Identifiers: NCT01057381 **Unique Protocol ID**: H-17558

Title: Dexmedetomidine in Pediatric Tonsillectomy

Date: 3 June 2005

Compare

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-17558
Status: Closed
Initial Submit Date: 6/3/2005

Section Aa: Title & PI

A1. Main Title

DOSE RESPONSE RELATIONSHIP OF DEXMEDETOMIDINE IN DECREASING POSTOPERATIVE ANALGESIC REQUIREMENTS IN THE PEDIATRIC TONSILLECTOMY PATIENT.

A2. Principal Investigator

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A3. Administrative Contact

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A3b. Cooperative Agreement

Is this a cooperative agreement protocol?
No

Which institution is the IRB of record?
BCM: Baylor College of Medicine

Section Ab: General Information

A4. Co-Investigators

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A5. Funding Source:

Baylor College of Medicine (Internal Funding Only)

A6a. Institution(s) where work will be performed:

TCH: Texas Children's Hospital

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

A8. Therapeutic Intent

Does this trial have therapeutic intent?
Not set yet

A9. ClinicalTrails.gov Registration

Section B: Review Path Determination

B1. Full Board or Expedited Review

Is this an compassionate/emergency use situation?
No

If this is a drug study, is an investigational new drug (IND) application required?
Yes

If this is a device study, is an investigational device exemption (IDE) application required?
N/A

If the research involves ONLY blood collection, are subjects healthy, non-pregnant adults whose weight is at least 110 pounds, with amount drawn less than 550 ml in an 8 week period, and with collection not occurring more frequently than 2 times per week?
N/A

If the research involves ONLY blood collection for other adults and children, considering age, weight and health of subjects, is the amount drawn in an 8 week period less than 50ml or 3 ml per kg, and with collection not occurring more frequently than 2 times per week?
N/A

Does the research involve ONLY the collection of biological specimens for research purposes by noninvasive means? (e.g. Hair; extracted teeth; excreta, sputum and external secretions; placenta removed at delivery; mucosal and skin cells collected by scraping or swab)
N/A

Does the research involve ONLY the collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves? (e.g. EKG, ECHO, EEG, Ultrasound, MRI)
N/A

Does the research involve ONLY materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis)?
N/A

Does the research involve ONLY the collection of data from voice, video, digital, or image recordings made for research purposes?

N/A

Does the research involve ONLY individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies?

N/A

Does the research involve pedigree studies, collection and/or storage of specimens for DNA analysis or gene transfer?

No

B2. Exempt From IRB Review

Not Applicable

B3. Waiver of Subject Authorization

Not Applicable

Section C: Background Information

Dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, has recently been approved for use by the FDA for sedation in adult critically ill patients. Perioperative use of this drug has been associated with reduced anesthetic requirements, sedation without respiratory depression and, in adults, a decrease in postoperative requirement of analgesics. In a recent study we conducted (H-16272), dexmedetomidine at a dose of 0.5 mcg/kg appeared to be equivalent to morphine at a dose of 0.05mcg/kg with regards to adequacy of pain control and sedation following tonsillectomy and/or adenoidectomy surgery. Tonsillectomy and adenoidectomy (T&A) is a common operation performed in children, some of whom have obstructive sleep apnea or frequent tonsillitis. It is usually associated with a moderate degree of post operative pain requiring narcotics. However, the use of narcotics may further aggravate postoperative somnolence in some of these patients. Dexmedetomidine may decrease the need for post-operative narcotics thereby reducing the incidence of somnolence following surgery.

Section D: Purpose and Objectives

The primary purpose of this study is to determine the dose related efficacy of dexmedetomidine in the management of postoperative pain in the pediatric patient undergoing tonsillectomy with or without adenoidectomy. The secondary purpose is to determine the dose of dexmedetomidine that will be superior to morphine, in providing analgesia and also decreasing somnolence following tonsillectomy with or without adenoidectomy.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender:

Both

Age:

Adolescent (13-17 yrs), Child (3-12 yrs)

Ethnicity:

All Ethnicities

Primary Language:

English, Spanish

Groups to be recruited will include:

Patients

Which if any of the following vulnerable populations will be recruited as subjects?

Children

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Subjects and/or parents/guardians will be approached during routine pre-operative anesthesia workup. At this time, the study will be explained with emphasis on the voluntary nature of participation. In children 7 years and above, assent will be obtained. A Spanish translator and short Spanish consent will be available for Spanish speakers. Subjects and parents/guardians will be assured that confidentiality of records will be maintained and that subject identifiers will be removed prior to publication of findings. Refusal to participate in the study will not preclude subjects from receiving standard anesthetic care.

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

E5. Children

Will children be enrolled in the research?

Yes

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:

z.z) ARCHIVED DO NOT USE - Other

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This will be a prospective randomized controlled study.

Inclusion Criteria:

Children who are classified as American Society of Anesthesiology (ASA) Class 1 and 2, between 3 to 17 years of age undergoing Tonsillectomy with or without Adenoidectomy will be included in the study.

Exclusion Criteria:

This will exclude children less than three years of age, females with a positive pregnancy test, those with uncorrected cardiac lesions as determined by a history of cyanotic congenital heart lesions pending surgical correction, as well as children classified as ASA 3 or 4. Children with diagnosed heart block or liver impairment will also be excluded from the study.

F2. Procedure

Subjects will receive oral midazolam 0.5 mg/kg as premedication (10 mg maximum dose). They will be randomized preoperatively to receive either morphine 0.05 mg/kg, morphine 0.1 mg/kg or dexmedetomidine at one of the following doses: 0.75mcg/kg or 1mcg/kg. Routine intraoperative monitors will be applied, which at Texas Children's Hospital include pulse oximeter, heart rate monitors and non-invasive oscillometric blood pressure. These are all routine monitors and not part of the study protocol. General anesthesia will be induced with nitrous oxide, oxygen and sevoflurane via mask. After establishment of intravenous access, tracheal intubation will be facilitated with atracurium 0.5mg/kg IV. Once the endotracheal tube has been secured, the patient will receive morphine 0.05 mg/kg, morphine 0.1 mg/kg or dexmedetomidine at a dose of 0.75mcg/kg or 1mcg/kg (based on prior randomization) over 10 minutes. The practitioner will be blinded as to which medication the patient is receiving. Postoperatively, the patients will be transferred to the post anesthetic care unit where a blinded observer will record heart rate, respiratory rate and arterial blood pressure every 5 minutes for the first 15 minutes and every 15 minutes for 60 minutes. The patients' excitement will also be graded on a scale of 0-4 (0=no excitement and 4= severe excitement) for the same duration with documentation every 15 minutes. Supplemental Oxygen will be administered to keep the oxygen saturation above 95%. Pain will be assessed using the Children's Hospital of Eastern Ontario Pain scale (CHEOPS). Additional Morphine, in incremental doses of 25ug/kg, will be administered for CHEOPS score greater than 8. The time to first oral intake will also be recorded. The primary endpoint will be the amount of narcotics required to make the patient comfortable in the post anesthesia recovery unit. The secondary end point will be the patient's level of somnolence. Using the Ramsay scale, somnolence will be assessed at 15 minute intervals. The Ramsay score assigns a score of 1-6 based on the clinical assessment of the level of sedation (1 = anxious, agitated, restless; 2 = awake but co-operative, tranquil, orientated; 3 = responds to verbal command only; scores

4-6 are an asleep patient and are graded according to the response to a loud noise or glabellar tap: 4 = brisk response, 5 = sluggish response; 6 = no response).

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 240 Worldwide: 240

Please indicate why you chose the sample size proposed:

This power analysis is for a one-way fixed effects analysis of variance with 4 levels. The groups are formed based on the drug and dosage levels: 1) morphine 0.05 mg/kg 2) morphine 0.1 mg/kg 3) dexmedetomidine 0.75mcg/kg, or 3) dexmedetomidine 1mcg/kg. The study will include 60 cases per group for a total of 240 cases. The criterion for significance (alpha) has been set at 0.05. The analysis of variance is non-directional (i.e. two-tailed) which means that an effect in either direction will be interpreted. The effect size (f) is expected to be moderate 0.25, which yields power of 0.80. An interim analysis is planned after 100 cases have been randomized to reassess the sample requirements for this study.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Data analysis for the primary outcome variable in this protocol will be an analysis of variance. The primary outcome variable will be the total amount of additional morphine required following surgery. The main effect of drug/dose will determine if there are differences in the amount of additional morphine needed following surgery in the four groups. If the main effect shows a significant difference then post hoc contrasts will compare the morphine 0.05 mg/kg group and the morphine 0.1 mg/kg group to each of the dexmedetomidine dosage groups to determine if there is a significant difference between the groups. The secondary outcome variable is the level of somnolence as measured by the Ramsay scale. This is a rating that provides ordinal data, which will be analyzed using appropriate non-parametric approaches assuming equal dispersion of ratings in each drug\dose group.

Section H: Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

Dexmedetomidine has been investigated in the adult population for sedative and analgesic properties. It has also been studied in the pediatric population for procedural sedation, sedation during mechanical ventilation and for weaning patients on mechanical ventilation with chronic narcotic dependence. The potential unfavorable changes with use of this drug in the literature include hypotension and bradycardia, mostly seen with infusion of the drug at high doses and also observed when administered to patients concomitantly taking drugs with negative chronotropic effects. Changes in blood pressure and heart rate seen usually did not exceed 30% of baseline; these anticipated blood pressure and heart rate changes are not different than those observed with morphine. Alterations in cardiovascular variables will be avoided by administering lower doses of the drug as well as careful patient selection. The criteria for stopping the study in an individual patient (i.e. during study drug administration) will include: immediate skin reaction at site of administration, heart block, anaphylaxis, severe bradycardia resulting in a 30 mmHg or greater drop in systolic blood pressure, or sudden hypotension. The number of patients with adverse events or serious adverse events that would result in stopping the trial in general are as follows: a). Asystole: If 1 patient develops asystole, appropriate resuscitation measures will be instituted and the cause will be investigated, If the etiology of asystole is found not to be related solely to the drug, the study would continue. If however, no other cause can be determined and the event is deemed to occur primarily as a result of the drug then the study would be stopped.

b). Heart block: This is known to occur if dexmedetomidine is used in patients that are currently taking negative chronotropic agents. The use of negative chronotropic agents is an exclusion criterion for participation in this study. If heart block occurs despite the precautions, it would be treated and investigated thoroughly. If it were found to occur solely as a result of dexmedetomidine, the study would be stopped after observing this in 2 patients.

c). Persistent hypotension: This is defined by hypotension that does not respond to crsytalloids or vasoactive medication. If this occurs in 3 patients, and is evaluated to occur solely as a result of dexmedetomidine, the study would be stopped.

d). Severe persistent bradycardia: This will be defined as bradycardia less than 60 beats per minute that results in an accompanying decrease in systolic blood pressure (greater than 30 mmHg decrease). If this occurs in 3 patients and no other cause is found, the study would be stopped.

e). Anaphylaxis: This will be investigated and if no other reason is found, the study will be stopped if it is observed in 2 patients.

f). Skin reaction at the site of administration: This would be further classified into mild skin reaction or severe and generalized skin reaction. i. If severe and generalized skin reaction occurs in 3 patients and is believed to occur as a result of dexmedetomidine, the study would be stopped. ii. If a localized skin reaction occurs in 3 patients and is believed to occur as a result of dexmedetomidine the study would be stopped.

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

Postoperative pain and oxygen requirement following Tonsillectomy and Adenoidectomy continues to be a major etiology of prolonged post anesthesia recovery room stay. The analgesia sparing effects of dexmedetomidine as well as the effects of sedation without respiratory depression may allow for quicker postoperative recovery from this surgery.

Describe potential benefit(s) to society of the planned work.

It is possible that dexmedetomidine will decrease the need for perioperative analgesia following this surgery thereby allowing quicker transition through the recovery room phase and reducing hospital as well as patient cost.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

The risk to benefit ratio is low, routine anesthetic monitoring during and after surgery will not be altered by this study. Expected heart rate and blood pressure changes seen with dexmedetomidine are not different from those seen with morphine, a drug routinely used in general anesthesia. The very small risk to a subject from study participation would not outweigh the potential benefit to society that may result from study findings.

Section J: Consent Procedures

J1. Waiver of Consent

Will this research require a waiver of consent and authorization?

No

Will additional pertinent information be provided to subjects after participation?

No

Explain why providing subjects additional pertinent information after participation is not appropriate.

J1a. Waiver of requirement for written documentation of Consent

Is this research subject to FDA regulations?

No

Explain how the research involves no more than minimal risk to the participants, and the specifics demonstrating that the research does not involve procedures for which written consent is normally required outside of the research context.

Explain how the only record linking the participant and the research would be the consent document, and how the principal risk would be potential harm resulting from a breach of confidentiality, and how each participant will be asked whether he or she wants documentation linking the participant with the research and their wishes will govern.

J2. Consent Procedures

Who will recruit subjects for this study?

PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

Subjects will be identified from the pediatric surgery schedule for Texas Children's Hospital, which is routinely available to the Division of General Pediatric Anesthesia for the purpose of pre-operative evaluation. The PI, co-investigators, or staff will approach subjects meeting the inclusion criteria, and the study will be explained with emphasis on the voluntary nature of participation. A Spanish translator and short Spanish version of the consent will be available for Spanish speakers. Consent may be obtained from one or both parents (Texas law allows consent to be obtained from one parent) and the child clause will be included in the consent i.e. the parent can state that the child assents according to his or her own level of understanding.

Are foreign language consent forms required for this protocol?

Yes

Which of the following ways will you document informed consent in languages other than English?
Short-Form consent documents

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?
No

J4. Children

Will children be enrolled in the research?
Yes

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?
No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?
No

J7. Prisoners

Will Prisoners be enrolled in the research?
No

Section K: Confidentiality

Will research data include health information by which subjects can be identified?
Yes

Where will research data be kept? How will such data be secured?
Data will be kept in a locked file cabinet in the PI's office. Computer data sets will be password protected.

Who, besides the PI, the study staff, the IRB and the sponsor, will have access to identifiable research data?
Data will be available only to the PI, co-investigators , and staff.

Will you obtain a Certificate of Confidentiality for this study?
No

Please further discuss any potential confidentiality issues related to this study.
NA

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.
The research procedures consist of the drug administration protocol. There will be no charge to the subject or subject's insurance company.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:
0

Distribution Plan:

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

None

Section O: Drug Studies

Is this study placebo-controlled?
No

Does the research involve a drug or biologic (including radioactive drugs) that is not approved by the FDA?
No

Will the research involve a radioactive drug?
No

IND Number:
79,290

Section P: Device Studies

Does this study need an IDE?
No

Regarding your device study, could potential harm to subjects be life-threatening?
No

Regarding your device study, could potential harm to subjects result in permanent impairment of a body function?
No

Regarding your device study, could potential harm to subjects result in permanent damage to a body structure?
No

Section Q. Consent Form(s)

Consent form elliciting possible participation in a double-blind, randomized study examining dexmedetomidine and morphine for analgesia in children having adenotonsillectomy

Section R: Advertisements

None