A Double-Masked Placebo Controlled Clinical Trial of the Postoperative Opioid Sparing Effects of Intraoperative Dexmedetomidine Infusion for Thoracic Surgery

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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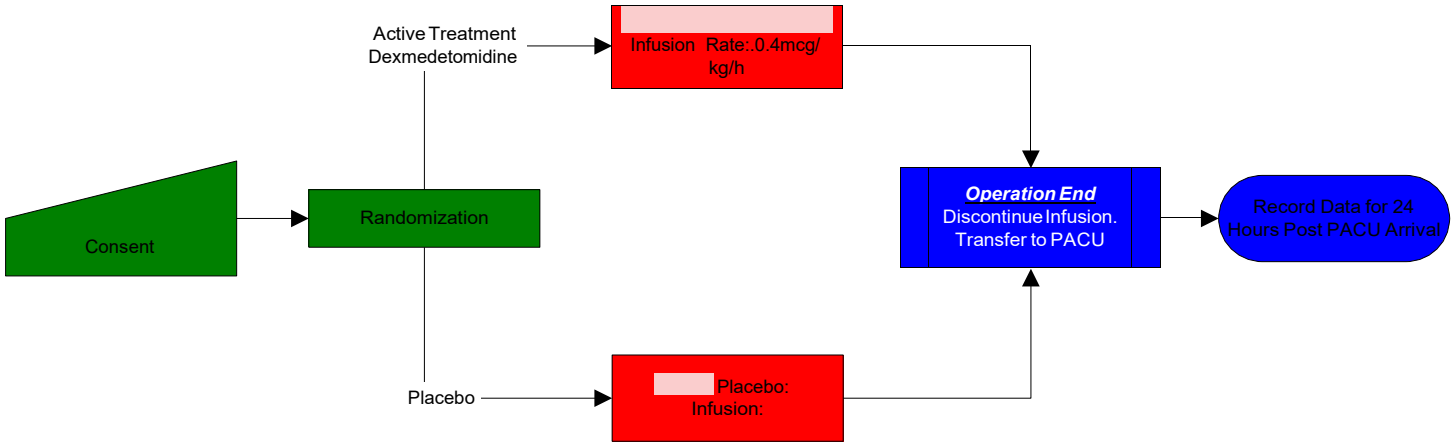
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This study is designed to assess whether the sedative Dexmedetomidine (PRECEDEX), when used intraoperatively only and stopped at the end of the operative procedure, provides analgesia up to 24 hours following surgery as well as fewer opioid side effects. If beneficial, the use of Precedex could be a component in the 23 hour surgical protocols.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.2 Primary Objective

To determine if the use of intravenous dexmedetomidine intraoperatively only and stopped at the end of the operative procedure, provides analgesia for up to 24 hours following surgery as well as fewer opioid side effects. This will be measured by total opioid administered postoperatively in opioid equivalents (the equivalent dose in intravenous morphine as defined at the end of section 10.0 below). The primary measure will be total opioid administered in the first 4 hours. Data will be collected up to 24 hours after arrival in PACU or discharge (if sooner).

2.3 Secondary Objectives

To explore whether the use of intravenous dexmedetomidine infusion intraoperatively:

1. Improves analgesia as measured by change in Pain Numerical Rating Scale (NRS) preoperatively to postoperatively at rest and with activity (such as coughing).
2. Results in fewer cumulative episodes of nausea or antiemetic doses and/or sedation as measured by incidence of recorded nausea, the use of antiemetics and RASS sedation scores, respectively.

3.0 BACKGROUND AND RATIONALE

The use of an epidural catheter with local anesthetic has demonstrated benefit in lessening certain opioid side effects such as post-operative ileus[1] by minimizing systemic opioid use [2]. For short stay cases, use of an epidural catheter is not routine because the risk of placement may not justify the short duration of benefit. An alternative means of providing adequate analgesia with minimal side effects must be sought. Without an epidural or another regional approach, opioids via intravenous patient controlled analgesics (IV-PCA) or as needed (prn) opioid systemic analgesics are the most common alternatives.

Selective α_2-adrenoceptor agonists such as clonidine already have approved uses for both acute and chronic pain when given epidurally. By interrupting pain signal transmission to the brain, α2-adrenoceptor agonists produce analgesia at presynaptic and postjunctional alpha2-adrenoceptors in the spinal cord[3]. Activation of the former at the locus coeruleus results in decreased norepinephrine release in descending neural pathways which decreases pain transmission at the spinal cord. Other regions identified to have a high density of α_2-adrenoceptors include the substantia gelatinosa, and the intermediolateral cell column , sites of major pain signaling[4].

Dexmedetomidine is the active dextro-isomer of medetomidine with 8 times more specificity for α2-adrenoceptors than clonidine. It has sympatholytic, sedative, and analgesic properties but without significant respiratory effects. Unlike clonidine, it may be given intravenously to achieve analgesic effect. Dexmedetomidine was approved in 1999 for short-term use of less than 24 hours as a sedative in mechanically ventilated patients in the intensive care unit [5]. Sedative effects are observed within 5 minutes following intravenous dexmedetomidine administration. Unlike other sedatives such as midazolam and propofol, patients on dexmedetomidine were sedated but easily arousable without respiratory depression[6]. Its sedative, sympatholytic and pro-respiratory properties allow it to be used as an adjunct to general anesthesia resulting in lower anesthetic doses (17-50%) with more rapid return to a non-anesthetized state[7].

Used off-label, dexmedetomidine has been shown in several studies to have analgesic properties [5-9]. Direct spinal action on α_2-adrenoceptors inhibits the release of substance P, which also results in analgesia[10]. Randomized studies by Arain et. al. showed a decrease of morphine use by 66% for major intraabdominal and orthopedic surgery (n=34)[8]. This study may have had incomplete blinding and involved continuation of the dexmedetomidine infusion in the recovery room from its initiation intra-operatively. In studies by Aho and colleagues, dexmedetomidine was administered at low and high bolus doses (no infusion) only postoperatively (no intraoperative use) and found to be analgesic but also sedative[6]. Interestingly, respiratory parameters improved in the dexmedetomidine group. Wahlander and colleagues used IV dexmedetomidine postoperatively following thoracic lung surgery as an adjunct to epidural analgesia[11]. A bolus and an infusion were started postoperatively only and showed opioid sparing effect, but this was also associated with bradycardia and hypotension. Lin and colleagues demonstrated opioid sparing for patients undergoing hysterectomies when dexmedetomidine was used in a PCA (patient-controlled analgesic device). They did note dexmedetomidine related side effects of bradycardia and hypotension postoperatively but also reported decreased morphine induced nausea. All

these effects were most pronounced in the initial 4 hours postoperatively. In all these studies, dexmedetomidine administration continued postoperatively with consequent hemodynamic effects and sedation in the recovery room as well as analgesia[12].

Patient"s presenting for thoracic surgery often have significant preexisting lung disease which narrows the therapeutic window between risk and benefit, both intraoperatively and postoperatively. Anesthetics are adjusted intraoperatively to promote extubation, while postoperative analgesia must be maximized to prevent reintubation. Patients undergoing major procedures such as lobectomy or pneumonectomy can achieve both goals using an epidural catheter to minimize anesthetic and maximize analgesia. Patients undergoing thorascopic procedures (VATS) for wedge resections or other simpler procedures (such as mediastinoscopy) are often discharged sooner (1-2 days) making the use of an epidural catheter sometimes impractical.

In this study, we wish to examine the effect of an intraoperative only infusion of dexmedetomidine on postoperative pain and opioid use for patients undergoing Thoracic Surgery providing residual analgesia after the infusion is terminated. These patients represent a population for whom epidural may provide benefit; but, for some surgeries, the risk of epidural placement may outweigh the benefit. However, given that such patients may have significant pre-existing lung disease, there is a desire to minimize opioid use and side effects. Specifically, we wish to examine if there is residual analgesia postoperatively from dexmedetomidine if the infusion ends in the operating room. Residual analgesia has been demonstrated where dexmedetomidine was used as an alternate to Propofol sedation for Monitored Anesthetic Care in regional cases[7] but no such examination has occurred for general anesthesia cases. The infusion in this study would be started in the operating room by a continuous intravenous infusion. Before arrival to the recovery room, the infusion will be stopped in the operating room. The goal is to assess if the intraoperative dose of dexmedetomidine will provide residual analgesia in the recovery room resulting in less opioid use and fewer opioid side effects and improved analgesia avoiding any delays in discharge.

No comparable protocol of this type has yet to be undertaken (i.e. with dexmedetomidine used intraoperatively only). The advantage of this study design over previous designs is the intraoperative use of the drug infusion only during the general anesthetic. In this way, any sedation resulting from the drug occurs during anesthesia where it may potentiate the anesthetic, blunting the sympathetic response, which may maximize the cardio-protective effects. Also, any potential bradycardia and hypotension from the drug will be identified and treated in a monitored setting with anesthesia providers continually present. Discontinuation of dexmedetomidine will occur before transport to the recovery room, minimizing ongoing side effects such as sedation, bradycardia and hypotension while allowing assessment of potential ongoing analgesia. The average Length of Stay over July and August 2011 was 3.67 days for 117 patients VATs patients. Given the institution"s goal to reduce some surgeries (such as VATs) to 23-hour stays, in part by maximizing analgesia and minimizing side effects, this study may represent a component towards that end.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

In this study, we wish to examine the analgesic effect of intraoperative dexmedetomidine use on postoperative pain, opioid use, and opioid related side effects for patients undergoing Thoracic Surgery. The study is a double masked parallel design with patients randomized to either an active agent (dexmedetomidine) or a placebo. The infusion will be started in the operating room through a continuous infusion. Before arrival in the recovery room, the infusion will be stopped in the operating room and all patients will receive a dose of ketorolac and IV acetaminophen, if no contraindications exist. In addition, the surgeon will infiltrate the wound with local anesthetic. On arrival to the recovery room, all patients will receive a patient-controlled analgesic (PCA) of intravenous Fentanyl (or equivalent) as a rescue dose only, without a basal rate. In addition all patients will be given acetaminophen as a standing order every 8 hours and ketorolac as needed assuming no contraindications exist.

The goal is to assess if the intraoperative dose of dexmedetomidine will provide residual analgesia in the recovery room resulting in less opioid use, improved analgesia and fewer opioid side effects. Analgesic use intraoperatively will be recorded to assess any confounding effects of dose of intraoperative opioid received on postoperative analgesia. Specifically, we wish to account for any post-operative analgesic effect of excess intraoperative opioids as this will affect the primary endpoint. Postoperative opioid use, pain scores and opioid side effects (use of antiemetics and RASS sedation scores) will be recorded to assess differences between active and placebo groups.

For details on the measures used, please see section 10.0.

4.2 Intervention

The study involves the use of dexmedetomidine infusion intraoperatively during thoracic surgical procedures (not using an epidural) with discontinuation in the immediate postoperative period. A key feature in this study is to employ the drug infusion intraoperatively only. Therefore, sedation resulting from the drug will occur during general anesthesia, where it may potentiate the anesthetic. Also, any potential bradycardia and hypotension from the drug will be identified and treated in a fully monitored setting with anesthesia providers continually present.

For this study, the research pharmacy will prepare both the active and placebo agent in a syringe at a fixed concentration. This will be used on a syringe infusion pump and dosed on a per kg basis. The study dose of dexmedetomidine is a continuous infusion of 0.4 mcg/kg/hr. This is consistent with prescribing recommendations for ICU sedation and most studies investigating dexmedetomidine"s use as an analgesic[12]. . Both active and placebo agents will be dosed in mls in an identical fashion. Before arrival in the recovery room, the infusion will be stopped in the operating room.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The active agent used in the study is dexmedetomidine, which is currently part of the MSK formulary. Dexmedetomidine is the active dextro-isomer of medetomidine and is about 8 times more specific for α_2-adrenoceptors than clonidine[10]. Dexmedetomidine was approved in 1999 for short-term use of less than 24 hours. The agent is FDA approved for use for sedation of non-intubated patients before and during surgical and other procedures and for sedation of intubated and mechanically ventilated patients during treatment in an intensive care unit[10]. It has no current analgesic properties, an endpoint of this study.

Dexmedetomidine is rapidly distributed to tissues with a rapid distribution phase half-life of approximately 6 minutes and a large volume of distribution[13].

Dexmedetomidine exhibits linear kinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by IV infusion for up to 24 hours.

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were lower than in healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64%, and 53% of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59%, 51%, and 32% of those observed in the normal healthy subjects, respectively. Although dexmedetomidine is dosed to effect, dosage reduction may be necessary in patients with hepatic impairment. Because of this, evidence of liver disease represents an exclusion criteria.

Pharmacokinetic values of dexmedetomidine were similar for patients with a creatinine clearance (CrCl) < 30 ml/min as compared with healthy subjects, but the pharmacokinetic values of the metabolites of dexmedetomidine have not been evaluated in patients with impaired renal function. As dexmedetomidine is extensively metabolized and most of the metabolites are excreted in the urine, metabolites may accumulate upon long-term infusions in patients with impaired renal function.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Adult patients (>=21 years old) scheduled for Thoracic Surgery.

6.2 Subject Exclusion Criteria

- 2nd or 3rd degree heart block as assessed by preoperative EKG
- Use of dexmedetomidine within 28 days prior to day of surgery
- Use of long acting opioids pre-operatively 28 days prior to day of surgery
- Current or past diagnosis of a Major Psychiatric disorder precluding adequate outcome responses such as Schizophrenia, dementia, delirium etc. as recorded in the Pre-Operative Record.
- Documentation of congestive heart failure and Ejection fraction < 30% if recorded in the Pre-Operative Record.
- Planned use of an epidural for surgery for post-operative pain relief

- Contraindication to use of NSAID, Acetaminophen or IV opioids.
- Any known hypersensitivity to dexmedetomidine
- Pregnant or breastfeeding
- Abnormal liver function tests as related to the MSK guidelines for use of IV Acetaminophen:

  Yes or NO?; Is ALT greater than 2 x Upper Limit of Normal (> 75 U/L)?

- Abnormal renal function tests as related to contraindications to use of IV Ketorolac:

  Yes or No?; Is Serum Creatinine < 1.5 mg/dl?

7.1 RECRUITMENT PLAN

This study will be available to all patients seen at Memorial Sloan-Kettering Cancer Center that meet the eligibility criteria. Patients scheduled for Thoracic Surgery will be identified for potential inclusion and recruited from the Thoracic Surgery clinics or Pre-Surgical Testing. Both men and women of all races and ethnic groups are eligible for this trial.

A consenting professional (typically the Thoracic Surgeon or Nurse Practitioner in conjunction with the RSA) will discuss the details of the study with the patient in the pre-surgical clinic. These details include but are not limited to the following:

- That the study involves research of an FDA approved drug (for sedation) but for an unapproved indication (pain).
- That participation is voluntary
- An explanation of the purposes of the research are to determine if this drug has any analgesic effect and permitting a decrease in opioid side effects
- The expected duration of participation is at most 24 hours or until discharge
- That the patient will be randomized to this drug or placebo and that the randomization will be unknown unless knowledge is required.
- Identification that only FDA approved drugs are being used and they are not experimental drugs awaiting approval.
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others which may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, such as not participating

Patients who expressed an interest but did not sign consent in the pre-surgical clinic or pre-surgical testing will be contacted by phone on any day prior to surgery. If appropriate, a consent discussion will occur on the phone with appropriate documentation of that discussion. Signing of the informed consent and any outstanding questions will be completed just prior to surgery on the day of surgery.

Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to study participation.

The goal is to recruit 280 evaluable patients total (140 per arm) over 12 months. Based on the withdrawal rate, we will need to recruit an estimated 335 patients to meet our target of evaluable participants.

Limited Waiver of Authorization

Potential research subjects will be identified by a member of the patient"s treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient"s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. A screening log will be maintained by the research team for review of the progress and potential barriers for the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

All patients will be evaluated by attending surgeons in the Thoracic Service. Extent of disease and potential resectability will be determined using a variety of cross-sectional imaging and other studies that will vary depending on the underlying diagnosis.

Prior to operation, the following will be performed.

- The patient will sign informed consent for the surgery
- The patient will be confirmed to have a documented pre-operative history and physical examination in the EPIC system. Current history will include any Psychiatric disorder precluding adequate outcome responses (based on investigator judgment) as determined by the preoperative Anesthetic Evaluation in the EPIC system. Patient demographics will be recorded
- Standard Preoperative testing, including EKG (to determine any exclusions) will be confirmed
- Notation will be made of any tests done as part of pre-operative clearance documenting ejection fraction.
- Serum pregnancy test for women of childbearing potential prior to therapy (to determine any exclusions) as per the MSK standard prior to surgery will be followed.
- A preoperative Numerical Rating Scale (NRS) for pain at rest and with activity (such as coughing) will be completed within 4 hours prior to surgery, in the pre-surgical center as a baseline.
- A preoperative query for nausea, vomiting and a RASS sedation score will be completed within 4 hours prior to surgery, in the pre-surgical center as a baseline.

9.0 TREATMENT/INTERVENTION PLAN

Patients scheduled for Thoracic Surgery will undergo no change in their routine care or preoperative testing except for inclusion of the study drug or placebo. As part of the study, the intravenous infusion will commence with the induction of general anesthesia. The infusion should end during the commencement of surgical closure, always prior to arrival in the recovery room. All patients will receive a dose of ketorolac and IV acetaminophen, unless there is a clinical consideration to avoid dosing (e.g. concern of bleeding postoperatively with ketorolac). In addition, the surgeon will perform intercostal blocks as standard practice (unless not advisable clinically). On arrival to the recovery room, all patients will receive a patient-controlled analgesic (PCA) of intravenous Fentanyl (or equivalent) as a rescue dose only, without a basal. In addition all patients will be given acetaminophen as a standing order every 8 hours and ketorolac as needed assuming no clinical contraindications exist. There is no plan to take any specimens as part of this study.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

The following data will be collected from the Electronic Medical Record.

Data recorded intraoperatively:

- Total Opioid Use Intraoperatively as measured from the electronic intraoperative record in the EPIC system.
- Average hourly % of Agent/MAC of agent used intraoperatively as measured from the electronic intraoperative record in the EPIC system.
- Change in Heart Rate (HR) and Mean Arterial pressure (MAP) measured from the electronic intraoperative record in the EPIC system. The HR and MAP reading just

prior to drug infusion will be taken as the baseline. The absolute change in HR and MAP from this baseline will be noted q5 minutes and the difference summed over the duration of the case. The final number will be divided by the duration of the case in hours.

- Any clinically relevant change in Heart Rhythm as reported by intraoperative anesthetist in the EPIC system.
- Total doses in mg or mcg of pressor agents used intraoperatively during the study drug infusion period as noted from the electronic intraoperative record in the EPIC system. These include phenylephrine, ephedrine, epinephrine and atropine.
- Total volume of intravenous fluids (crystalloids and colloids)
- Duration of the operation as measured from the electronic intraoperative record in the EPIC system.

Data recorded in the PACU and on the floor:

- Opioid use for the first 24 hours (or until discharge, if sooner) as recorded in the hospital record (AIF-Analgesic Infusion Form) at a frequency consistent with the PACU and hospital routine. The PACU routine is on admission, then every 15 min x 2 hrs then every 30min x 2 hrs then every 1 hr. The hospital routine is every 8 hours.
- NRS (Numerically Rating Scale) pain scores as recorded in the hospital record (AIF) for the first 24 hours (or until discharge, if sooner) q4hr at rest and with any activity (such as coughing). The PACU routine is on admission, then every 15 min x 2 hrs then every 30min x 2 hrs then every 1 hr. The hospital routine is every 8 hours.
- Sedation scores for the first 24 hours as recorded in the hospital record (AIF) post-operatively (or until discharge, if sooner) at a frequency consistent with the PACU and hospital routine. Sedation scores are specifically the Richmond Agitation Sedation Scale, an ordinal value measuring from +4(combative) to -5 (unarousable) and is the hospital standard.
- Heart Rate (HR), Mean Arterial Pressure (MAP), Respiratory Rate (RR) for the first 24 hours post-operatively (or until discharge, if sooner) as recorded in the hospital record at a frequency consistent with the PACU and hospital routine.
- Total volume of intravenous fluids (crystalloids and colloids)
- Incidences of Hypoxia (SpO2 < 90%) as recorded in the hospital record in PACU

Additional postoperative data recorded include:

- Inability to extubate prior to PACU as measured by presence of endotracheal tube in PACU and recorded by PACU on intake.
- Need for re-intubation in PACU as determined by medical record.
- Time to PACU discharge (and/or readiness for discharge, if different) as recorded by PACU
- Time to first opioid rescue as measured from PCA device record (AIF)

Side effects to be recorded:

- Cumulative incidence of nausea recorded in medical record (AIF) at a frequency consistent with the PACU and hospital routine from arrival to the PACU until 24 hours later (or until discharge, if sooner).
- Cumulative use of an antiemetic as recorded in the hospital record from arrival to the PACU until 24 hours later (or until discharge, if sooner).

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When the patient is discharged to the regular floor, the above measures will be recorded according to the floor routine (typically q8hr).

All opioid doses will be converted to the equivalent dose of intravenous morphine based on standard MSK guidelines using the MSK interactive converter (http://mskweb6.mskcc.org/painservice/meds/conversion_interactive.htm)

11.1 TOXICITIES/SIDE EFFECTS

The safety of Dexmedetomidine was assessed by the manufacturer. Those adverse reactions are listed below:

From the Product Insert[13]:

"From the placebo-controlled, continuous infusion trials of Precedex for sedation in the surgical intensive care unit setting in which 387 patients received Precedex for less than 24 hours. The most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia"

Adverse Event	Randomized Dexmedetomidine (N=387)	Placebo (N=379)
Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial Fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Hemorrhage	3%	4%
Anemia	3%	2%
Dry Mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycemia	2%	2%
Acidosis	2%	2%
Pleural Effusion	2%	1%
Oliguria	2%	< 1%
Thirst	2%	< 1%

In addition, the following events will be reported as SAEs:

- New Arrhythmia in PACU (excluding sinus tachycardia and bradycardia that does not require treatment with a continuous infusion agent)
- Reintubation
- Sedation requiring use of naloxone
- Hypotension requiring a continuous infusion of a Vasopressor postoperatively

CTCAE v4.0 will be used for toxicity grading.

11.1 Complications of Surgery

Patients in both study arms are scheduled to undergo routine Thoracic Surgery which will not vary based on involvement in this protocol. The potential complication associated with these procedures, such as bleeding and infection are the same as those associated with these procedures when done as part of routine care and will not be collected or reported unless a grade 3 or higher..

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Primary endpoints

1. Opioid sparing as measured by
    a. total opioid equivalents used postoperatively as measured by the total opioid administered in approximately the first 4 hours and

Secondary endpoints to be measured include:

1. Change in analgesia as measured by change in Pain Numerical Rating Scale (NRS) preoperatively to postoperatively. Specifically measured is pain:
    a. at rest,
    b. with activity (such as coughing) and
2. Cumulative episodes of
    a. nausea,
    b. antiemetic use and/or
    c. sedation as measured by the incidence of side effects and sedation scores, respectively

13.1 CRITERIA FOR REMOVAL FROM STUDY

Termination of the Study Drug is left to the Anesthesiologist based upon the clinical care of the patient. Reasons for termination may or may not include the following:

- New Arrhythmia (excluding sinus tachycardia and bradycardia that does not require treatment with a continuous infusion agent)
- Suspected anaphylaxis

Criteria for censoring of the patient‟s data include:

- Patient‟s decision to withdraw prior to surgery
- Conversion to open thoracotomy
- Placement of Epidural Catheter prior to end of data collection
- Removal of IV PCA drug
- Failure to initiate the infusion.
- Complete Inability to adequately obtain any NRS pain scores, e.g. secondary to mental status changes or death

The rate of removal will be reported with the study results. Patients who are removed from the study intraoperatively will continued to be followed and data analyzed in an intention-to-treat fashion.

14.0 BIOSTATISTICS

The goal of this randomized, double-masked study is to evaluate the extent to which intra-operative dexmedetomidine infusion improves post-operative analgesia in patients undergoing Thoracic Surgery. We will measure each patient‟s analgesic consumption periodic pain self-assessment and side-effects for up to 24 hours. The primary outcome

measure will be opioid consumption during the approximate first four hours post-anesthesia, when data will be collected more frequently, dosage will be electronically recorded in real time and the effect is expected to be most pronounced. All opioids will be converted to morphine equivalents per standard conversion tables used at Memorial Sloan Kettering (http://mskweb6.mskcc.org/painservice/meds/conversion_interactive.htm)

The simplest measure will be a comparison of total opioid administered during that initial time period, averaged across patients within each treatment arm: dexmedetomidine infusion vs. null (saline) infusion. Opioid consumption is widely accepted as a “hard measure” in pain management studies. Most if not all of the opioid will be delivered by patient controlled analgesia (PCA) during this time period.

The plan is to study 140 evaluable patients per treatment arm (total 280 evaluable patients). With the current withdrawal rate we expect to recruit 335 patients in total. Approximately 50 potential eligible patients undergo this procedure per month. If we assume only 25 patients per month are feasible, the study will take approximately 14 monthsto complete. This sample size will be sufficient to have 80% chance of having a statistically significant ($p<0.05$) result between-arms comparison for the criterion outcome, total opioid use at 4 hours. This is based on data from a study of analgesic requirements in similar patients [14] and the assumptions that the 4-hour cumulative opioid consumption (morphine-equivalents) is log-normally distributed and that there is 32% treatment effect, with mean consumption +/- std dev 4.0 +/- 4.0 mg in the control group and 2.72 +/- 2.72 mg in the Dexmedetomidine-treated group. Similar considerations may apply to other outcomes, such as time to first post-anesthesia opioid dose.

The primary analysis will be a simple comparison of average opioid consumption between the two randomized treatment arms. Post-operative analgesic requirements may be affected by demographic or clinical factors such as patients‟ age, weight, gender, American Society of Anesthesia Risk score, length of operation, and amount of intra-operative analgesic drugs administered. Randomization will be stratified by gender (male / female) and age (<45 / 45 to 65 / >65).In addition to the primary analysis, we will perform an ancillary analysis of covariance to adjust for these covariates when comparing treatment arms. Furthermore, we may apply data transformation to more closely satisfy implicit assumptions of the General Linear Model and more readily identify possible outlying observations.

We will also perform more exploratory analyses to data such as the total opioid use at 8 hours and self-reported numeric (numerical reporting score) pain scores, applying the repeated measures model to the time curve or trajectory data per patient as an efficient way of summarizing results. Side effects will be reported as per-patient means and standard deviations for each treatment group and compared using Student‟s t-test, after applying data transformation if appropriate. These analyses are exploratory because they are of secondary interest and we do not have prior data to estimate statistical power

Accrual and withdrawal/dropout rates will be reported with the study results. Patients who withdraw from the study after randomization but prior to surgery (and hence did not receive treatment) will not be included in the analyses; patients who withdraw from the study after surgery will be included in the study. In rare cases in which patients receive an intraoperative

treatment different from the intended randomized treatment will remain in the intended arm for analyses. Patients with cancelled surgeries (and hence do not have the primary outcome) will not be included in the analyses.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

This is a double masked placebo controlled randomized trial. After eligibility is established and immediately after consent is obtained, patients will be registered in the Protocol Participant Registration (PPR) system. Patients will be randomized using the Clinical Research Database (CRDB) at the time of registration, by calling the MSKCC PPR office at 646-735-8000 between the hours of 8:30am and 5:30pm, Monday – Friday. Randomization will be accomplished by the method of random permuted block, stratified by gender (male / female) and age (<45 / 45 to 65 / >65). Since this is a double masked study, the patients" treatment assignments can be viewed in the CRDB only by the hospital pharmacists who are dispensing the study drugs. The patient"s randomization status will also be unblinded at the request of clinical personnel if medical care warrants such knowledge to adequately treat the patient including development of a new arrhythmia (excluding sinus tachycardia and bradycardia that does not require treatment), use of vasopressor infusion intraoperatively suspected anaphylaxis.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the protocol. They will identify potential patients eligible for consenting. They will also be responsible for collection of data from the EPIC system for intraoperative measures. They will also be responsible for data collection in the PACU and patient floor based on nursing records and the CIS system. Additional responsibilities of the RSA include project compliance, data entry, data reporting, regulatory monitoring, identification of potential withdrawals, and SAE reporting. The data recorded for this study will be entered into a secure database compliant with HIPAA

regulations. Any paper used to record data will be scanned into the EMR. There are no patient questionnaires.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration of data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent of accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the Principal Investigator.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

http://cancertrials.nci.nih.gov/researchers/dsm/inde x.html.

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://msk web2.msk cc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center"s Research Council and Institutional Review Board

17.1 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines.

1. Risks to the subject

Human Subjects Involvement and Characteristics: All patients at MSCKK who meet the inclusion criteria will be eligible. 280 evaluable patients will be entered on this study but based on the withdrawal rate, an estimated 335 patients will be needed to achieve that target of evaluable patients; patients will be 21 years of age or older. Both men and women of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study.

Also, the majority is already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research involving Human Subjects.

2. Adequacy of protection against risk

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. Informed consent may be taken by those individuals described as Consenting Professionals. All patients will be required to sign a statement of informed consent, which must conform to institutional IRB guidelines. The informed consent procedure is described in section 18.

Possible Toxicities/Adverse Effects: There are risks associated with Precedex as described in section 11.0; however, patient screened for enrollment will have been deemed appropriate for treatment independent of this study.

Cost: The cost of the study drug/placebo will be covered by the study. All other costs will be the responsibility of the patient since these are standard of care charges.

Alternatives: The alternative to this trial would be Thoracic Surgery with standard of care as described in section 3.0.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospitals records are confidential. Patients" names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate personnel (e.g. Qualified monitors from MSKCC) may review patient records as required.

17.2 Privacy

MSKCC"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant"s last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject"s initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject"s condition
    - Indication if the subject remains on the study

- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI"s signature and the date it was signed are required on the completed report.
For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. On the day of surgery, prior to going to Pre-Surgical Bed, patients will be approached by a Consenting professional who will fully consent the patients and answer any questions. Patients will have had the consent form to review at home prior to being fully consented on the day of surgery, in order to ensure that patients have ample time to review the consent including weighing the risks/benefits. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.1 REFERENCES

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20.0 Appendices Appendix AStudy Cover Summary Sheet