COVER PAGE

TITLE: The use of dexmedetomidine as an adjuvant for perioperative pain management in morbidly obese adolescents undergoing bariatric surgery

NCT02880540

February 17, 2018

CHILDREN'S HOSPITAL
Department of Anesthesiology
111 Michigan Avenue, NW
Washington, DC 20010
(202) 476-2025

RESEARCH PROTOCOL

TITLE: The use of dexmedetomidine as an adjuvant for perioperative pain management in morbidly obese adolescents undergoing bariatric surgery

RESEARCH PLAN

A. Specific Aims

The anesthetic management of obese adolescents undergoing bariatric surgery presents a number of challenges. These patients often have obstructive sleep apnea (OSA), increased sensitivity to opioids, and are at risk for postoperative respiratory complications. Therefore, during the postoperative period, obese adolescents are at increased risk for opioid-related respiratory complications. These issues pose a challenge, as bariatric surgery in obese adolescents can be associated with significant postoperative pain. Given that opioids are the mainstay of perioperative pain management, achieving a balance between adequate pain control and avoiding respiratory complications in obese adolescents can be challenging. This is particularly important because agents without respiratory depressant effects, such as non-steroidal anti-inflammatory drugs, acetaminophen, and local anesthetics, are often inadequate to treat postoperative pain. Our overall goal is to improve pain management of morbidly obese adolescents undergoing bariatric surgery at Children's National Health System (CNHS) and to decrease respiratory complications associated with opioid use during the perioperative period.

Dexmedetomidine, a selective α_2-adrenoreceptor agonist that has sedative and analgesic properties but no respiratory depressant effects, has been used in perioperative settings and shown to have opioid-sparing effects. Our overall hypothesis proposes that intraoperative administration of dexmedetomidine will decrease opioid requirement, prolong the opioid-free dosing interval, and decrease the incidence of respiratory depression and nausea that is typically associated with opioid analgesia. If successful, the proposed intervention has the potential to greatly improve pain management of obese adolescents undergoing bariatric surgery.

The two aims of this study are geared toward determining the pharmacodynamic and pharmacokinetic profile of dexmedetomidine in obese adolescents undergoing bariatric surgery at our institution.

Specific Aims 1: To determine the pharmacokinetic (Pk) profile of dexmedetomidine in obese adolescents undergoing bariatric surgery.
Aim 1A: To collect venous blood samples at several time points before and after the administration of dexmedetomidine.
Aim 1B: Describe the Pk model of dexmedetomidine.
Hypothesis 1: The concentration of dexmedetomidine during blood sampling will be higher in obese adolescents.

Specific Aims 2: To determine the pharmacodynamic (Pd) profile of dexmedetomidine in obese adolescent bariatric patients.
Aim 2A: To compare postoperative pain scores in dexmedetomidine-treated patients with those who received the standard of care pain management.
Aim 2B: To compare postoperative opioid use between dexmedetomidine-treated patients and patients who received the standard of care pain management.
Hypothesis 1: Dexmedetomidine-treated patients will have decreased postoperative pain scores and an increased opioid-free dosing interval in the PACU.
Hypothesis 2: Dexmedetomidine will decrease the incidence of nausea in the PACU.

B. Background and Significance

Obesity represents one of the most important public health issues according to the World Health Organization and it has reached epidemic proportions globally. The prevalence of childhood obesity has rapidly increased over the past decade and is associated with multiple co-morbid disease states [1,2]. It is estimated that approximately 15.5% of children and adolescents are obese (body mass index [BMI] of ≥95th percentile for age) [3]. This not only poses health concerns for the patient, but also places increased demands on our healthcare system that is already overwhelmed by burgeoning costs. Moreover, obese children and adolescents who maintain excessive weight as adults are predisposed to cardiovascular disease and premature death [4].

In carefully selected patients who have failed to lose weight by diet and exercise, bariatric surgery provides an option to obtaining a healthy weight [5]. It is increasingly becoming an attractive option, with the number of adolescents undergoing bariatric surgery in the United States tripling between 2000 and 2003 [6].

Obese patients are often afflicted with multi-organ dysfunction and obstructive sleep apnea (OSA), which presents unique challenges to the anesthesiologist managing their perioperative care [7]. Bariatric surgery in obese adolescents may be associated with significant postoperative pain. Potent intravenous opioids such as fentanyl and morphine are at the mainstay of the perioperative pain management. Unfortunately, respiratory depression and airway obstruction can often occur following administration of opioids in obese patients [8,9]. This makes providing a safe analgesic regimen difficult during the perioperative setting. As opioids can be associated with respiratory depression and upper airway obstruction, surgeons and anesthesiologists alike must reconcile the adequacy of pain control with the risk of respiratory complications after surgery in obese adolescents.

Dexmedetomidine is a non-opioid drug that has shown some utility during bariatric surgery in the adult population because of its analgesic properties [10,11]. It is a lipophilic imidazole derivative that is a selective α_2-adrenoreceptor agonist with sedative and analgesic properties devoid of respiratory depressant effects [12]. Dexmedetomidine produces sedation by modulating the release of the neurotransmitter norepinephrine within the locus coeruleus of the brain, which is vital to producing an awake state [12]. In addition, by directly stimulating α_2-receptors in the spinal cord, dexmedetomidine inhibits the firing of nociceptive neurons responsible for the propagation of pain signals [12].

Although dexmedetomidine is an agent with many off-label clinical applications in the pediatric setting, much about its pharmacokinetics (Pk) and pharmacodynamics (Pd) remain unknown [13]. This is even more evident for our pediatric patients that are obese. Currently, there are no reported Pk/Pd studies that have investigated dexmedetomidine in obese children and adolescents. Our previous experience with the use of dexmedetomidine in the perioperative period along with our robust obese surgical population certainly supports the notion that we are well poised to conduct the proposed trial.

C. Preliminary Studies

At our institution, we have previously conducted a randomized clinical trial of dexmedetomidine during the perioperative period of children undergoing tonsillectomies who are at high risk for respiratory complications. We showed that dexmedetomidine lengthens the opioid-free interval after surgery and appears to decrease overall morphine requirements during the postoperative period [14]. We also showed that dexmedetomidine administered as a single bolus dose appears to attenuate the hemodynamic changes (increases in heart rate and blood pressure) known to occur at stimulating times during tonsillectomy and the initial PACU stay [14]. With that trial, we showed that a selective α_2-adrenoreceptor agonist such as dexmedetomidine has favorable opioid-sparing effects and perhaps should be considered as an adjunct for analgesia during the perioperative period. The literature supports the use of dexmedetomidine as a safe and effective adjunct in morbidly obese patients undergoing anesthesia [15,16,17].

D. Research Design and Methods

This is a single-center, open-label pilot study enrolling 50 obese adolescent patients undergoing bariatric surgery. Per standard of care, all patients who undergo bariatric surgery at CNHS must receive a preoperative evaluation at the Preoperative Care Clinic (POCC) approximately one week prior to surgery. During this visit, patients will be identified and approached for participation and the study will be explained in detail. They will be given an opportunity to ask questions and will be provided with adequate time to consider participating in the study. On the day of surgery, consent and assent will be obtained by one of the investigators. Subjects will be assigned to one of two treatment groups: intraoperative dexmedetomidine or current standard of care.

The study procedures are divided into three phases: screening, treatment and follow-up. The measurements and activities to be conducted during each phase are described below.

Screening Phase

All subjects will have a medical history taken including medications taken within the last 24 hours prior to surgery. A complete physical examination including baseline vital signs (heart rate, respiratory rate and blood pressure), pulse oximetry and physical measurements (height and weight) will be performed. All screening procedures and the investigator's assessment of the inclusion/exclusion criteria must be completed and evaluated by the investigator before enrolling the subject. Demographics such as age, race and gender will be recorded.

Subjects will be randomly assigned to one of the following two treatment groups:

- Treatment Group 1: intraoperative dexmedetomidine
- Treatment Group 2: current standard of care using fentanyl

Treatment assignments will be based on an alternate schedule. All drugs, including the study drug, are on the CNHS formulary. The anesthesiologist in the procedure will prepare and administer all the drugs. As per standard of care, each drug syringe will be prepared on the day of treatment and labeled with the subject's initials, subject number, date and time of expiration.

Treatment Phase

The treatment phase starts in the preoperative holding area (AMSAC) and ends at the time of discharge from the Post Anesthesia Care Unit (PACU).

Two intravenous (IV) lines will be used for this study. The first IV (standard of care) will be placed before induction of anesthesia by one of the investigators or preoperative caregiver while in AMSAC. Prior to venous cannulation, a topical anesthetic patch (Synera) will be provided. When the patient is under general anesthesia, the second IV (study practice) will be placed.

<u>Induction and maintenance of general anesthesia:</u>

The patient will then be transported to the operating room on a stretcher by the anesthesiologist. Prior to the induction of anesthesia, vital signs (heart rate, blood pressure) and oxygen saturation via pulse oximetry will be obtained.

Per standard practice, the patient will receive pre-oxygenation via a facemask. He/she will receive intravenous induction using propofol 2-3 mg/kg (based on ideal body weight) and a paralytic agent, succinylcholine dosed at 1 mg/kg (based on total body weight) to facilitate instrumentation of the airway with an endotracheal tube (ETT). Time of anesthesia induction (as indicated by loss of eyelash reflex) will be recorded. Vital signs (heart rate and blood pressure) and oxygen saturation via pulse oximetry measurements will be obtained at this time (immediately post-induction). Time of intubation will be recorded. If respiratory

depression or apnea occurs during induction, ventilation will be supported manually. Any stress responses to intubation should be treated at the investigator's discretion.

Vital signs (heart rate and blood pressure) will be assessed for response to inadequate (light) anesthesia, hypotension or bradycardia during surgery.

A response to surgical stimuli (inadequate anesthesia) is defined as one or more of the following:

- Hypertension--Systolic blood pressure ≥ 20% above baseline for ≥1 minute (for 2 consecutive readings)
- Tachycardia--Heart rate ≥ 20% above baseline for ≥1 minute (for 2 consecutive readings)
- Somatic--movement, swallowing, grimacing, eye opening
- Autonomic--Tearing, sweating, mydriasis

Hypotension and bradycardia are defined as:

- Hypotension--Systolic blood pressure ≥ 20% below baseline for ≥1 minute
- Bradycardia--Heart rate <60 for ≥1 minute

Hypotension will be treated initially with a fluid bolus 20 ml/kg IV of crystalloid and then, if necessary, phenylephrine 5 µg/kg IV followed by an infusion, if necessary.

For bradycardia, glycopyrrolate 0.01 mg/kg IV (ideal body weight) may be given for clinically significant bradycardia as determined by the investigator.

If treatment is given, the subject's heart rate and blood pressure will also be recorded at this time.

Standard monitoring consisting of a pulse oximeter will be placed for continuous measurement of oxygen saturation (SpO_2) and heart rate. Blood pressure readings will be obtained per standard of care. The leads for a standard Lead II electrocardiogram will be placed for continuous monitoring of the subject throughout the treatment phase. A capnometer will be used to monitor $P_{ET}CO_2$ concentrations while the subject is being ventilated. Subjects $P_{ET}CO_2$ should be maintained within a range of 35-45 mmHg and SpO_2 should be maintained > 93% during the treatment phase.

These procedures/assessments will be started whenever practical during induction, usually coinciding with loss of eyelash reflexes, and monitored continuously and recorded at 5 minute intervals throughout the study. Any cardiovascular incidents, which are considered clinically significant, i.e., where intervention or medication is administered, will be recorded as an adverse event. Medication administered in response to these incidences will also be recorded.

In the operating room, subjects will have maintenance of general anesthesia with a mixture of desflurane, oxygen and air. Desflurane will be adjusted throughout the case to reflect anesthetic needs, keeping the heart rate and blood pressure within 20% of

baseline. End-tidal desflurane concentrations will be recorded on the anesthesia record per standard of care.

Surgical incision should be performed only after the steady state end-tidal desflurane concentration has been maintained for at least 5 minutes. Time of surgical stress events (surgical incision) will be recorded. Vital signs (heart rate and blood pressure), pulse oximetry, $P_{ET}CO_2$ concentration, and end-tidal desflurane concentration will be obtained and recorded at these events. Response to the surgical stress will be recorded and compared with recorded vital signs.

Towards the completion of surgery, desflurane will be reduced then discontinued when at the end of surgery. Vital signs (heart rate and blood pressure), pulse oximetry, $P_{ET}CO_2$ and end-tidal desflurane concentration will be recorded at this time then every 5 minutes until extubation.

Prior to extubation, subjects will be allowed to breathe spontaneously and awake and following commands. Vital signs (heart rate and blood pressure), pulse oximetry, $P_{ET}CO_2$ and end-tidal desflurane concentration will be recorded just prior to extubation and time of extubation will also be recorded. Following extubation, the subjects vital signs (heart rate and blood pressure) and pulse oximetry measurements will be obtained. The subject will then be transferred from the operating room to the Post Anesthesia Care Unit (PACU).

Pharmacokinetic assessment:

Subjects in the treatment arm will receive dexmedetomidine after ETT placement. They will receive an intravenous loading dose of dexmedetomidine 2 mcg/kg via syringe pump over 30 min, followed by a continuous infusion at a dose of 0.5-0.7 mcg/kg/h that will be discontinued upon completion of surgery. Of note, dexmedetomidine doses will be based on ideal body weight. Total dexmedetomidine doses will be recorded for each patient.

Vital signs (heart rate and blood pressure), pulse oximetry and end-tidal carbon dioxide concentrations ($P_{ET}CO_2$) will be obtained just prior to start of study drug treatment and then every five minutes.

For subjects in the dexmedetomidine-treated group, blood samples for the determination of dexmedetomidine levels will be obtained at time 0, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours and 6 hours after the administration of dexmedetomidine. At each blood withdrawal, 2 mL of blood will be obtained by a member of the research team.

In total, (10) 2-ml blood samples will be collected from each subject in the dexmedetomidine-treated group for research purposes. The blood samples will be drawn in the OR, PACU and in-patient units. In addition, the samples will be processed in the Clinical Research Center (CRC). Plasma will be separated from whole blood by centrifugation and stored appropriately at -80 degrees. Dexmedetomidine levels will be determined by a method using reverse-phase high-performance liquid chromatography triple quadrupole mass spectrometry.

Subjects in the standard of care group will receive fentanyl at the discretion of the anesthesiologist and the total dose will be recorded. Heart rate and blood pressure will be recorded at induction of anesthesia, at skin incision, 5 minutes after incision, at 10-minute intervals after incision, at extubation, and 5 minutes after extubation.

Pharmacodynamic assessment:

Recovery

Upon admission to the PACU, the nurse will perform the following assessments:

- vital signs (heart rate, respiratory rate, blood pressure)
- oxygen saturation
- pain using the Numerical Rating Scale, Appendix I
- agitation using the Agitation Scale, Appendix II
- recovery using the Steward Recovery Scoring System, Appendix III

These assessments will be recorded every five minutes for the first fifteen minutes; then every fifteen minutes until discharge from PACU. Eligibility time for discharge from the PACU and actual time of discharge from the PACU will be recorded Patients will receive 2 mg of morphine when they have a NRS > 5. Fifty micrograms of fentanyl may be used for break-through pain fifteen minutes after the initial morphine PACU dose. If higher pain scores persist, an additional 2 mg morphine dose may be given. The PI will be notified for bedside evaluation and treatment if pain scores continue above a NRS>7.The use of morphine and fentanyl for pain agitation will be recorded from PACU entry through discharge from PACU. After discharge from the PACU, pain will be assessed and managed per standard of care.

The incidence and time of post-operative nausea and vomiting (PONV) will be recorded up until 24 hours post study drug administration. The presence of nausea will be established by verbal complaints of feeling "nauseated", "sick to the stomach" or "going to throw up" from the subject. An episode of vomiting is defined as expulsion of any stomach contents through the mouth. An episode of retching (i.e. dry heaves) is an attempt to vomit that is not productive of any stomach contents. An emetic episode is defined as a single vomit or retch or any number of continual vomits and/or retches. PONV will be recorded as mild (nausea only), moderate (nausea and one or two emetic episodes) and severe (three or more emetic episodes).

Subjects who experience nausea or an emetic episode will receive rescue anti-emetic medication and will be treated with ondansetron 0.15 mg/kg IV every six hours as needed. The administration of rescue anti-emetic medication for PONV will be recorded.

In this study, the recovery period is defined as the time from the end of the emergence period until the subject is deemed ready for discharge from the PACU.

Follow-up Phase

The follow-up phase starts at time of discharge from the Post Anesthesia Care Unit (PACU) and ends at time within 24 hours following surgery when the final study assessments are obtained.

After discharge from the PACU vital signs (heart rate, respiratory rate, blood pressure) and pulse oximetry assessments will be obtained in the designated recovery area every hour for the first 4 hours then every 2 hours for 4 hours per standard of care.

Patients will receive intravenous ketorolac 30 mg every 6 hours; morphine 2 mg every 2-3 hours. Total opioid use (fentanyl, morphine) will be recorded and converted to total morphine equivalent dose. NRS scores will be recorded per standard of care while in the in-patient unit.

Within 24 hours following surgery, all subjects will be interviewed by a member of the study team to assess for the incidence PONV, pain, and medication use since discharge from the PACU. The occurrence of any adverse events will also be assessed. Any findings and treatments used will be recorded.

Medications administered during the clinical trial other than those required for anesthesia will be recorded.

An adverse event (AE) is defined as an unusual and most often undesirable symptom or sign that occurs in subjects participating in a clinical trial. The subject will be observed for the occurrence of adverse events until 24 hours after study drug administration or until hospital discharge, whichever comes first.

All adverse events occurring during this clinical trial will be recorded. All serious adverse events as defined under the guidelines of this Institution's Institutional Review Board (IRB) will be reported to the IRB, though none are expected.

Statistical Considerations

There are no data about the Pk profile and the effects of dexmedetomidine in obese adolescents undergoing bariatric surgery. Therefore, the data collected in the proposed study will show the Pk profile of the drug in our patient population and in turn inform the best dexmedetomidine dosing regimen for future studies in the obese adolescents. Opioid consumption will be converted to morphine equivalents. The mean difference of the morphine equivalents during the perioperative course will be analyzed for the dexmedetomidine-treated and control groups. The mean difference of numeric variables (such as pain scores, time to extubation, time to purposeful movement) will also be calculated. Furthermore, the observed effect on opioid requirements and pain scores in this pilot study will inform the design of a follow-up appropriately-powered randomized clinical trial to determine the efficacy of dexmedetomidine in treating postoperative pain in bariatric surgery. Dichotomous variables (incidence of nausea/vomiting, hypotension or bradycardia requiring treatment) will be analyzed as risk ratios.

Efficacy Evaluations

Primary Efficacy Endpoint (Analgesia)

The following assessments will be evaluated as the primary efficacy endpoint in this study:

- Response to surgical stress events
  1. Hemodynamic response to incision and/or placement of laparoscopic ports
  2. Postoperative pain scores using Numeric Rating Scale
  3. Opioid consumption in morphine equivalent
  4. Incidence of rescue medication to treat inadequate anesthesia responses, hypotension or bradycardia

- Need for pain rescue medication (morphine) post-operatively and pain scores
- Need for anti-emetic medication (ondansetron) post-operatively

Secondary Efficacy Endpoint (Recovery Characteristics)

The following assessments will be evaluated as the secondary efficacy endpoint in this study:

- Time to extubation
  The criteria for extubation include:
  1. Return of laryngeal and pharyngeal reflexes
  2. Resume spontaneous ventilation

- Recovery from anesthesia
  Recovery from anesthesia will be assessed for the following at the end of the surgical procedure:
  1. Time to purposeful movement (Steward Score of 6)
  2. Incidence of nausea and vomiting (analyses will be performed to determine if there is a decreased incidence of PONV between treatment groups)
  3. Qualification for discharge from PACU (when criteria are met)
  4. Patient qualification for discharge from hospital (absence of severe pain, no nausea or mild nausea not requiring pharmacologic intervention, absence of vomiting)

- Safety parameters to be collected include review of medical history and physical examination, hemodynamic parameters (heart rate, blood pressure), respiratory function (respiratory rate, oxygen saturation, end-tidal CO_2), use of concomitant medications and clinical adverse events.

E. Study Population (Gender and Minority Inclusions)

The population for this study will be both male and female adolescent subjects from all ethnic backgrounds, scheduled to undergo elective laparoscopic sleeve gastrectomy for morbid obesity. Total enrollment will amount to 50 subjects; 25 subjects in each treatment group.

Inclusion criteria:

All of the following criteria must be met for the potential subject to be eligible for participation:

1. The subject is between 12-20 years of age

2. Those with BMI ≥ 95th percentile. At our bariatric center the minimum BMI is 35 to qualify for surgical intervention for weight loss.
3. The subject will be hospitalized overnight after surgery
4. The subject's parent/legally authorized guardian has given written informed consent to participate; and where applicable, the subject has given appropriate consent or assent to participate

Exclusion Criteria:

The potential subject is NOT eligible for participation if any of the following exclusion criteria apply:

1. The subject has a history or a family (parent or sibling) history of malignant hyperthermia
2. The subject has known significant renal or hepatic disorders determined by medical history, physical examination or laboratory tests.
3. The subject has a known or suspected allergy to opioid analgesics
4. An allergy to α2-adrenergic agonists or sulfa drugs
5. A history of uncontrolled hypertension
6. Clinically significant neurologic diseases
7. The subject is a pregnant or lactating female (if post-menarche, a negative pregnancy test must be confirmed prior to the planned surgery time in AMSAC, consistent with current standard of care).
8. The subject has history of cardiovascular issues which would preclude the use of dexmedetomidine, (e.g. Down's Syndrome, dysrhythmias, conditions where hypotension is to be avoided).

F. Human Subjects (Risks & Benefits)

The research material obtained from human subjects will be in the form of data collection as previously described. Data will be obtained specifically for research purposes. Controls will come from the same population as the subjects.

The investigator will identify subjects who are eligible for this study after review of the surgical schedule and consultation with the subject's surgeon.

Subjects and their parents will be approached regarding participation in the study during the preoperative evaluation prior to the day of surgery. The investigator or his designee will describe the study protocol and procedures and answer any questions pertaining to the study to their satisfaction. On the day of surgery, written informed consent will then be obtained from the subject's parent or legal guardian in accordance with all applicable regulatory requirements. Informed consent/assent will be obtained prior to conducting any study related tests or procedures.

Duration of study participation will begin from the time the informed consent (and assent, when applicable) document is obtained through to the time the 24 hour post-surgical interview is conducted. During this interview, it will be disclosed to the subjects and their parents whether they received intraoperative dexmedetomidine or the standard pain

medication. Once the study has been completed and the data analyzed, the subjects will be notified of the results.

G. Risks and Side Effects

Potential risks are included in the risks of surgery and anesthesia. The use of fentanyl and morphine have become routine practice at CNHS with no serious side-effects when administered. The most common side effects noted with the use of fentanyl are those often associated with opioid use. They include respiratory depression, pruritus, nausea and/or vomiting and constipation. The administration of fentanyl and morphine for this study should not pose additional risks.

In contrast to the standard of care, dexmedetomidine does not induce these risks since it is not an opioid. The potential risk with use of dexmedetomidine include hypotension/hypertension, increased sleepiness, and bradycardia if administered too quickly or at too high of a dose.

All study records will be kept confidential. Provisions to protect the privacy of patients and maintain the confidentiality of data will include the use of an assigned study number instead of the patient's name on all records and documents produced in performing and reporting the results of this study. These records will be kept in a secure location.

No other risks are anticipated.

H. Benefits

The analgesic and sedative effects of dexmedetomidine with the lack of respiratory depression make it a potentially attractive agent to provide perioperative analgesia for a variety of procedures. An agent without the emetic potential or respiratory depressant effects of opioids is very attractive in this surgical population who is very sensitive to the respiratory depressant effects of opioids.

The information generated by this study will provide clinically useful information regarding the effectiveness of dexmedetomidine and characterize the hemodynamics and post-operative analgesia profile when compared to conventional opioids such as fentanyl and morphine. Although participation in this study may not benefit all subjects, the information obtained can be directly applied to obese adolescents for future use.

I. Outside Consultants/Collaborators

No outside consultants will be used.

J. Contractual Agreements

There are no contractual agreements.

K. Costs To Subjects

There are no additional costs to subjects for participation in this study. Subjects will still be charged for medications and medical care per standard of care at CNHS.

L. Conflicts Of Interest

There are no conflicts of interest.

M. Confidentiality

Subject confidentiality will be maintained at all times. Each subject will be assigned a subject number and the initials of each subject will be used when recording data collected on the subject's worksheet. A master enrollment log containing the subject's name and medical record number will be kept in a secured area by the Study Coordinator.

The Principal Investigator and members of the study team involved with this study shall not disclose or use for any purposes (other than performance of the study) any data, records or other information.

N. Subject Compensation

There is no subject compensation for participation in this study.

O. Facilities and Equipment

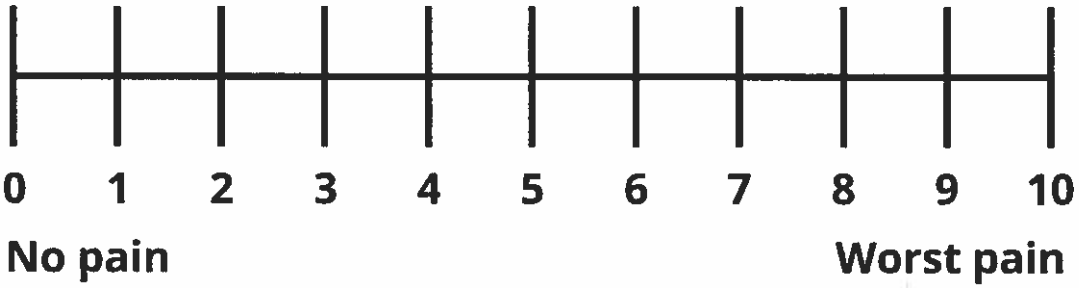
This study will be conducted primarily within the Peri-Operative area (AMSAC, Operating Room, PACU) and the 23-hour Recovery Unit of Children's National Health System. All materials for this study are a part of routine care.

P. References & Literature Cited

1. Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. *J Pediatr* 2007; 150:12-7, e2.
2. Thompson DR, Obarzanek E, Franko DL, et al. Childhood overweight and cardiovascular risk factors: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr* 2007; 150:18-25.
3. Finkelstein EA, Fiebelkorn IC, Wang G. National medical spending attributable to overweight and obesity: how much, and who's paying. *Health Affairs* 2003(suppl W3);219-226.
4. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. *Gastroenterology* 2007; 132:2087-2102.
5. Inge TH, Krebs NF, Garcia VF, et al. Bariatric surgery for severely overweight adolescents: concerns and recommendations. *Pediatrics* 2004; 114:217-223.

6. Tsai WS, Inge TH, Burd RS. Bariatric surgery in adolescents: recent national trends in use and in-hospital outcome. *Arch Pediatr Adolesc Med.* 2007; 161(3):217-221.
7. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. *Br J Anaesth* 2000; 85:91-108.
8. Benumof JL. Obesity, sleep apnea, the airway and anesthesia. *Curr Opin Anae* 2004; 17(1):21-30.
9. Ingrande J, Lemmens HJM. Dose adjustment of anaesthetics in the morbidly obese. *Br J Anaesth* 2010; 105(S1):i16-i23.
10. Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. *J of Clinical Anesth* 2006; 18: 24-28.
11. Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, Skrivanek G, Macaluso A, Shah M, Provost DA. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. *Anesth Analg* 2008; 106:1741-8.
12. Ramsay MA. Bariatric surgery: the role of dexmedetomidine. *Seminars in Anesthesia, Perioperative Medicine and Pain* 2006; 25:51-56.
13. Mason KP, Lerman J. Dexmedetomidine in children: current knowledge and future applications. *Anesth Analg* 2011; 113:1129-42.
14. Pestieau SR, Quezado ZMN, et al. High-dose dexmedetomidine increases the opioid-free interval and decreases opioid requirements after tonsillectomy in children. *Can J Anesth* 2011; 58:540-50.
15. Andersen LP, Werner MU, et al. Analgesic treatment in laparoscopic gastric bypass surgery: a systematic review of randomized trials. *Obes Surg* 2014; 24(3):462-70.
16. Hofer RE, Sprung J, et al. Anesthesia for a patient with morbid obesity using dexmedetomidine without narcotics. *Can J Anaesth* 2005; 52(2):176-80.
17. Gaszynski T, Gaszynska E,Szewczyk T. Dexmedetomidine for awake intubation and an opioid-free general anesthesia in a superobese patient with suspected difficult intubation. *Drug Des Devel Ther* 2014; 8:909-12.
18. Hannivoort LN, Eleveld DJ, Proost JH, et al. Development of an optimized pharmacokinetic model of dexmedetomidine using target-controlled infusion in healthy volunteers. *Anesthesiology* 2015; 123: *in press.*
19. Petroz GC, Sikich N, James M, et al. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. *Anesthesiology* 2006; 105:1074-5.

Appendix I: Numerical Rating Scale



Rate your pain or pain relief from 0-10

Appendix II: Agitation Scale

Behavior	Score
Asleep	0
Awake, Calm	1
Mildly agitated, but consolable	2
Hysterical, crying inconsolably	3

Appendix III: Steward Recovery Scoring System

Consciousness	
Awake	2
Responding to Stimuli	1
Not Responding	0
Airway	
Crying or Coughing on Command	2
Maintaining Good Airway	1
Airway Requires Maintenance	0
Movement	
Moving Limbs Purposefully	2
Non-purposeful Movements	1
Not Moving	0