Does dexmedetomidine decrease the incidence of untoward airway events after deep or awake extubation in patients undergoing adenotonsillectomy with or without myringotomy and tube placement?

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COVER PAGE

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Dexmedetomidine hydrochloride (Precedex)

Regulatory Sponsor:

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Funding Sponsor:

Curing Kids Fund

Study Monitor

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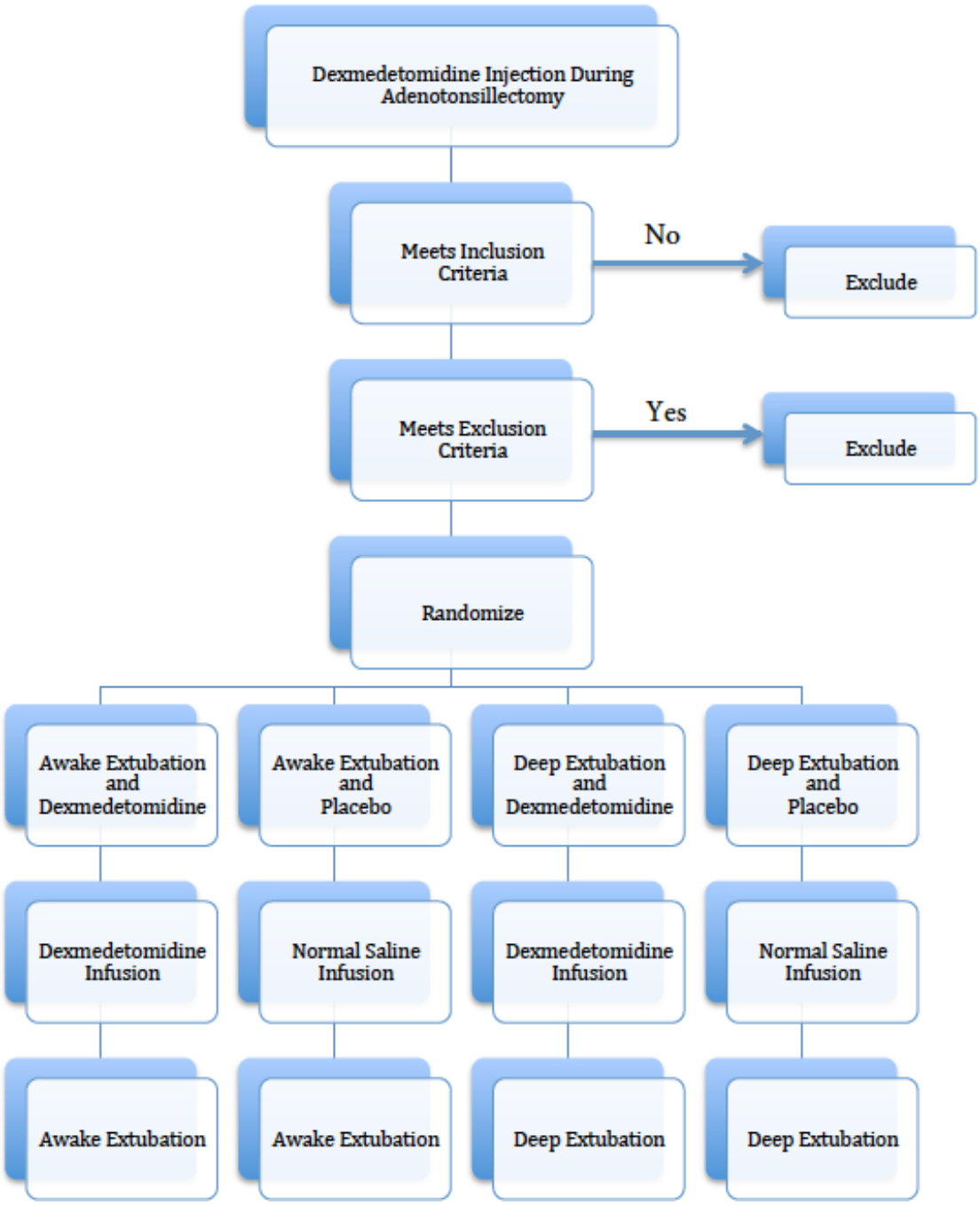
Clinical Laboratory(ies), Technical Department(s), and Institution(s) Providing Clinical Study Services:

Department of Anesthesia, Pharmacy, and PACU nursing at Massachusetts Eye and Ear Infirmary.

STUDY DESIGN SCHEMATIC



1. CLINICAL PROTOCOL

1.1 Background

Adenotonsillectomy (T&A) is the most frequently performed surgical procedure in the pediatric population. T&A is associated with a high incidence of perioperative respiratory adverse events (11.2%)[1] including coughing, breath-holding, desaturation, partial or complete laryngospasm, bronchospasm, and negative pressure pulmonary edema. These respiratory complications in the postoperative period frequently lead to prolonged post-anesthesia care unit (PACU) and hospital stays in this patient population. Therefore, the postoperative period can be highly stressful for both children and their parents.[2]

The incidence of these respiratory adverse events is highest following tracheal extubation and in the recovery period.[3] Consequently, during emergence from anesthesia, tracheal extubation constitutes the most perilous event that may determine the incidence of adverse respiratory complications in the postoperative period. There remains a controversy as to whether tracheal extubation should be performed in a deeply anesthetized patient or in an awake patient.[3] Given the serious nature of the respiratory complications following T&A, the identification of an adjuvant drug therapy that could decrease these untoward events would be highly desirable.

Dexmedetomidine hydrochloride is a highly selective α2-adrenoceptor agonist. Its properties include sedation, anxiolysis, analgesia with little respiratory depression.[2,4] In addition, dexmedetomidine has minimal effect on coagulation parameters.[5] The potential risks of the use of dexmedetomidine, bradycardia and hypotension, are very rare.[2]

The use of this agent has been increasing in the pediatric population undergoing different surgical procedures.[6,7,8,9] The drug's opioid-sparing property in patients undergoing T&A is of particular interest. Pain-control in patients undergoing T&A can be extremely challenging, as many of these children may have an altered central opioid function that could enhance their responsiveness to opioid drugs.[2,10,11] This
hypersensitivity to opioids, potentially leading to severe respiratory complications, increases the risk of perioperative adverse airway events, thus limiting the application of such drugs in this population.

Dexmedetomidine is an attractive drug for managing pediatric patients undergoing T&A: it combines mild analgesic effects, opioid-sparing properties, and minimal respiratory depression.[2,4] Dexmedetomidine also appears to be a safe and effective agent in reducing the incidence of early emergence agitation in children after tonsillectomy.[12]

However, the effects of dexmedetomidine on postoperative adverse airway events have not been fully studied, and the literature is limited to two studies. In one study investigating emergence agitation in sixty children undergoing T&A, Guler et al also studied untoward airway events in these patients.[6] In this investigation, one group received dexmedetomidine 0.5 μg/kg over 5 minutes, while the control group received a placebo five minutes before the end of surgery. The number of severe coughs per patient in the dexmedetomidine group was significantly reduced compared to the control group ($p < 0.05$). Another study by Akin et al compared the effects of dexmedetomidine to midazolam administered as premedication on ninety patients undergoing T&A. The midazolam group resulted in five cases of laryngospasm, compared to the dexmedetomidine group, which exhibited none.[13]

Given the serious nature of untoward respiratory events in the perioperative period associated with T&A, coupled with the paucity of literature on the effects of dexmedetomidine on these events, we aim to investigate the effect of dexmedetomidine on the perioperative respiratory complications in this patient population undergoing both awake and deep tracheal extubation.

References:

1. Ye J, Liu H, Zhang G, et al. Postoperative respiratory complications of adenotonsillectomy for obstructive sleep apnea syndrome in older children: prevalence, risk factors, and impact on clinical outcome. *J Otolaryngol Head Neck Surg*. 2009; 38(1):49-58.

2. He XY, Cao JP, Shi XY, et al. Dexmedetomidine versus morphine or fentanyl in the management of children after tonsillectomy and adenoidectomy: A meta-analysis of randomized controlled trials. *Ann Otol Rhinol Laryngol* 2013; 122(2):114-120.

3. Ungern-Sternberg BS, Davies K, Hegarty M, et al. The effect of deep vs. awake extubation on respiratory complications in high-risk children undergoing adenotonsillectomy: A randomized controlled trial. *Eur J Anaesthesiol* 2013; 30:529–536.

4. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000; 4:302-308.

5. Mizrak A, Karatas E, Saruhan R, Kara F, Oner U, Saricicek V, Baysal E. Does dexmedetomidine affect intraoperative blood loss and clotting tests in pediatric adenotonsillectomy patients? *J Surg Res* 2013; 179(1):94-98.

6. Chrysostomou C, Schulman SR, Herrera Castellanos M, et al. A phase 2/3, Multicenter, Safety, Efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. *J Pediatr* 2014; 164(2): 276-282.

7. Guler G, Akin A, Tosun Z, et al. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. *Pediatr Anesth* 2005; 15:762–766.

8. Su F, Nicolson SC, Zuppa AF. A dose-response study of dexmedetomidine administered as the primary sedative in infants following open heart surgery. *Pediatr Crit Care Med* 2013; 14(5): 499-507.

9. Cai Y. et al. Efficacy and safety of spontaneous ventilation technique using dexmedetomidine for rigid bronchoscopic airway foreign body removal in children. *Pediatr Anaesth* 2013; 23: 1048-1053.

10. Brown KA, Laferrière A, Moss IR. Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirement for analgesia. *Anesthesiology* 2004; 100:806-810.

11. Brown KA, Laferrière A, Lakheeram I, et al. Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. *Anesthesiology* 2006; 105:665-669.

12. Meng QT, Xia ZY, Luo T, et al. Dexmedetomidine reduces emergence agitation after tonsillectomy in children by sevoflurane anesthesia: A case-control study. *Int J Pediatr Otorhinolaryngol* 2012; 76:1036–1041.

13. Akin A, Bayram A, Esmaoglu A, et al. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. *Pediatr Anaesth* 2012; 22:871-876.

Provide a brief description of, and justification for, the proposed route of administration, dosage, dosage regimen, and duration of dosing of the investigational drug(s) or the investigational device(s)

0.5 µg/kg of dexmedetomidine diluted in NaCl 0.9% with a maximum concentration of 4 µg/ml will be administered through the infusion pump over 5 minutes.

Summarize the nature of the individuals (e.g., age range, sex, disease state or underlying condition) who will be included in the proposed clinical evaluation

Children 3-16 years of age undergoing adenotonsillectomy.

Specify whether or not (i.e., to your knowledge) the investigational drug(s) or device(s) has been marketed in any other country. Specify if the investigational drug(s) or device(s) has been withdrawn from research or market in any country for any reason related to its safety or effectiveness. If the drug or device has been the subject of controlled clinical trials, detailed information of such trials that is relevant to an assessment of the drug's or device's effectiveness for the proposed investigational use should also be provided.

N/A

2. STUDY OBJECTIVES

2.1 Primary Objective

We aim to investigate the effect of dexmedetomidine on the perioperative respiratory complications in this patient population undergoing both awake and deep tracheal extubation.

(Note: For Phase 1 clinical research studies, the primary objective should be an evaluation of the safety of the investigational drug or device)

2.2 Secondary Objective(s)

We also aim to investigate the effect of dexmedetomidine on the incidence of nausea and vomiting as well as emergence agitation. In addition, we will evaluate the effect of dexmedetomidine on the requirement of postoperative pain control medication.

3. STUDY DESIGN

3.1 Study Design Description

We propose a prospective double-blinded randomized controlled trial. 336 pediatric patients presenting to Massachusetts Eye and Ear Infirmary (MEEI) for adenotonsillectomy with or without myringotomy and tube placement who are eligible for the study based on inclusion and exclusion criteria will be recruited. A Clinical Pharmacy specialist, will in charge of preparing the dexmedetomidine and placebo doses and will randomize the patients to four equally numbered groups. The anesthesiologist will receive the assignment for the extubation method in a sealed envelope from the Clinical Pharmacy specialist. Multiple parameters will be recorded in perioperative period to quantify perioperative adverse respiratory events. 1- Oxygen saturation will be measured at the following intervals: 5 minutes prior to extubation; immediately before extubation; every minute for the first 10 minutes following extubation; and subsequently, every 5 minutes for the ensuing 20 minutes. The following parameters will be noted:

1- desaturation to less than 95% for more than 10 seconds;
2- breath holding;
3- complete or partial laryngospasm;
4- bronchospasm;
5- croup;
6- number of episodes of persistent cough (three or more consecutive coughs);
7- negative pressure pulmonary edema;
8- stridor.

Add sub studies (if applicable):

We will also investigate the following parameters:

1) Incidence of emergence agitation;

2) Incidence of postoperative nausea and vomiting (PONV);

3) Length of time from end of surgery to leaving the operating room;

4) The length of stay from admission to the PACU to discharge home;

5) 24-hour postoperative pain control requirements assessed by the questionnaire given to parents at the time of discharge;

6) Any unplanned hospital admission due to perioperative respiratory adverse events.

3.2 Allocation to Treatment (Incorporate only if the proposed clinical study involves multiple treatment arms)

1. Awake extubation receiving dexmedetomidine;
2. Awake extubation receiving placebo;
3. Deep extubation receiving dexmedetomidine;
4. Deep extubation receiving placebo.

3.2.1 Randomization Procedures:

The Clinical Pharmacy specialist preparing dexmedetomidine and placebo for study will apply randomization and the anesthesiologist will receive the assignment for extubation method in a sealed envelope.

3.2.2 Masking Procedures:

The patient, anesthesiologist and data analyst will be blinded as to which group receives which medication. All members of the perioperative care will remain blinded to the study drug arm.

3.2.3 Breaking the Mask (only if proposed study is *masked*)

The mask will be broken in case of severe bradycardia or hypotension, and the patient will be withdrawn from the study.

Severe bradycardia is define as follows:

- Children 3-5 years of age: heart rate < 60 beats per minute;
- Children 6-16 years of age: heart rate <50 beats per minute;

Severe hypotension is defined as a drop in systolic blood pressure of more than 40% drop compared to the baseline systolic blood pressure.

The treatment of bradycardia in children involves the administration of atropine or epinephrine, and in case of isolated hypotension, depending on the severity, fluid, phenylephrine or epinephrine will be administered.

4. SUBJECT SELECTION

4.1 Subject Inclusion Criteria

- Patients between 3 to 16 years of age undergoing adenotonsillectomy with or without myringotomy and tube placement;
- ASA class 1 or 2.

4.2 Subject Exclusion Criteria

- Known allergy or hypersensitivity reaction to dexmedetomidine;
- Organ dysfunction (renal/hepatic failure or leukemia);
- Cardiac disease (congenital or acquired);
- Airway or thoracic malformation;
- Cerebral palsy;
- Hypotonia;
- Need for premedication with midazolam, ketamine, or dexmedetomidine;
- Current/recent upper respiratory infection (within four weeks prior to the surgery);
- Asthma;
- Allergy or intolerance to clonidine;
- Non-English speaking parents/patients

5. STUDY DRUG(S)/DEVICE(S)

5.1 Study Drug/Device Information

Dexmedetomidine is an FDA approved drug for use in adults.
Dexmedetomidine is not an FDA approved drug for use in children.
0.5 µg/kg of dexmedetomidine diluted into 4 µg/ml concentration and drawn up to the appropriate volume with NaCl 0.9% will be administered through the infusion pump over a 5-minute period.
Overweight and obese patients will receive a dose of dexmedetomidine based on their estimated lean body mass.
The volume of normal saline administered to control patients will mimic the volume of dexmedetomidine in the treatment group and will be administered through an infusion pump over a 5-minute period. The volume of NaCl 0.9% for the placebo works out to be 0.125 ml/kg.

5.2 Study Drug/Device Compliance/Adherence

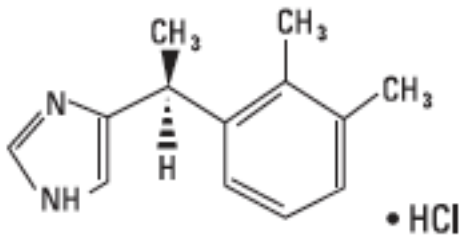
N/A

5.3 Study Drug Supplies

Formulation and Packaging

Precedex (dexmedetomidine hydrochloride) injection is a sterile, non-pyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Precedex has a molecular weight of 236.7 with the empirical formula of C13H16N2 · HCl.

The structural formula is:



Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Precedex is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each mL of Precedex Injection, Concentrate contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water. Each mL of Precedex Injection contains 4.72 mcg of dexmedetomidine hydrochloride equivalent to 4 mcg dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers. Dexmedetomidine is not FDA approved for use children undergoing adenotonsillectomy.

Preparing and Dispensing

The dexmedetomidine and placebo syringes will be prepared by an independent investigator (Clinical Pharmacy specialist) not involved in the perioperative care of the study patients.

Administration

Dexmedetomidine will be diluted in NaCl 0.9% to a concentration of 4 µg/ml. 0.5 µg/kg dexmedetomidine will be administered to the patients through an infusion pump over 5 minutes.

Normal Saline (Placebo) 0.125 ml/kg will be administered to the patients through an infusion pump over 5 minutes.
The procedure will be investigator-directed for the study drugs. We will inform the research subjects before the surgery that they will receive either dexmedetomidine or a placebo during the anesthesia process.

5.4 Study Drug/Device Storage and Accountability

Precedex Injection, Concentrate
Precedex (dexmedetomidine hydrochloride) injection, Concentrate 200 mcg/2 mL (100 mcg/mL) is available in 2 mL clear glass vial. Vials are intended for single use only.

NDC No. Container Size
0409-1638-02 Vial 2 mL

Precedex Injection
Precedex (dexmedetomidine hydrochloride) injection is available as 200 mcg/50 mL (4 mcg/mL) and 400 mcg/100 mL (4 mcg/mL) in 50 mL and
100 mL clear glass bottles, respectively.

NDC No. Container Size
0409-1660-50 Bottle 50 mL
0409-1660-10 Bottle 100 mL

Dexmedetomidine vials and placebo (sodium chloride 0.9%) vials will be stored in the Pharmacy at controlled room temperature (15-25 degrees Celsius). The Pharmacist will maintain drug accountability records for both dexmedetomidine and sodium chloride. All activities related to drug receipt, drug dispensation to subjects, and drug waste will be documented on the drug accountability log for each medication. Additionally, a perpetual inventory is maintained for each medication.

5.5 Other Medications

The following drugs are part of the anesthesia process and will be administered to all patients undergoing surgery regardless of the proposed research study protocol:

- **Administration**
  - Acetaminophen 15 mg/kg orally to the maximum of 650 mg at least 30 minutes prior to surgery;
  - Patients 10 years or older will receive LMX-4 cream (Lidocaine 4%; Ferndale Pharmaceuticals; Deed; UK) on the dorsum of both hands 30 minutes prior to surgery, unless contraindicated;
  - Propofol 1-3mg/kg IV in patients undergoing IV induction and 1-2mg/kg IV in patients undergoing inhalational induction;
  - Remifentanil 1-2 μg/kg IV;
  - Dexamethasone (0.5 mg/kg to a maximum of 10 mg) IV;
  - Ondansetron (0.1 mg/kg to a maximum of 4 mg) IV;
  - Morphine 0.05- 0.1 mg/kg IV.

- **Rescue Medication or Therapy**
    - Atropine 0.02 mg/kg for bradycardia;
    - Phenylephrine 1 mcg/kg for hypotension;
    - Epinephrine 1 mcg/kg in case of severe bradycardia or hypotension.

6. BIOSPECIMEN COLLECTION (IF APPLICABLE)

6.1 Specimen preparation, handling, and shipping

N/A

6.2 Instruction for specimen preparation, handling and storage

N/A

6.3 Specimen shipment

N/A

6.4 Future use of stored specimens

N/A

7. STUDY PROCEDURES

7.1 Recruitment Procedures

A letter with detailed summary of the study will be sent to referring physicians to provide the letter to study eligible patients and their family members at the time of pre-operation. The referring physician will also explain to them that the study coordinator will be approaching them on the day of the surgery to discuss.

7.2 Screening Procedures

Pregnancy test for children of more than 12 years of age will be performed. Patients will also be screened for any conditions that increase the risk of complications, allergies or intolerance, current medications, and ASA classification.

7.3 Enrollment/Baseline Procedures

All patients meeting inclusion criteria and not excluded by exclusion criteria.

7.4 Study Drug or Device Procedures

Dexmedetomidine and normal saline will be infused through an infusion pump.

7.5 Standard of Care Procedures

Deep or awake extubation of patients.

7.6 Follow-up Procedures (Incorporate only if follow-up procedures will be performed)

We will contact all study subjects by phone 24 hours after discharge in order to assess their pain level and pain control requirement. This follow-up will be performed only in study participants.

7.7 Unscheduled Visits

N/A

7.8 Early Termination

In case of severe bradycardia or hypotension requiring CPR following dexmedetomidine administration, the patient's participation in the study will be terminated. The data from patients withdrawn from the study will not be used.

7.9 Schedule of Activities (Study Table)

Provide a table that summarizes the clinical protocol procedures; to include the procedures that will be performed at screening, during the study drug administration, and at follow-up (if applicable) to the study drug or device administration. Please contact HSC@meei.harvard.edu if you would like to see an example.

Preoperative Evaluation	• Children ≥ 12 years old will be screened by pregnancy testing. • Research only: We will discuss the research study with the patient and family in the pre-operative area; the risks and benefits will be explained to the patient and family by the anesthesiologist two hours before the surgery. • Research only: Patients' parents will be asked to sign a consent form, and the patient, if eligible, will sign a child assent. • Patient demographics and characteristics, including ASA classification and comorbid conditions, will be recorded. • Patients will receive acetaminophen 15 mg/kg to the maximum of 650 mg orally at least 30 minutes prior to surgery in the preoperative holding area on the pediatric floor. • Research only: Patients will be assigned to four groups according to the pharmacy randomization: 1-awake extubation receiving dexmedetomidine; 2-awake extubation receiving placebo; 3-deep extubation receiving dexmedetomidine; 4-deep extubation receiving placebo. • An IV catheter will be placed in all children 10 years or older in the preoperative holding area on the surgical floor. • Standard ASA monitors, including pulse-oximetry, ECG, non-invasive blood pressure, and capnography, will be used in all patients.

	• Research only: The anesthesiologist will be informed as to whether the patient belongs to the deep or awake extubation group in a sealed envelope. • Research only: All members of the perioperative team will be blinded to the drug arm of the study. • Patients will be transferred to the operation room.
Intraoperative Phase	• **Induction:** The anesthesia process will start with intravenous (IV) induction with propofol (1-3mg/kg) (for children ≥ 10 years old) or inhalation induction with 70% nitrous oxide and 8% sevoflurane (for children <10 years old). After inhalational induction, an IV will be placed in children < 10 years old, and propofol 1-2mg/kg. Next, all children will be administered remifentanil 1-2 µg/kg and then intubated with a cuffed endotracheal tube. • Research only: **Study intervention:** Following tracheal intubation, patients will receive either dexmedetomidine (dexmedetomidine 0.5 µg/kg diluted in NaCl 0.9% to achieve concentration of 4µg/ml) or a placebo (same volume of NaCl 0.9%), both over a 5-minute time period. • **Maintenance:** The maintenance of anesthesia will be achieved with sevoflurane. All children will receive dexamethasone (0.5 mg/kg to a maximum of 10 mg), ondansetron (0.1 mg/kg to a maximum of 4 mg) for antiemetic prophylaxis, and morphine 0.05-0.1 mg/kg for pain control. The dose of morphine will be adjusted for patients with OSA to receive 0.05 mg/kg.

	• **Extubation:** At the end of the procedure, all patients will be placed on 100% oxygen: at this point, they will undergo either deep or awake tracheal extubation based on the prior randomization. However, the anesthesiologist will be able to overrule this decision based on his/her clinical judgment should the alternate method of extubation be indicated at the end of the case. Awake extubation will be performed when the patient demonstrates stable vital signs and adequate tidal volume, combined with one or more of the following responses: following commands, eye opening, purposeful movement, or coughing. Deep extubation will be performed when the patient's end-tidal sevoflurane level is greater than one minimum alveolar concentration (MAC), and he/she is in the surgical plane of anesthesia.
Postoperative Phase	• All patients will be transported to PACU in lateral decubitus position on a facemask receiving oxygen or blow by oxygen (≥ 6L/min). Oxygen will be administered for 30 minutes continuously once in the PACU. • The anesthesiologist will remain with the patient until he/she is stable enough to be handed off to the PACU nurse. • After 30 minutes, supplemental oxygen can be discontinued if patient is able to maintain an oxygen saturation of greater than 95% on room air. • Research only: Oxygen saturation will be measured at the following intervals: 5 minutes prior to extubation; immediately prior to extubation; every minute for the

Postoperative Phase Continued	first 10 minutes following extubation; and subsequently, every 5 minutes for the ensuing 20 minutes. • Research only: Heart rate and blood pressure will be measured at the following intervals: upon arrival at the PACU; every subsequent 5 minutes for the first 30 minutes. • Research only: Multiple parameters will be recorded in perioperative period to quantify perioperative adverse respiratory events: 1- desaturation to less than 95% for more than 10 seconds will be noted; 2- breath holding; 3- complete or partial laryngospasm; 4- bronchospasm; 5- croup; 6- number of episodes of persistent cough (more than three consecutive coughs); 7- negative pressure pulmonary edema; and 8-stridor. • Research only: In addition to the above measures, the patient's pain level in the PACU will be assessed using the FLACC Scale or Wong Baker faces charts, depending on the age of the patient. • Research only: Finally, the following parameters will also be recorded by the Study coordinator or anesthesiologist: 1- occurrence of emergence agitation using the PAED Scale; 2- episodes of vomiting; 3- length of time from the end of surgery to leaving the operating room; 4- length of stay in minutes from admission to the PACU to discharge home; 5- any unplanned hospital admission due to perioperative respiratory adverse events.

Discharge	• Patients meeting the discharge criteria will be discharged home. • Patients with planned or unplanned hospital overnight admission will be discharged to the pediatric floor or PICU depending on the patient's disposition. • Research only: During discharge home, the patient's parents will be given a sheet to record breathing issues, including hoarseness, snoring (longer than 10 seconds), breath holding, and severe coughing. Parents will also be asked to record the amount of pain medication administered postoperatively to their children during the first 24 hours. They will also be asked to record any incidence of nausea and vomiting. Patients will be followed up to ascertain how they fared postoperatively. All data from the parents' sheet will be recorded. • In patients admitted overnight, breathing issues, including hoarseness, snoring (longer than 10 seconds), breath holding, and severe coughing will be recorded. The amount of pain medication administered during the first 24-hours postoperatively will be noted, as will be any incidence of nausea and vomiting.
Data Analysis	• Research only: Data will be analyzed using chi-square or Fisher's exact test for all four groups and pairwise

	comparison between any 2 groups.

8. SAFETY AND EFFECTIVENESS ASSESSMENTS

8.1 Safety Assessments

The vital signs of the patient will be continuously monitored during the procedure. Heart rate and blood pressure will be monitored during the entire surgery for bradycardia and hypotension. Vital signs will be monitored in the PACU in order to detect any respiratory complications or adverse effects due to medications.

8.2 Effectiveness Assessments

Oxygen saturation will be monitored continuously intraoperatively, as well as postoperatively in the recovery room. For the purpose of this study, oxygen saturation will be recorded at the following intervals: 5 minutes prior to extubation; immediately before extubation; every minute for the first 10 minutes following extubation; and subsequently, every 5 minutes for the ensuing 20 minutes. Blood pressure and heart rate will be monitored intraoperatively every 5 minutes, on arrival in the PACU, then every 5 minutes in the recovery room for the first 30 minutes.

The following parameters will also be monitored and recorded in the perioperative period to quantify adverse respiratory events:

1- desaturation to less than 95% for more than 10 seconds;
2- breath holding;
3- complete or partial laryngospasm;
4- bronchospasm;
5- number of episodes of persistent cough (three or more

consecutive coughs);

6- croup;

7- negative pressure pulmonary edema;

8- stridor.

The occurrence of one or more of these postoperative respiratory complications constitutes the primary outcome measure for analysis in this study.

9. ADVERSE EVENT RECORDING AND REPORTING

9.1 Recording Requirements

Research subjects will be monitored for adverse events during and after the procedure. All observed adverse events regardless of study group or suspected causal relationship to the study drug will be recorded in the subjects' case histories (source data) and electronic anesthesia records. For all adverse events, any pertinent information will be collected to permit: 1- adequate determination of the outcome of the event (whether the event should be classified as a serious adverse event); and, 2- assessment of the casual relationship between the adverse event and the study drug.

Adverse events associated with the study drug will be followed until the event resolves and the patient stabilizes to a level acceptable to the Sponsor-Investigator.

9.2 REPORTING PROCEDURES

- **REPORTING OF ADVERSE EVENTS TO FDA**
  Adverse events will be reported to the FDA.
- **Reporting Adverse Events to Other External Entities**
  Adverse events will be reported to the manufacturer of Precedex.

- **Reporting Adverse Events to the Human Studies Committee**
  Any adverse effects including hypotension and bradycardia will be reported.

9.3 Withdrawal of Subjects due to Adverse Events?

In case of severe hypotension and bradycardia, we will withdraw the subjects from the study. In case of severe hypertension, the subjects will also be withdrawn from the study

10. STATISTICAL METHODS/DATA ANALYSIS

10.1 Primary endpoint(s) or outcome measure(s)

The occurrence of one or more of these postoperative respiratory complications constitute the primary outcome measure for analysis in this study:

1- Desaturation to less than 95% for more than 10 seconds;
2- Breath holding;
3- Complete or partial laryngospasm;
4- Bronchospasm;
5- Croup;
6- Number of episodes of persistent cough (three or more consecutive coughs);
7- Negative pressure pulmonary edema;
8- Stridor.

10.2 Secondary endpoints or outcome measure(s)

We will also investigate the following parameters:

1. Incidence of emergence agitation;
2. Incidence of postoperative nausea and vomiting (PONV);
3. Length of time from the end of surgery to leaving the operating room;
4. The length of stay from admission to the PACU to discharge home;
5. 24-hour postoperative pain control requirements;
6. Any unplanned hospital admission due to perioperative respiratory adverse events.

10.3 Sample Size Determination

Based on the study by Patel *et al* comparing the untoward outcomes in children undergoing awake versus deep extubation after adenotonsillectomy, a difference in complication rate has been shown between the two groups, with 11% (2 out of 18) versus 30% (6 out of 20), respectively, exhibiting airway complications during extubation.[1] Based on these results, a two-group χ^2 test with a 0.05 two-sided significance level would have an 80% power to detect the difference between the 'awake' group and 'deep' group given a sample size of 71 in each group.

Guler *et al* compared untoward events after awake extubation in patients undergoing tonsillectomy who received dexmedetomidine 0.5 mcg/kg during the procedure to a placebo group who did not: they observed that the rate incidence of severe cough was significantly lower in the dexmedetomidine group (0%) compared to the placebo group (30%).[2] Based on these results, a two-group χ^2 test with a 0.05 two-sided significance level would have an 80% power to detect the difference between the 'dexmedetomidine' group and 'placebo' group given a sample size of 22 in each group.

Since we will be comparing the results of the 'deep' versus 'awake' as well as those of the 'dexmedetomidine' versus 'placebo' outcomes, each group will require a sample size of 71.

We anticipate that, at most, 15% of randomized patients will not provide complete data on their assigned drug/extubation combination randomized arm because the anesthesiologist overrules the assigned extubation method due to the clinical needs of the patient during the case. Therefore, in order to assure that there will be at least 71 subjects on each study arm with complete data, we will enroll and randomize a

total of 336 patients with equal probability to the four arms (84 patients in each group) using a block randomization scheme.

References:

1. 1- Patel RI, Hannallah RS, Norden J, et al. Emergence airway complications in children: a comparison of tracheal extubation in awake and deeply anesthetized patients. *Anesth Analg* 1991; 73:266–270.

2. Guler G, Akin A, Tosun Z et al. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. *Pediatr Anaesth* 2005; 15:762–766.

10.4 Analysis Population (if applicable)

Children between 3 months and 16 years old undergoing adenotonsillectomy constitute the population of analysis.

10.5 Effectiveness Analysis (if applicable)

N/A

10.6 Safety Analysis

A Data Safety Monitoring Board will conduct a safety analysis after the following numbers for patient recruitment in each arm have been reached:

- 40 total patients recruited with approximately 10 patients in each group
- 84 total patients recruited with approximately 21 patients in each group
- 168 total patients recruited with approximately 42 patients in each group
- 252 total patients recruited with approximately 63 patients in each group

This data reflects approximately 12%, 25%, 50%, and 75% of the total estimated subject recruitment population, respectively. The Data Safety Monitoring Board will specifically monitor for any adverse events in each group. In case of serious concerns regarding adverse events in either group, the study will be terminated.

10.7 Interim Analysis

A statistician will perform an interim analysis when half of the sample size for each group has been recruited

11. DATA AND SAFETY MONITORING

11.1 Data and Safety Monitoring Plan

The research coordinator will be responsible for data gathering. The study coordinator will be responsible for filling out the data collection sheet in the OR with input from the anesthesiologist assigned to the patient. The research coordinator or principal investigator will record the data collection sheet in the PACU. The anesthesiologist assigned to the patient will monitor for any adverse events. In case of severe bradycardia or hypotension following dexmedetomidine administration, the mask will be broken and the patient will be withdrawn from the study. All anesthesiologists involved in the study have access to the protocol and their feedback and concerns have been already added to the protocol. Progress notes of the study will be sent to the IRB annually. A statistician will perform an interim analysis when half of the sample size for each group has been recruited. A Data Safety Monitoring Board will be responsible for safety monitoring.

12. DATA HANDLING, RECORD-KEEPING AND MONITORING

12.1 Data Recording, Record-Keeping and Monitoring

The Source Data are the clinical findings and observations, laboratory and test data, and other information contained in the Source Documents and electronic anesthesia records. The Source Documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, and recorded data from automated instruments, x-rays, etc. All Source data and documents will be stored in patients' paper and LMR charts. The electronic anesthesia records will be searched for any deviation from the study protocol, including drug administrations and vital signs.

All research data collected, including monitoring data, will be recorded as research records on an MEEI password protected computer. The signed parental consent forms and child assents will be locked in the drawers located in anesthesia office on the 7th floor of MEEI main building. Only the study coordinator and the principal investigator have access to these drawers.

13. STUDY DISCONTINUATION CRITERIA

13.1 Discontinuation of Individual Research Subjects

In case of any major drug side effects (bradycardia and hypotension) or at the patient or parents' request, patient participation will be terminated.

13.2 Sponsor-Investigator Discontinuation of the Clinical Research Study

In case of significant advantages or disadvantages, the principal investigator or sponsor will discontinue the clinical research study.

14. APPENDICES

14.1 Schedule of Events

1. Parents will be informed about the research at the time of the surgery scheduling and will receive the consent form from the surgeon's office;
2. Patients will present to MEEI two hours prior to surgery on the day of the surgery and will be assessed by the anesthesiologist;
3. Parents of patients who meet the inclusion and exclusion criteria will be informed about the study;
4. Written consent will be obtained from the parents and eligible children will be asked to sign an assent form;
5. Patients will be randomized to one of the four study groups by the pharmacy
6. All patients will receive oral acetaminophen in the preoperative area;
7. An IV will be placed preoperatively on the surgical floor in all patients ≥ 10 years;
8. Prior to induction, the anesthesiologist will be informed about which method of extubation the patient will undergo;
9. All patients will undergo parent-present induction;
10. Patients will receive all the intraoperative induction medication according to the study protocol;
11. Patients < 10 years will undergo inhalational induction;
12. Patients ≥ 10 years will undergo IV induction;
13. Patients will receive dexmedetomidine or placebo infusion after induction;
14. At the end of the procedure, the patients will undergo either deep or awake extubation according to the prior randomization;

15. The anesthesiologist will record all the study data in the OR until the patient has been handed off to the PACU nurse;
16. After extubation, the patient will be transferred to the PACU and handed off to the PACU nurse;
17. A data recorder will record all the study data during patient's PACU stay;
18. During discharge, parents will be asked to fill out a data sheet during the first 24-hours after discharge;
19. A follow-up phone call will be made 24 hours after discharge to obtain parent-documented data.

14.2 Case Report Form(s)

14.3 DSMB Charter