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Randomized, placebo-controlled study on the effects of intravenous dexmedetomidine on pain in patients undergoing elective spinal surgery

New York University Langone Medical Center, Department of Anesthesiology, Perioperative Care and Pain Medicine

Study Drug: Dexmedetomidine

Principal Investigator: Lisa Doan, MD

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Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, applicable international standards of good clinical practice, and institutional research policies and procedures.

Study Rationale

It has been observed in a meta-analysis that intravenous dexmedetomidine, an alpha-two-agonist, decreases postoperative cumulative opioid consumption and/or pain intensity (1). Furthermore, this meta-analysis demonstrated that the perioperative use of intravenous dexmedetomidine decreased the risk of postoperative nausea and did not lengthen recovery times (1). An article by Bekker et al. also demonstrated improvement in quality of recovery after major spinal surgery with the use of intraoperative dexmedetomidine infusion (2). Conversely, a study on intraoperative dexmedetomidine infusion in patients undergoing multilevel spine surgery found dexmedetomidine use did not reduce opioid consumption or pain scores (3). However, in this study both treatment and placebo groups received a dose of methadone preoperatively, potentially affecting the outcomes.

The use of opioids with nonopioid analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs, ketamine and alpha-two agonists) has increased in popularity with aims to decrease postoperative opioid requirements and subsequently opioid induced adverse effects. Thus the effects of dexmedetomidine on perioperative pain control are important to study. Outcomes beyond the immediate perioperative period are important to study as well. It is hypothesized that intraoperative dexmedetomidine infusion will have a positive effect on pain control in patients undergoing lumbar spinal fusion.

Study Objective

The aim of the proposed study is to examine the effect of intravenous dexmedetomidine on patients undergoing lumbar spinal fusion.

The primary outcome is opioid consumption during the first 48 hours after surgery. We hypothesize that intraoperative dexmedetomidine will decrease opioid use by 30%.

The secondary outcomes include numeric rating scale scores during the first 48 hours after the procedure and at approximately 6 weeks, morphine equivalents during the first 48 hours and at approximately 6 weeks, hemodynamic changes from baseline in the intraoperative and 48 hour postoperative period, pressor use in the intraoperative and 48 hour postoperative period, duration of PACU and hospital stay, and scores on the QoR-15 and Short Form McGill Pain Questionnaire.

Overall Study Design and Plan

This is a randomized, assessor-blinded, placebo-controlled study. Anesthesiologists will be aware of patients' group assignments, but patients and assessors will not be.

One hundred ten subjects (55 in each arm) will be enrolled. Subjects, over the age of 18, undergoing lumbar spinal fusion (allowing for surgeries extending into thoracic and sacral segments) under general anesthesia will be screened for eligibility to participate in the study. Subjects will be screened, recruited, and randomized during the preadmission visit or the day of surgery. Those patients whose recruitment is completed on the day of surgery will have been given details of the study during the preadmission visit. Eligible subjects will be randomized to one of the two treatment groups in a 1:1 ratio to receive either IV dexmedetomidine or matching placebo. Both men and women will be recruited, and there is no limitation as to racial and ethnic origin.

Patients will be randomized using a block randomization scheme generated via the website randomization.com (http://www.randomization.com). The anesthesiologist will be informed of the randomization.

Participation in the study will not alter the patient's anesthetic management. Routine anesthesia monitors used during general anesthesia will be used. Arterial and/or central lines will be placed at the discretion of the anesthesiologist. After pre-oxygenation, general anesthesia will be induced with lidocaine (1 mg/kg), propofol (1-2 mg/kg), and fentanyl (up to 5 mcg/kg). Tracheal intubation will be facilitated with rocuronium (0.6 mg/kg). Anesthesia will be maintained with air/oxygen (60%/40%), propofol infusion, fentanyl infusion, and muscle relaxant if indicated. The anesthesiologist will be allowed to administer additional doses of propofol and fentanyl at his/her discretion. The bispectral index will be targeted from 40 to 60. Patients will receive either intravenous dexmedetomidine infusion (0.5 mcg/kg loading dose over 20 min followed by an infusion at 0.6 mcg/kg/hr) or placebo starting prior to surgical incision. The dexmedetomidine infusion will be stopped during closure of the fascia. Mean arterial pressures less than 65 will be treated with vasoactive agents, chosen at the discretion of the anesthesiologist. All patients will receive ondansetron 4 mg prior to the end of operation. Patients will be awakened and extubated in the OR and will be transferred to the PACU after following simple commands. All patients will also be able to receive rescue doses of opioids as indicated by a Numeric Pain Rating Scale score >2 or upon request. There is no restriction on the use of analgesics throughout the hospital stay. Patients are followed until postoperative day 2 and followed up by telephone call approximately 6 weeks postoperatively.

Study site: Tisch Hospital

Outcome measures

The primary endpoint will be morphine equivalents used during the first 48 hours after surgery. We hypothesize patients who receive dexmedetomidine will require 30% less opioids than those who do not receive dexmedetomidine.

Secondary endpoints include:

1) Numeric Pain Rating Scale (NRS)scores during the first 48 hours after the procedure and at approximately 6 weeks;

2) morphine equivalents during the first 48 hours and at approximately 6 weeks,

3) hemodynamic changes from baseline in the intraoperative and 48 hour postoperative period;

4) pressor use in the intraoperative and 48 hour postoperative period;

5) duration of PACU stay;

6) duration of hospital stay;

7) scores on the QoR-15;

8) scores on Short Form McGill Pain Questionnaire.

The QoR-15 measures patients' overall satisfaction with postoperative recovery. The QoR-15 will be administered preoperatively to establish baseline scores and repeated on postoperative days 1 and 2 and at approximately 6 weeks. The Short Form McGill Pain Questionnaire measures the subjective experience of pain and will be administered preoperatively and on postoperative days 1 and 2 and at approximately 6 weeks.

Safety endpoints include:

1) hemodynamic changes requiring pressor use in the intraoperative and 48 hour postoperative period and

2) hemodynamic changes requiring termination of drug infusion.

Study Population

Inclusion criteria

1. Adults, 18 and over, who will undergo lumbar spinal fusion, including surgeries extending into thoracic and sacral segments,
2. Subject is non-lactating and is either:
    a. Not of childbearing potential
    b. Of childbearing potential but is not pregnant at time of surgery as determined by pre-surgical pregnancy testing
3. Subject is ASA physical status 1, 2, or 3

Exclusion criteria

1. <18 years of age
2. Subject is pregnant or breastfeeding
3. Any subject whom the investigators deem unable to complete any/all research related tasks
4. Subjects who are cognitively impaired (by history)
5. Subject requires antipsychotic medications
6. Subject has received treatment with alpha-2 agonists or antagonists within 2 weeks prior to surgery
7. Subject has known allergy to dexmedetomidine

8. Subjects with impaired renal or hepatic function
9. Subjects with advanced heart block
10. Subjects with severe ventricular dysfunction

Subject Identification, Recruitment, and Consent

IRB approved study flyers will be distributed to the surgeons' offices and the pre-admissions testing clinic (PAT) at the Ambulatory Care Center (ACC). Patients will be approached at PAT or after contacting the researchers through flyers. We will be approaching all subjects (male and female) who are undergoing lumbar spinal surgery (including those undergoing surgery extending to the thoracic or sacral segments) and who are 18 years or older.

Because of Covid, patients are not going into PAT and having virtual visits, surgeons have said we can contact their patients by phone and/or email. Subjects will be identified by surgical coordinators – the list they send includes whether or not the patients have opted-in for contact, and we would only reach out to those who have opted in.

Additionally, for surgeons agreeable to the study, we can search their surgery schedules on EPIC. We will send them a list of potential participants to get their approval to contact them. No PHI will be used to search through EPIC, rather the surgery schedules for the month ahead will be reviewed. From that we can see minimum inclusion/exclusion criteria (age/type of surgery), and we can pre-screen people who may qualify and ask surgeons for permission to contact them. We will forward surgeons the phone script and email template for approval, as well as the flyer, which was reviewed by them when study was initiated.

The upcoming surgical schedules will be reviewed by the PI and research coordinators only.

Any recruitment information sent by email will utilize Send Safe email.

1) Recruitment over the phone
    a. The telephone script will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Research team members will call prospective subjects or arrange a video conference session (WebEx only). The following methods will be implemented to obtain informed consent.
        i. The prospective subject will be emailed a copy of the informed consent via SendSafe to review. If prospective subject is interested in participating, a phone call or webex can take place, and consent can be obtained in person on the day or surgery.
        ii. The prospective subject will be emailed a copy of the informed consent form via SendSafe after on-site discussion taking place between study personnel and prospective subject or an initial telephone call or video conference takes place between study personnel and the remote prospective subject and the research team member will obtain prospective subject signature in-person on the day of surgery. The prospective subject can print and sign a physical copy and return later in person.

A general discussion regarding the study will be done in a private area. The subject will have the opportunity to ask questions during the PAT visit or telephone call until the day of surgery, and all questions will be answered. Consents will be done at the PAT visit or on the day of surgery. A copy of the signed consent will be placed in the medical record as well as given to the patient. The original consent will be collected as a source document and securely stored.

Early Withdrawal of Subjects

Subjects may be withdrawn from the study prior to completion due to safety issues, consent withdrawal, or failure to adhere to protocol requirements. Adverse effects of dexmedetomidine include bradycardia and hypotension. The anesthesiologist is not blinded as to study drug. If adverse effects such as bradycardia and hypotension are considered excessive and due to dexmedetomidine based on the anesthesiologist's clinical judgment, the study drug can be stopped at any time.

Data Collection and Follow-up for Withdrawn Subjects

Data on morbidity related to hemodynamic changes will be collected on subjects withdrawn from the study. Survival data will also be collected on subjects withdrawn from the study up to the end of the approximately 6 week follow-up period. For patients who have withdrawn consent, attempts will be made to obtain permission to record survival data. Three phone calls will be made prior to considering a patient lost to follow-up.

Study Drug

Description

Dexmedetomidine is an alpha-2-adrenergic agonist. It is commonly used for sedation and as an adjunct to general anesthetics. Side effects include hypotension, bradycardia, atrial fibrillation, and nausea.

The use of dexmedetomidine, in this case, is exempt from an IND.

Treatment Regimen

Intravenous dexmedetomidine or saline placebo will be given prior to surgical incision. The drug will be administered with a loading dose of 0.5 mcg/kg given over 20 min followed by an infusion at 0.6 mcg/kg/hr. The infusion will be stopped during closure of the fascia.

Method for Assigning Subjects to Treatment Groups

Patients will be randomized using a block randomization scheme generated via the website randomization.com (http://www.randomization.com). The anesthesiologist will be informed of the randomization.

Preparation and Administration of Study Drug

Study drugs will be prepared and administered as indicated above by the anesthesiologist.

Subject Compliance Monitoring

Subjects will be asked to track opioid and adjunctive analgesic use at approximately 6 weeks postoperatively.

Prior and Concomitant therapy

Subjects' preoperative medications will be recorded. Intraoperatively subjects may receive fentanyl at the discretion of the anesthesiologist. Postoperatively there are no restrictions on the use of opioids and adjunctive analgesics.

Study Drug Storage

Study medications will be kept in the Omnicell machine in the operating room suite.

Dispensing of Study Drug – covered in a preceding paragraph, treatment regimen.

Study Procedures

The following procedures will be done at each visit.

Visit 1: Consenting, NRS, QoR-15 and McGill Short Form

(Day of surgery): Randomization and administration of dexmedetomidine or placebo

Visit 2/POD1: NRS, QoR-15 and McGill Short Form

Visit 3/POD2: NRS, QoR-15 and McGill Short Form

Visit 4/~6 weeks post-op: NRS, QoR-15 and McGill Short Form and list of medications taken

Statistical Analysis

Sample Size Justification

Previous studies of the analgesic effects of dexmedetomidine in patients without chronic opioid consumption have yielded a mean difference in postoperative opioid consumption of 30-50%. Hypothesizing a 30% reduction in analgesic use, power analysis yields n=55 patients in each arm with a 5% type I error rate and 80% power. An interim analysis will be done after 55 total patients have been recruited such that if statistically significant differences are found further patient recruitment will be halted to avoid unnecessary risk.

Interim Data analysis

Although this is a low risk study, an interim analysis will be done after 55 total patients have been recruited such that if statistically significant differences are found in primary endpoints further patient recruitment will be halted to avoid unnecessary risk. The interim data analysis will be of primary and secondary endpoints.

Data Analysis

Differences between groups will be analyzed with an unpaired student's t- test. For non-normally distributed data, the Kruskall-Wallis test will be used for global significance, and the Mann-

Whitney U test will be used for subsequent pairwise comparisons. Univariate analysis of postoperative opioid consumption as a function of preoperative opioid use, sex, and comorbidities will be done. A multivariate regression analysis will be done to assess potentially confounding variables.

Subject Population(s) for Analysis

All-treated subjects (randomized into the study and received dexmedetomidine or placebo) will be included in the analysis of both primary and secondary endpoints.

Safety and Adverse Events

Definitions

Unanticipated Problems Involving Risk to Subjects or Others: Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event – An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event – Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to

prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period – The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as ~6 weeks following the last administration of study treatment.

Preexisting Condition – A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings – At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event – All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values – A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery – Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse

event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording of Adverse Events – At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Reporting of Serious Adverse Events and Unanticipated Problems

This section describes the requirements for reporting specific types of unanticipated problems including adverse events.

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:
- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions).

For Narrative Reports of Safety Events – If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Investigator reporting: notifying the IRB – Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The

following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Investigator Reporting: Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements.

Report promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*

- ***Breach of confidentiality***

- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Data Acquisition and Storage

Data Safety and Monitoring Plan

The principal investigator, Dr. Lisa Doan, will be primarily responsible for monitoring the study. All adverse events will be collected and evaluated every 6 months. The study principal investigator will evaluate the data to determine whether to continue the study or to change the protocol to decrease risk.

Adverse events will include events reported by the subject and thought to be associated with the research. Unanticipated problems and adverse events will be gathered by study investigators. Adverse events will be evaluated throughout the hospital stay and during telephone call follow-up. Any serious adverse effects will be reported to the IRB according to regulatory requirements. Because patients are having major surgery, we will only be reporting those serious adverse events that are directly related to the study drug, and will report them to the IRB within 24 hours of discovery. All patients having a serious adverse event will be followed until it is resolved.

Reports summarizing the data safety monitoring reviews will otherwise be submitted to the IRB annually.

Data Handling and Record Keeping

Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

All of the patient data used in this study will be kept confidential and will be used for professional purposes only. All research data will be collected in Case Report Forms (CRFs). Clinical safety data, screening information, informed consent, and progress notes will be collected in Source Documents. Patient records will be accessible only to study personnel in locked drawers or in password protected computers in locked rooms of the Department of Anesthesiology, Perioperative Care and Pain Medicine suite. Only those investigators directly involved in the protocol will have access to these records. Patient records will be coded for analysis and publication. After completion of the study data will be kept for five years before secure disposal.

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Study Monitoring, Auditing and Inspecting

Study Monitoring Plan

As noted above, reportable events will be monitored on an ongoing basis. The study will be monitored every 6 months for adverse events. The principal investigator will evaluate the data to determine whether to continue the study or to change the protocol to decrease risk. An interim analysis will be done after 65 total patients have been recruited such that if statistically significant differences are found further patient recruitment will be halted to avoid unnecessary risk.

Auditing and Inspecting

The investigator will permit study related monitoring, audits, and inspections by the IRB/EC, government regulatory bodies, and University Compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

As stated previously, research subjects will be approached at PAT or after contacting the researchers through flyers. We will be approaching all subjects (male and female) on chronic opioid therapy who are undergoing lumbar spinal surgery (including those undergoing surgery extending to the thoracic or sacral segments) and who are 18 years or older. A general discussion regarding the study will be done in a private area either at pre-admission testing (PAT) or in the pre-operative area on the 4th floor. Subjects approached in PAT will also have the time to consider and decide and sign the consent in pre-op. The subject will have the opportunity to ask questions during the PAT visit until the day of surgery, and all questions will be answered. A copy of the signed consent will be placed in the medical record as well as given to the patient. The original consent will be collected as a source document and securely stored.

Risk/Benefit Assessment

Risks

Other than general risk associated with anesthesia and surgery, there are few risks associated with the study drug which is in routine use in the surgical setting.

The use of dexmedetomidine is a standard of care in the perioperative period. Risks most commonly associated with dexmedetomidine administration include bradycardia and hypotension. Anesthesia providers routinely handle such eventualities in all surgeries. If necessary, vasoactive agents may be administered. There is no additional risk of study drug use compared to routine anesthetic use.

The following risks are outlined in the informed consent document:

C*ardiovascular:* Hypotension (24-56%) and hypertension (28%) may occur. Bradycardia (5-42%) or other change in heart beat may occur.

Central nervous system: Agitation or anxiety may occur (5-14%).

Respiratory: Respiratory depression (2-10%), pleural effusion (2%), or wheezing (<1%) may occur.

Endocrine and metabolic: Hypokalemia (9%), hyperglycemia (7%), hypoglycemia (5%), hypocalcemia (1%), or hypomagnesemia (1%) may occur.

Renal: Acute renal failure (2-3%) or decreased urine output (1%) may occur.

Additionally, there is the possible risk of loss of confidentiality associated with participating in a research study. All information pertaining to this study will be kept in a locked file cabinet in a locked office area. The risk of loss of confidentiality is considered to be minimal. However, the researchers involved in this study will take every precaution necessary to ensure that privacy is protected.

Potential Benefits

There are conflicting studies on whether perioperative dexmedetomidine administration decreases opioid consumption following surgery. This study will elucidate whether dexmedetomidine will have a beneficial effect on perioperative pain control which may benefit subjects who receive the drug as well as others in the future.

Study Finances

Funding Source

The study will be supported by departmental funds.

Conflict of Interest

No one involved with the study has any conflicts.

Subject Stipends or Payments: There is no cost to the study subject and the subject will not be compensated for participating in the study.

Publication Plan

Abstracts and peer-reviewed publications will be prepared when appropriate.

References

1. Blaudszun G, Lysakowski C, Elia N, Tramer M. Effect of perioperative systemic alpha 2 agonists on postoperative morphine consumption and pain intensity. Anesthesiology 2012; 6: 1312-1322.

2. Bekker A, Haile M, Kline R, Didehvar S, Babu R, Martiniuk F, Urban M. The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery. Journal of Neurosurgical Anesthesiology 2013 Jan; 25(1):16-24.

3. Naik B, Nemergut E, Kazemi A, Fernandez L, Cederholm S, McMurry T, Durieux M. The effect of dexmedetomidie on postoperative opioid consumption and pain after major spine surgery. Anesth Analg 2016; 122(5): 1646-53.