Prospective Randomized Clinical Trial to Evaluate the Use of Caudal Nerve Blocks in Penile Prosthesis Surgery
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Principal Investigator: Dr. Bobby Bellard
Co-Investigator: Dr. Farzin Goravanchi

Collaborator: Lei Feng

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1.0 Objectives

1.1 Primary Objective

To determine whether the use of a caudal nerve block (CNB) in combination with general anesthesia (GA) in patients undergoing penile prosthesis surgery results in decreased post-operative pain medication usage compared with patients having GA-only.

1.2 Secondary Objectives

1.2.1 To determine whether the use of a CNB in patients undergoing penile prosthesis surgery results in decreased immediate post-operative pain in the first 24 hours after surgery compared with patients having only general anesthesia as determined by postop pain score.

1.2.2 To determine whether the use of a CNB in patients undergoing penile prosthesis surgery results in a decreased length of hospital stay compared with patients having only general anesthesia.

2.0 Background

2.1 Penile Prosthesis Surgery and Anesthesia

According to the Prostate Cancer Foundation, prostate cancer is the most common non-skin cancer in America, affecting 1 in 6 men. In 2014 approximately 233,000 men will be diagnosed with prostate cancer (1). Regardless of whether the nerves were spared during surgery or whether the most precise dose planning was used during radiation therapy, nearly all men will experience some erectile dysfunction for the first few months after treatment (2). The majority of these men will not require penile prosthesis surgery, however, a significant subset will. In addition, there are other factors that may lead to the decision for penile prosthesis surgery such as severe diabetes, pelvic trauma or neurological dysfunction. Each year, about 20,000 American men opt for a penis implant, according to the Cleveland Clinic (3).

In 2013, fifty-eight penile prosthesis surgeries were performed here at MD Anderson. Traditionally, this surgery is performed under general anesthesia. Nearly all of these patients experienced an overnight stay in the hospital as well as a hospital course that included difficult pain control with conventional narcotics and anti-inflammatory drugs.

Alternative forms of anesthesia for patients undergoing penile prosthesis surgery have been sought to reduce postoperative pain and eliminate the need for an overnight stay. In an era where medical costs and patient preference have led to an increase in the number of outpatient surgical procedures, regional anesthesia is being increasingly utilized. Proposed advantages of regional anesthesia include decreased neuroendocrine "stress" response and improved postoperative pain control. It also reduces medical costs by decreasing the need for postoperative opioid analgesics, antiemetics and hospitalizations (4). Regional anesthesia in the form of a caudal nerve block (CNB) has been utilized as an alternative or adjunct to general anesthesia. A CNB can provide patients with anesthesia during the procedure in addition to the possible effect of decreased postoperative pain, nausea, vomiting and decrease their length of hospitalization.

2.2 Caudal Nerve Blocks in Patients Undergoing Penile Prosthesis Surgery

To date, there are no publications regarding caudal nerve blocks for penile prosthesis surgery.

The goal of this study is to determine the effectiveness of CNB in patients undergoing penile prosthesis surgery with respect to postoperative pain control and length of hospital stay compared with patients undergoing general anesthesia alone. We also seek to understand patient satisfaction and cost savings when CNB has been utilized.

2.3 Complications of Caudal Nerve Blocks

Complications have been reported with the use of CNBs. Those of significance include local anesthetic toxicity, subarachnoid puncture, rectum puncture and ineffective block.

2.4 Risks and Side Effects of Caudal Nerve Blocks

Risks and side effects of the caudal nerve block are pain at site of injection, allergic reaction to the local anesthetic, epidural block, subarachnoid block, infection, ineffective block, and injection into blood vessel.

A test dose of the CNB is injected prior to the full dose, to ensure that it is not being injected into the bloodstream. If the full dose of CNB is injected into a blood vessel, which is never done, tachycardia, and subsequently seizure or cardiac arrest may occur.

3.0 Background Drug Information

Ropivacaine is FDA approved for use in caudal nerve blocks. This is not a drug study. Drug information for Ropivacaine is shown below:

ROPIVACAINE HYDROCHLORIDE
Common Trade names Naropin
Class Amino Amide (Anesthetic, Local)

Dosage, Adult (usual) – Ropivacaine 5mg/kg per patients maximum dose (max 350mg per patient)

- Cesarean section – Local anesthetic lumbar epidural: 20-30 ml of 0.5% solution (100-150 mg) OR 15-20 ml of 0.75% solution (113-150 mg)
- Labor pain: initial, lumbar EPIDURAL 10-20 ml (20-40 mg) of 0.2% solution
- Labor pain: continuous lumbar EPIDURAL infusion, 6-14 ml/hr (12-28 mg/hr) of 0.2% solution
- Labor pain: incremental lumbar EPIDURAL injections (top-up), 10-15 ml/hr (20-30 mg/hr) of 0.2% solution
- Local anesthetic lumbar epidural block – Surgical procedure: 15-30 ml (75-150 mg) of 0.5% solution
- Local anesthetic nerve block – Surgical procedure: FIELD BLOCK 1-40 ml of 0.5% solution (5-200 mg)
- Local anesthetic nerve block – Surgical procedure: major NERVE BLOCK 35-50 ml of 0.5% solution (175-250 mg) OR 10-40 ml of 0.75% solution (75-300 mg)
- Local anesthetic thoracic epidural block – Surgical procedure: 5-15 ml of 0.5% solution (25-75 mg) or 0.75% solution (38-113 mg)
- Postoperative pain: continuous lumbar EPIDURAL infusion, 6-14 ml/hr (12-28 mg/hr) of 0.2% solution

- Postoperative pain: continuous thoracic EPIDURAL infusion, 6-14 ml/hr (12-28 mg/hr) of 0.2% solution
- Postoperative pain: INFILTRATION 1-100 ml of 0.2% solution (2-200 mg) OR 1-40 ml of 0.5% solution (5-200 mg)

Dose Adjustments:
- Liver disease: dosage reduction is recommended to avoid accumulation with the potential for enhanced toxicity

Indications
FDA labeled indications
- Cesarean section – Local anesthetic lumbar epidural block
- Labor pain
- Local anesthetic lumbar epidural block – Surgical procedure
- Local anesthetic nerve block – Surgical procedure
- Local anesthetic thoracic epidural block – Surgical procedure
- Postoperative pain

Contraindications
- Hypersensitivity to Ropivacaine/amide-type anesthetics

Precautions
- Not recommended for emergency situations
- Unintended IV administration may result in cardiac arrhythmia or cardiac arrest
- Do not use for production of obstetrical paracervical block anesthesia, retrobulbar block or spinal anesthesia (subarachnoid block)
- Intravenous regional anesthesia (Bier block) should not be performed, risk of toxic blood levels
- Patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, toxic effects are additive
- Concomitant administration of CYP1A2 inhibitors
- Debilitated, elderly patients and acutely ill patients
- Heart Block
- Hypotension
- Hypovolemia
- Impaired cardiovascular function
- In brachial plexus block, using 300 mg dose may approach plasma threshold concentrations for central nervous system toxicity
- Injection of small doses in head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional IV injections of larger doses
- Patients treated with class III antiarrhythmic
- Supraclavicular brachial plexus blocks (higher rate of serious adverse reactions)

- Major peripheral nerve blocks (increased risk of intravascular injection and/or overly rapid absorption)

Adverse Effects
COMMON
- Gastrointestinal: Nausea (25%), Vomiting (12%)
- Musculoskeletal: Back pain (5%)

SERIOUS
- Cardiovascular: Bradyarrthymia (9%), Hypotension (37%)
- Neurologic: Parasthesia (6%)
- Ophthalmic: Horner's syndrome pupil (rare)

Drug Interactions
- Bupivacaine (major, probable)
- Ciprofloxacin (moderate, probable)
- Fluvoxamine (moderate, probable)
- Hyaluronidase (major, theoretical)
- St John's Wort (major, probable)

Pregnancy Category
- Ropivacaine: B

Breast Feeding
- Ropivacaine: Infant risk cannot be ruled out

4.0 Patient Eligibility

4.1 Inclusion

4.1.1 Patients that consent to participate
4.1.2 Patients undergoing penile prosthesis surgery
4.1.3 Patients that are male
4.1.4 Patients that are 18 years of age or older

4.2 Exclusion

4.2.1 Patients on chronic pain medications (ie. Chronic = more than once every two days for greater than 2 weeks) excluding Aspirin, Acetaminophen and NSAIDs
4.2.2 Patients with a BMI > 40
4.2.3 Patients with chronic pain syndromes
4.2.4 Patients with hypersensitivity to Ropivacaine/amide-type anesthetics
4.2.5 Prior surgery of the sacrum
4.2.6 Patients taking anti-coagulants or other blood thinning medications prior to surgery during the specified time frames:
- Low molecular weight heparin less than 36 hours prior to surgery
- Coumadin less than 5 days prior to surgery

- Plavix and NSAIDs less than 7 days prior to surgery

4.2.7 Patients on any anti-seizure medications, such as gabapentin or Lyrica, specifically for chronic pain management less than 24 hours prior to surgery

4.2.8 Patients on Celebrex less than 24 hours prior to surgery

4.2.9 Patients taking more than 81 mg of Aspirin daily

5.0 Treatment Plan

5.1 Preoperative

5.1.1 After consents for surgery and study participation are signed, patients will be registered for the trial by the research staff. Patients will be randomized (1:1) using a computerized randomization scheme.

5.1.2 Patients will be randomized (1:1) to one of two groups:

- Group I, Treatment Group: Patients receive a caudal nerve block prior to surgery and receive general anesthesia during surgery.
- Group II, Control Group: Patients receive general anesthesia during surgery without a caudal nerve block.

5.1.3 Patients in both groups will receive Famotidine 20mg IV, up to 1-2mg IV Midazolam and 25-50mcg IV Fentanyl in the holding area prior to the start of surgery.

5.1.4 Patients who are age 70 and older will not receive Midazolam 2mg IV in the holding area prior to the start of surgery.

5.1.5 Patients in Group II will receive Fentanyl 50-250mcg IV in the holding area prior to the start of surgery.

5.2 Intraoperative

5.2.1 Group I – Treatment Group

- If the patient is randomized to Group I, the patient will receive general anesthesia using Propofol titrated for induction. The airway will be secured thereafter. The caudal block will be performed as a bolus injection into the caudal canal in the OR by the attending anesthesiologist using 1% Ropivacaine (max 5mg/kg) + 1:400,000 Epinephrine + Decadron 10mg + Clonidine 100mcg. Patients will be continuously monitored by ASA guidelines.
- Anesthesia will be maintained with Sevoflurane 1.3-2.5% or Desflurane 2.5-8.5%, oxygen, air, nitrous oxide and Fentanyl as needed. At the completion of surgery, reversal of muscle relaxant with Glycopyrrolate 0.2mg IV for each 1mg IV of Neostigmine (max 5mg) will be given as indicated.

5.2.2 Group 2 – Control Group

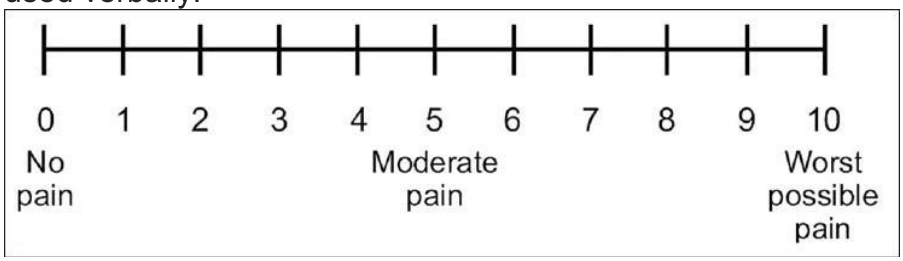
- Patients in Group II will receive general anesthesia using Propofol titrated for induction. The airway will be secured

thereafter. Anesthesia will be maintained with Sevoflurane 1.3-2.5% or Desflurane 2.5-8.5%, oxygen, air, nitrous oxide and fentanyl as needed. At the completion of surgery, reversal of muscle relaxant with Glycopyrrolate 0.2mg IV for each 1mg IV of neostigmine (max 5mg) will be given as indicated.

5.2.3 Patients in both groups will not receive Ketamine, Ketorolac, Celecoxib or local anesthesia field blocks.

5.3 Postoperative

5.3.1 Pain will be assessed using the numeric rating scale (NRS). The NRS is scored by numeric integers, 0 through 10. The NRS will be used verbally.



5.3.2 When using the NRS for pain, the provider will ask, “On a scale of zero to ten, where zero means no pain and ten equals the worst possible pain, what is your current pain level?”

5.3.3 Pain will be treated and documented in the PACU dependent on the patient’s pain score:

- Pain score 0-2 receive no treatment
- Pain score 3-5 receive fentanyl 25mcg iv then reassess pain score in 15 minutes ±5min.
- Pain score 6-8 receive fentanyl 50mcg iv then reassess pain score in 15 minutes ±5min.
- Pain score 9-10 receive fentanyl 75mcg iv then reassess pain score in 15 minutes ±5min.

5.3.4 If 250 mcg Fentanyl is exceeded, then change to use of Dilaudid 0.5mg IV to a maximum dose of 10mg total.

5.3.5 Patients in both groups will be discharged using the same standard PACU discharge criteria. Specifically, patients will be discharged from the PACU when they meet PACU discharge criteria.

5.3.6 Pain will be evaluated 15 minutes after arrival to PACU and every 15 minutes thereafter until discharge from PACU. If the patient has been discharged on the day of surgery, the follow-up will be performed by telephone call directly to the patient. Time to discharge, frequency of pain medications and pain medication totals will be recorded.

5.3.7 Pain will be evaluated using the NRS with scores of 0-10, where 0 is no pain and 10 is the worst pain. Pain will also be evaluated by the amount of IV and oral pain medicine administered in the first 24 hours post-operatively.

5.3.8 Equianalgesic values of IV morphine in mg will be tallied based on each patient's total pain medication administration.

5.3.9 An additional follow-up telephone call will occur 3 days after surgery to evaluate pain and amount of pain medications taken.

5.3.10 After surgery, pain will be evaluated subjectively by asking patients their pain score using the NRS of 0-10 immediately after surgery. If unable to assess due to heavy sedation, mark unable to assess and reassess every 15 minutes thereafter. The morning after surgery the amount of intravenous and oral pain medication received by the patient will be assessed. If the patient has been discharged this will occur by follow-up telephone conversation. Adjustment of the patient's oral pain regimen may be necessary if the patient is not receiving relief upon follow up evaluation. This will be assessed on an individual basis.

6.0 Pretreatment Evaluation

A complete history including age, history of use of chronic pain medication, history of anticoagulants and history of allergies to local anesthetics will be obtained within 4 weeks of randomization.

Physical examination including height, weight and body mass index will be recorded within 4 weeks of surgery.

7.0 Evaluation During Study

After surgery, pain can be assessed upon arrival to PACU.

Time to discharge and reason for delay in discharge will be assessed.

A follow-up phone call with the patient will occur three days after surgery to assess pain control as well as patient satisfaction. Participation in the study will terminate after the follow-up phone call three days after surgery.

8.0 Evaluation of Toxicity

Any side effects from the CNB will be noted including but not limited to side effects from block placement such as subarachnoid puncture, spinal anesthesia, epidural spread, hypotension, and hematoma. We will also assess toxicity from the local anesthetic agents with epinephrine including pre-seizure excitation, seizures, cardiac arrest, epinephrine absorption and desaturation from sedation.

9.0 Criteria for Response

Response to CNB will be assessed by differences in post-operative pain score, number of analgesic medications taken and time to discharge.

10.0 Criteria for Removal from the Study

Any patient requesting withdrawal from the study will be removed. Otherwise, study participation will terminate after the three day follow-up telephone conversation has been completed.

11.0 Statistical Consideration/Number of Patients

11.1 Objectives

This is a trial to determine whether the use of a caudal nerve block (CNB) and general anesthesia in patients undergoing surgery for penile prosthesis results in decreased post-operative pain compared with patients having only general anesthesia. Patients will be randomized with a 1:1 ratio to receive either CNB or general anesthesia. The primary endpoint is the post-operative pain medication usage during PACU stay. The secondary endpoint is the proportion of patients with no pain immediately after surgery.

11.2 Sample Size and Power

This is a randomized, blinded trial designed to evaluate the efficacy of the caudal nerve block (CNB) in combination with the general anesthesia (GA) comparing to the GA-only on patients undergoing penile prosthesis surgery. The primary objective is to determine if the CNB + GA can result in decreased post-operative pain medication usage during PACU stay comparing to the GA-only. One hundred four patients will be randomized with a 1:1 ratio to each of the treatment arms. In a retrospective trial, PA15-0080, the mean ± SD for the post-operative pain medication usage was 21.6 ± 13.6 mg for the GA-only group (n=59) and 13.9±11.0 for the CNB + GA group (n=26). With a sample size of 104 patients (52 for each treatment arm), the study will have at least 81% power to detect the difference in post-operative pain medication usage between 21.6 for the GA-only arm and 13.9 for the CNB + GA arm assuming a common standard deviation of 13.6 as observed in the retrospective study. A two-sided Type I error rate of 0.05 was used (EAST 6.3.1, Cytel Inc 2015). One interim analysis will be performed to allow for the early termination of the trial in light of evidence that the CNB + GA treatment is superior to the GA-only treatment or there is no difference between the two treatment arms. In order to provide an overall significance level of 0.05 for the study, the interim analysis will use an O'Brien-Fleming stopping rule. The interim analysis will be performed when 52 out of the 104 patients have been observed. Using O'Brien-Fleming test boundaries, we will reject the null hypothesis at the interim and final analyses when the absolute value of the Z-score is larger than or equal to 2.963 and 1.969 (the corresponding p-values are ≤ 0.003 and 0.049), respectively. We will reject the alternative hypothesis at the interim and final analyses when the absolute value of the Z-score is less than or equal to 0.338 and 1.969 (the corresponding p-values are ≥ 0.736 and 0.049), respectively. The secondary objective is to compare the post-operative pain in the first 24

hours after surgery between the two treatment arms. The patients will be blinded for the treatment assignment to avoid potential biases.

11.3 Analysis Plans

Patients' demographic information at baseline will be collected. We will use mean, standard deviation, median, and range to summarize continuous variables such as blood pressure, heart rate, temperature, pain medication usage, pain and nausea scores, and frequency counts and percentages for categorical variables such as adverse events. We will use the student t-test or the Wilcoxon rank sum test to compare continuous variables between two patient groups. The Fisher's exact test or Chi-square test will be applied to assess the association between two categorical variables. Linear regression will be utilized to assess the effects of patient prognostic factors on the post-operative pain medication usage and the pain score in the first 24 hours.

12.0 Reporting Requirements

Please see Appendix A: Guidelines for AE Reporting

13.0 Data Safety Monitoring Board

During the protocol review and approval process, The University of Texas M.D. Anderson Cancer Center IRB (Institutional Review Board) determines the level of safety monitoring required for each protocol on a case-by-case basis.

The principal investigator is responsible for submitting adverse events (AEs) to The University of Texas M.D. Anderson Cancer Center IRB.

All protocol participants must be registered in The University of Texas M.D. Anderson Cancer Center PDMS (Protocol Data Management System).

14.0 References

1 – Prostate Cancer Foundation, http://www.pcf.org/site/c.leJRIROrEpH/b.5800851/k.645A/Prostate_Cancer_FAQs.htm

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