures

The World SIVA adverse sedation event reporting tool (Figure 1) will be used to document and track adverse events (Mason, 2012). 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.



World SIVA adverse sedation event reporting tool

World SIVA adverse sedation event recording tool configured for a web page or paper form. Completion of this tool requires execution of all five steps. Responses to each step will often occupy different columns.

Step 1: Was there one or more adverse events associated with this sedation encounter?

- o No, this form is now complete.
- o Yes, fill out remainder of form below.

Step 2: Please DESCRIBE the adverse events(s). Check all that apply.

Minimal risk descriptors
- o Vomiting / Retching
- o Subclinical respriatory depression[a]
- o Muscle rigidity, myoclonus
- o Hypersalivation
- o Paradoxical response[b]
- o Recovery agitation[c]
- o Prolonged recovery[d]

Minor risk descriptors
- o Oxygen desaturation (75–90%) for <60 s
- o Apnoea, not prolonged
- o Airway obstruction
- o Failed sedation[e]
- o All ergic reaction without anaphylaxis
- o Bradycardia[f]
- o Tachycardia[f]
- o Hypotension[f]
- o Hypertension[f]
- o Seizure

Sentinel risk descriptors
- o Oxygren desaturation, severe (<75% at any time) or prolonged (<90% for >60 s)
- o Apnoea, prolonged (>60 s)
- o Cardiovascular collapse/ shock[g]
- o Cardiac arrest/absent pulse
- o Other, specify below

Step 3: Please note the INTERVENTIONS performed to treat the adverse events(s). Check all that apply.

Minimal risk
- o No intervention performed

Administration of:
- o Additional sedative(s)
- o Antiemetic
- o Antihistamine

Minor risk
- o Airway repositioning
- o Tactile stimulation

or the administration of:
- o Supplemental oxygen, new or increased
- o Antisialogogue

Moderate risk
- o Bag valve mask-assisted ventilation
- o Laryngeal mask airway
- o Oral/nasal airway
- o CPAP

or the administration of:
- o Reversal agents
- o Rapid i.v. fluids
- o Anticonvulsant i.v.

Sentinel intervention
- o Chest compressions
- o Tracheal intubation

or the administration of:
- o Neuromuscular block
- o Pressor / epinephrine
- o Atropine to treat bradycardia
- o Other, specify below

Step 4: Please note the OUTCOME of the adverse events(s). Check all that apply.

Minimal risk outcome
- o No adverse outcome

Moderate risk outcome
- o Unplanned hospitalisation or escalation of care[h]

Sentinel outcome
- o Death
- o Permanent neurological deficit
- o Pulmonary aspiration syndrome[i]
- o Other, specify below

Step 5: Assign a SEVERITY rating to the adverse event(s) associated with this sedation encounter.

- o If there are any options checked in the Sentinel columns above, then this is a Sentinel[j] adverse event.
- o If the most serious option(s) checked above are Moderate risk, then this is a Moderate[k] risk adverse event.
- o If the most serious option(s) checked above are Minor risk, then this is a Minor[l] risk adverse event.
- o If the most serious option(s) checked above are Minimal risk, then this is a Minimal[m] risk adverse event.

Additional details (including 'other' enteries):

Footnotes:

a. "Subclinical respiratory depression" is defined as capnographic abnormalities suggesting respiratory depression that do not manifest clinically.

b. "Paradoxical response" is defined as unanticipated restlessness or agitation in response to sedatives.

c. "Recovery agitation" is defined as abnormal patient affect or behaviors during the recovery phase that can include crying, agitation, delirium, dysphoria, hallucinations, or nightmares.

d. "Prolonged recovery" is defined as failure to return to baseline clinical status within 2 hours.

e. "Failed sedation" is defined as inability to attain suitable conditions to humanely perform the procedure.

f. Alteration in vitals signs (bradycardia, tachycardia, hypotension, hypertension) is defined as a change of >25% from baseline.

g. "Cardiovascular collapse/shock" is defined as clinical evidence of inadequate perfusion.

h. Examples of "escalation of care" include transfer from ward to intensive care, and prolonged hospitalisation.

i. "Pulmonary aspiration syndrome" is defined as known or suspected inhalation of foreign material such as gastric contents into the respiratory tract associated with new or worsening respiratory signs.

j. "Sentinel" adverse events are those critical enough to represent real or serious imminent risk of serious and major patient injury. Once recognized, they warrant immediate and aggressive rescue interventions. Once clinically concluded, they warrant immediate reporting within sedation care systems, and the highest level of peer scrutiny for continuous quality improvement.

k. "Moderate" adverse events are those that, while not sentinel, are serious enough to quickly endanger the patient if not promptly managed. Once clinically concluded, they warrant timely reporting within sedation care systems, and periodic peer scrutiny for continuous quality improvemet.

l. "Minor" adverse events are those encountered periodically in most sedation settings, and that pose little threat given appropriate sedationist skills and monitoring.

m. "Minimal" adverse events are those that alone present no danger of permanent harm to the patient.

Figure 1. World SIVA adverse sedation event reporting tool

F. Data Management Methods

Patient demographic, adverse events and hemodynamic data will be entered into an InFormdatabase and then exported into the SAS system for statistical analysis (version 9.2, 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

Baseline characteristics will be compared between the dexmedetomidine and propofol (DP) treatment group and the propofol (P) treatment group to determine any baseline imbalances which may occur despite randomization. Student *t*-test will be used to compare continuous (normally-distributed data) and Fisher's exact test for comparing binary proportions. Airway obstruction and other adverse event rates will be assessed and 95% confidence intervals will be constructed using Wilson's method (Newcombe 1998). Multivariate logistic regression will be applied to identify any variables (age, gender, ASA status, treatment) that are correlated with adverse events and with hemodynamic outcome exceeding the 20% boundary above the upper normal age-based reference range. Time to sedation, procedure time, and time to meet discharge criteria will be compared between Dexmedetomidine and Propofol groups using two-sample *t*-tests with analysis of variance (ANOVA) used to adjust for covariates such as age, gender and ASA classification which could influence the results. Two-tailed values of $P<0.05$ will be considered statistically significant. Statistical analysis will be performed using SAS statistical software (version 9.2, SAS Institute, Cary, NC).

I. Statistical Power and Sample Considerations

Power analysis indicated that a sample size of 32 patients randomly assigned to dexmedetomidine and propofol will provide 80% power (2-tailed $\alpha = 0.05$, $\beta = 0.20$) to detect a 50% difference (25% vs. 75%) in the propofol dose using a chi-square test of binomial proportions between two independent groups. To account for 10% possible dropout, we will increase this sample size to 35 patients per group. This means that a total of 70 patients will be randomized equally to the DP and P treatment groups.

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.

K. Data and Safety Monitoring Plan

Dr. Mason 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 10 subjects recruited or earlier 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 monitoring committee, 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. An interim analysis will be performed after 35 patients have been enrolled to review data and safety elements of the study and also to determine if patients have any obvious improvement in the DP group with a view to terminating the study early.

L. Risks and Discomforts

Patients enrolled in the study and randomized to the P treatment group would receive what had been normal standard of care for sedation in the GI Suite for upper and lower endoscopic procedures in

BCH. For the patients randomized to the DP treatment group, there is a slight increase in risk over the P group. However, these medications are commonly used together at Boston Children's Hospital and for sedation practices. There are limited studies for administering both drugs in pediatric patients; however, these studies have shown dexmedetomidine to be a safe and effective agent with beneficial effects.

M. Potential Benefits

The patients in the P group will not receive an immediate, direct benefit from participation in the study, aside from the sedation received. In the future, following completion of this study, we anticipate that the results obtained from this study will guide us in optimizing patient care by determining any advantage in administering dexmedetomidine with propofol. The patients in the DP group have the potential for an increased chance of emergence delirium, decreased need for analgesics and decreased propofol requirements. Decreasing the dose of propofol may decrease the risk of airway complications associated with propofol

N. Privacy Provisions

Access to the electronic database will be restricted to IRB approved study staff and will be password protected.

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.

P. References

Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. Anesthesiology. 1990 Aug;73(2):230-5.

Rao SH, Sudhakar B, Subramanyan PK. Haemodynamic and anaesthetic advantages of dexmedetomidine. South Afr J Anaesth Analg 201 18(6):326-31.

Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth. 2006 Jul;53(7):646-52.

Pestieau SR, Quezado ZM, Johnson YJ, Anderson JL, Cheng YI, McCarter RJ, Choi S, Finkel JC. High-dose dexmedetomidine increases the opioid-free interval and decreases opioid requirement after tonsillectomy in children. Can J Anaesth. 2011 Jun;58(6):540-50.

Le Guen M, Liu N, Tounou F, Augé M, Tuil O, Chazot T, Dardelle D, Laloë PA, Bonnet F, Sessler DI, Fischler M. Dexmedetomidine reduces propofol and remifentanil requirements during bispectral index-guided closed-loop anesthesia: a double-blind, placebo-controlled trial. Anesth Analg. 2014 May;118(5):946-55.

Memiş D, Turan A, Beyhan Karamanlıoğlu B, Şermin Şeker S, Zafer Pamukçu Z. Dexmedetomidine reduces rocuronium dose requirement in sevoflurane anaesthesia. Trends in Anaesthesia and Crit Care 2008 Jun;19(3):169–174.

Sen S, Chakraborty J, Santra S, Mukherjee P, Das B. The effect of dexmedetomidine infusion on propofol requirement for maintenance of optimum depth of anaesthesia during elective spine surgery. Indian J Anaesth. 2013 Jul;57(4):358-63

Al-Zaben KR, Qudaisat IY, Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Oweidi AS, Abu-Halaweh SA, Abu-Ali HM, Saleem MM. Intraoperative administration of dexmedetomidine reduces the analgesic requirements for children undergoing hypospadius surgery. Eur J Anaesthesiol. 2010 Mar;27(3):247-52.

Mason KP, Zurakowski D, Zgleszewski SE, Robson C, Carrier M, Hickey P, et al. High Dose Dexmedetomidine As The Sole Sedative for Pediatric MRI. Paediatr Anaesth 2008 18(5):403-411

Mason KP, Zgleszewski SE, Dearden JL, Dumont RS, Pirich MA, Stark CD, et al. Dexmedetomidine for pediatric sedation for computed tomography imaging studies. Anesth Analg. 2006 Jul;103(1):57-62.

Heard C, Burrows F, Johnson K, Joshi P, Houck J, Lerman J. A comparison of dexmedetomidine-midazolam with propofol for maintenance of anesthesia in children undergoing magnetic resonance imaging. Anesth Analg. 2008;107(6):1832-1839

Ozdemir KI, Egilmez H, Kaygusuz K, Gursoy S, Mimaroglu C. Open-label, prospective, randomized comparison of propofol and sevoflurane for laryngeal mask anesthesia for magnetic resonance imaging in pediatric patients. Clin Ther. 2008;30(1):175-181

Koroglu A, Teksan H, Sagir O, Yucel A, Toprak HI, Ersoy OM. A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg. 2006 Jul;103(1):63-67.

Cravero JP, Beach ML, Blike GT, Gallagher SM, Hertzog JH; Pediatric Sedation Research Consortium. The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. Anesth Analg. 2009 Mar;108(3):795-804

Guenther E, Pribble CG, Junkins EP Jr, Kadish HA, Bassett KE, Nelson DS.Propofol sedation by emergency physicians for elective pediatric outpatient procedures. Ann Emerg Med. 2003 Dec;42(6):783-91

Bassett KE, Anderson JL, Pribble CG, Guenther E. Propofol for procedural sedation in children in the emergency department. Ann Emerg Med. 2003 Dec;42(6):773-782.

Anderson JL, Junkins E, Pribble C, Guenther E. Capnography and depth of sedation during propofol sedation in children. Ann Emerg Med. 2007 Jan;49(1):9-13

Nafiu OO, Kheterpal S, Morris M, Reynolds PI, Malviya S, Tremper KK. Incidence and risk factors for preincision hypotension in a noncardiac pediatric surgical population. Paediatr Anaesth. 2009 Mar;19(3):232-239.

Miller P, Mack CD, Sammer M, Rozet I, Lee LA, Muangman S, Wang M, Hollingworth W, Lam AM, Vavilala MS. The incidence and risk factors for hypotension during emergent decompressive craniotomy in children with traumatic brain injury. Anesth Analg. 2006 Oct;103(4):869-875.

Assessment: oxygenation and blood pressure. In: Badjatia N, Carney N, Crocco TJ, Fallat ME, Hennes HM, Jagoda AS, Jernigan S, Lerner EB, Letarte PB, Moriarty T, Pons PT, Sasser S, Scalea TM, Schleien C, Wright DW. Guidelines for prehospital management of traumatic brain injury. 2nd ed. New York (NY): Brain Trauma Foundation; 2007. p. 16-25.

Thomas RG, Conlon M. Sample size determination based on Fisher's exact test for use in 2 x 2 comparative trials with low event rates. Controlled Clinical Trials 1992;13:134-147.

Piantadosi S. Clinical Trials: A Methodologic Perspective, 2nd ed. New York: John Wiley & Sons, 2005:331-353.

Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857-872.

Hauber JA1, Davis PJ, Bendel LP, Martyn SV, McCarthy DL, Evans MC, Cladis FP, Cunningham S, Lang RS, Campbell NF, Tuchman JB, Young MC.; 'Dexmedetomidine as a Rapid Bolus for Treatment and Prophylactic Prevention of Emergence Agitation in Anesthetized Children.'; Anesth Analg. 2015 Nov;121(5):1308-15.

Kadam P, Bhalerao S. Sample size calculation. International Journal of Ayurveda Research. 2010;1(1):55-57.

Chandran V, Jagadisan B, Ganth B. Validation of adapted Dartmouth operative conditions scale for sedation during pediatric esophagogastroduodenoscpy. Pediatric Anesthesia. 2017 Apr 3. [Epub ahead of print]

** If you are an investigator submitting an IND or IDE, this document alone does not constitute and complete protocol. You must submit your full IND/IDE application as an attachment for this section.*