Protocol Title: Complete motor sparing protocol versus Fascia Iliaca suprainguinal technique for total hip arthroplasty, a prospective randomized clinical trial.
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Principal Investigators: Scott Byram, MD, Michael Majewski, MD.
Co-Investigators: Stephen McCracken, MD. with APS team to perform the blocks: Neal Mugve, MD, Michael Wiisanen, MD, Michael O'Rourke, MD, Michael Ander, MD, Jonathan Metry, MD, Mallikarjun Reddy, MD, MPH; Orthopedic team representatives: Nicholas Brown, MD;
Biostatistician: William Adams, Ph.D.

I. Abstract

Hip arthroplasty is one of the most common surgeries performed around the world. As mentioned by Hannon et al from Rush medical center in Chicago, only 10% of the hip arthroplasties are performed with the addition of a nerve block. (Hannon et al., 2019) Currently at our institution we perform a Fascia Iliaca suprainguinal approach regional block for each patient that present to the hospital for total hip arthroplasty previous consent of the patient. The Fascia Iliaca suprainguinal approach has been a technique described recently and numerous studies have superiority when compared to the Fascia Iliaca infrainguinal technique (Kumar et al., 2015) and femoral nerve block (Liu, Wu, Liang, Deng, & Meng, 2019). More recently, descriptions of different types of blocks that target individual nerves have been described. These techniques are very novel, and little research has been done to compare those new techniques with the current management that we perform at LUMC for hip arthroplasty. The pericapsular nerve group block (PENG) (Girón-Arango, Peng, Chin, Brull, & Perlas, 2018) has been described to target the innervation of the anterior part of the joint capsule (Birnbaum, Prescher, Hepler, & -D. Heller, 1998), and the cluneal nerve block ultrasound technique has been described (Nielsen et al., 2019) to target innervation of the lateral hip. Since physical therapy and rehabilitation post surgery is fundamental to recovery, techniques that provide analgesia but also are motor-sparing should be ideal. We have designed a complete motor-sparing protocol (CMP) that we expect to increase patient satisfaction and faster recovery with at the same time less need for opioid use, making the multimodal anesthesia technique the best choice.

II. Background and Significance/Preliminary Studies

Hip arthroplasty can be performed using different approaches, the most common being the posterior approach. Other approaches have also been described, and the surgeon normally decides which approach to perform depending on patient characteristics.

The Fascia Iliaca suprainguinal approach is a great technique that involves injection below the Fascia Iliaca plane with the goal of cranial local anesthetic spread. The

expected nerves to be blocked include the of the femoral nerve (sensory and motor), lateral femoral cutaneous nerve (sensory), and obturator nerve (sensory and motor). The PENG block has shown to block the obturator nerve, the accessory obturator and a branch of the femoral nerve providing good pain control at the level of the joint (Girón-Arango et al., 2018). The fascia Iliaca block cannot cover the full incision site however, and depending on what approach the surgeon performs, some patients are left with pain and discomfort in the postoperative unit despite a properly performed block.

Other techniques exist that can offer better coverage of the incision for better pain control such as the lumbar plexus block or the transmuscular quadratus lumborum block (Adhikary, Short, El-Boghdadly, Abdelmalak, & Chin, 2018), but these techniques are more difficult to perform, have a high degree of difficulty, and include more severe and frequent complications. They also provide a significant motor block, increasing the risk of patient falls.

The cluneal nerve technique allows for coverage of the cranial part of the posterior approach incision, increasing the analgesic coverage after surgery. (Nielsen et al., 2019). As per Nielsen et al., for an anterior approach the best coverage for the cranial portion of the incision would be with a transversalis fascia plane block as this would cover the ilioinguinal and iliohypogastric nerves.

Looking at the cutaneous innervation and at the different approaches the surgeons can perform, we have designed the complete motor sparing protocol (CMP) that should achieve numbness in the incision site as well as at the joint area. The CMP combines the lateral femoral cutaneous nerve block, PENG block, cluneal nerve block or transversalis fascia plane block, depending on the surgical approach. In this study, all surgeries will be performed with the posterior approach, and the CMP will consist of the lateral femoral cutaneous, PENG, and cluneal blocks.

III. Study Aims

The null hypothesis of this research study is that there will be no significant difference in morphine requirements between the Fascia Iliaca suprainguinal approach and the complete motor-sparing protocol.

Primary Aim: To compare the morphine equivalents administered in the first 24h after arrival in the recovery area between the two groups.

Secondary Aim: To measure pain via a numeric rating scale (NRS) immediately after arrival to recovery area from surgery (time: 0hr), and again at 2, 6, 12, and 24 hrs., hospital stay time to first demand of opioid, and complications.

IV. Administrative Organization

The main participating unit will be the operating rooms of Loyola University Medical Center in the Russo Surgical Pavilion, under coordination of Dr. Scott Byram and Dr. Carlos Martinez Parra. Data will be stored on an institution-provided fileserver with limited access. Data will be de-identified for data analysis and therefore for any future publication. The Clinical Research Office Biostatistics Core will assist with data management and statistical analyses.

V. Study Design

This study will be a prospective randomized unblinded clinical trial. Patients undergoing total hip arthroplasty who meet the inclusion criteria will be invited to participate in this study. A total of 38 patients will be recruited to participate. Patients will be randomized via a 1:1 ratio to either the Fascia Iliaca block group or the complete motor-sparing protocol group.

VI. Study Procedures

Inclusion Criteria:

- Patients ≥ 18 years old
- Patients undergoing total hip arthroplasty posterior approach.
- Patients willing to participate and sign informed consent

Exclusion Criteria:

- Severe COPD/other contraindication to general anesthesia that spinal would be more suitable.
- Patient with a weight of less than 41 kg
- Dementia, not alert or Oriented to person, place, or time
- Chronic pain patient with daily opioid use at home.
- Patient with allergy to local anesthetics
- Patient refusal
- Total hip arthroplasty revision
- Concomitant pain in different area from operative site.
- Pregnancy
- Patient with active infection on the injection sites for the blocks
- Patients unable or willing to understand or comply with the study protocol

Recruitment and Informed Consent: Patient will be informed of the study in the Pre-anesthesia screening clinic during their preoperative visit. This visit normally takes places 3 weeks to 3 days prior to surgery. The delegated study staff will discuss the study information and consent with the patient. The patient will be given the opportunity to have all questions answered. The patient may sign the consent that day or if would like

to think further about it, may sign on the day of the surgery along with the surgical consent and blood consent. No study activities will be conducted prior to the patient signing the consent.

Randomization: After patient has consented and found to be eligible for the study, the patient will be randomly assigned to either the Fascia Iliaca block or the complete motor-sparing protocol. The randomization will be in a 1:1 ratio.

Pre-Operative: After all paperwork has been completed and surgical site has been marked by the orthopedic team, the patient will then have an intravenous (IV) line inserted by the pre-op nurse, or anesthesia team if available. Once the IV is in place patient will be started on the standard orthopedic ERAS protocol that consists of: celecoxib 200 mg, acetaminophen 975 mg, oxycodone 10 mg, a transdermal scopolamine patch, and gabapentin 600 mg if creatinine clearance >15 mL/min or gabapentin 300 mg if creatinine clearance is <15 mL/min.

After all oral medications have been given to the patient, the acute pain (APS) team will perform the nerve block. Once randomized, the patient will receive light sedation during the performance of the nerve blocks. This sedation will be administered by the APS team while patient is monitored with EKG, blood pressure monitoring and peripheral capillary oxygen saturation (SpO2) as per standard department protocol, nasal cannula oxygen will be delivered at an oxygen flow of 2 L/min. Monitor will remain on the patient during the performance of the block until the patient is transported to the operating room. The medications used for sedation will be 50 mcg of fentanyl, 1 mg midazolam.

Nerve block administration:
Patients that are randomized to the Fascia Iliaca block: The APS team will position the patient and perform a time out with the preop nurse present to verify consent and block laterality. After cleaning the area with chloraprep and ultrasound visualization of the area for the Fascia Iliaca suprainguinal approach, 2% lidocaine will be used for skin infiltration. All blocks will be performed with a Stimuplex® Ultra 360 insulated echogenic needle. Once adequate needle visualization is achieved within the correct anatomic position and plane, 50mL of 0.25% bupivacaine will be injected. Patient will remain in the pre-op holding area until operating room is ready. During that period, the patient will be monitored as mentioned above, and all vital signs will be monitored every 5 minutes.

Patients that are randomized to the complete motor-sparing protocol: The APS team will position the patient and perform a time out with the preop nurse present to verify consent and block laterality. After cleaning the area with chloraprep and ultrasound visualization of the area for the PENG approach, 2% lidocaine will be used for skin infiltration. All blocks will be performed with a Stimuplex® Ultra 360 insulated echogenic needle. Once adequate needle visualization is achieved within the correct anatomic position and plane, 20mL of 0.25% bupivacaine will be injected under ultrasound visualization. Following the PENG block the patient will be positioned for the lateral femoral cutaneous nerve

block. Again after chloraprep and with ultrasound guidance, 1mL of 2% lidocaine for skin infiltration followed by injection of 10mL of 0.25% bupivacaine surrounding the lateral femoral cutaneous nerve. To complete the complete motor sparing protocol we will place the patient in lateral decubitus to perform the cluneal nerve technique. We will proceed as the other nerves using an aseptic technique with chloraprep and local infiltration with lidocaine 2%. Under ultrasound guidance, 20mL of 0.25% bupivacaine will be injected in the area of the cluneal nerve.

Hip Replacement Procedure: All subsequent management moving forward for both groups will be the same. Once patients have their nerve block(s) performed, they will proceed to the operating room. On arrival patients will be connected to the monitors, and 100% oxygen will be given. Induction of anesthesia will be performed using 100 mcg of fentanyl, 2-4 mg/kg of propofol at the discretion of the anesthesiologist, and rocuronium 0.6mg/kg followed by intubation. Additional intraoperative medications will include antibiotics per protocol, 8 mg of decadron, 30 mg of ketamine, and tranexamic acid 2000 mg total given as two divided doses.

Maintenance of general anesthesia will be with sevoflurane at a MAC of 0.5 and started on a remifentanil infusion of 0.125 mcg/kg/min with titration to hemodynamic stability.

Prior to extubation, patients will be reversed with an appropriate dose of sugammadex (dose will depend in the number of twitches on the train of for and weight of the patient). If contraindication to sugammadex exists, patients will be reversed using glycopyrrolate 0.01 mg/kg and neostigmine 0.07 mg/kg up to maximum doses of 1mg and 5mg, respectively.

Post-Procedure: Once the patient is extubated, the patient will be transported to the recovery room. Time of arrival to the recovery room will be considered zero time. It will be at that time the patient will be assessed for their pain level using a numerical rating scale from 0-10, zero being no pain and 10 the worst possible pain. This question will be repeated during the hospitalization of the patient at 2, 6, 12, and 24 hours. The answers will be recorded by the nurse and documented in the EPIC flowsheet.

Depending on the pain score, the nurse in post-op and on the floor will administer medication as needed. Per protocol, the anesthesiologist will order either fentanyl, morphine, or hydromorphone.

- If patient complains of severe pain in the recovery area (NRS 7-10), patient can receive: morphine injection 2 mg intravenous every 5 min PRN, fentanyl 25 mcg intravenous every 5 minutes PRN, or hydromorphone 0.2mg IV every 5 minutes.
- If patient complains of moderate pain (NRS 4-6), the patient can receive hydrocodone 5 mg with acetaminophen 325 mg, tramadol 50mg, or oxycodone 5 mg.
- If patient pain is rated as <4, the patient can receive acetaminophen 975 mg.

Once the patient meets the criteria to be discharged from the recovery area, pain control medications will be per the orthopedic team protocol based on their pain score.

All of the above treatments are standard preop, intraop, and postop anesthetic practice. The ONLY difference will be the location of the injection of the bupivacaine.

Data Collection and Storage: All data will be collected from EPIC. From the MAR summary report, the total amount of morphine equivalent the patient needed to keep their pain under control will be collected. The conversion of all the opioid medication used to morphine equivalent will be done by using the CDC morphine milligram equivalents calculator. Pain scores will be retrieved from the nursing flowsheet within EPIC. Values at 0, 2, 6, 12, and 24 hours will be collected.

Data will be stored on an institution-provided fileserver with limited access. Data will be de-identified for data analysis and therefore for any future publication. The Clinical Research Office Biostatistics Core will assist with data management and statistical analyses.

VII. Safety Monitoring Plan

The standard of care at Loyola already includes a nerve block (currently Fascia Iliaca suprainguinal technique). Within the CMP the same amount of medication will be used but targeted to different nerves that are purely sensory. The current Fascia Iliaca injection consists of 50-60 mL of 0.25% bupivacaine. Safe dosing of bupivacaine depends on injection site and additives but is generally thought to be up to 3 mg/kg. In order to not vary the injectate dose, patient under 41kg will not be included. For the patients being enrolled in this study, the study poses no additional risk to the patients when compared to current practice. It is current practice to report any adverse events to the Department of Anesthesiology Committee on Quality and Patient Safety. Any adverse events will also be reported to the IRB per protocol.

VIII. Power Analysis

In this study, patients will be randomly assigned to a standard Fascia Iliaca suprainguinal technique or an experimental complete motor-sparing protocol. The study will use a 1:1 permuted random-block allocation. One goal of the proposed trial is to test the null hypothesis that there is no difference in the average morphine equivalent dose between the two cohorts at 24 hours. With a proposed sample size of 19 assigned to the standard Fascia Iliaca suprainguinal technique and 19 assigned to the experimental complete motor-sparing protocol (total N = 38), the study will have power of 81.3% to yield a statistically significant result. This computation assumes a mean difference between the two cohorts of 1.9 morphine equivalent units and a common within-group standard

deviation of 2.0 units. This computation also assumes the criterion for significance (alpha) is 0.05 and that the test will be 2-tailed, meaning an effect in either direction will be interpreted.

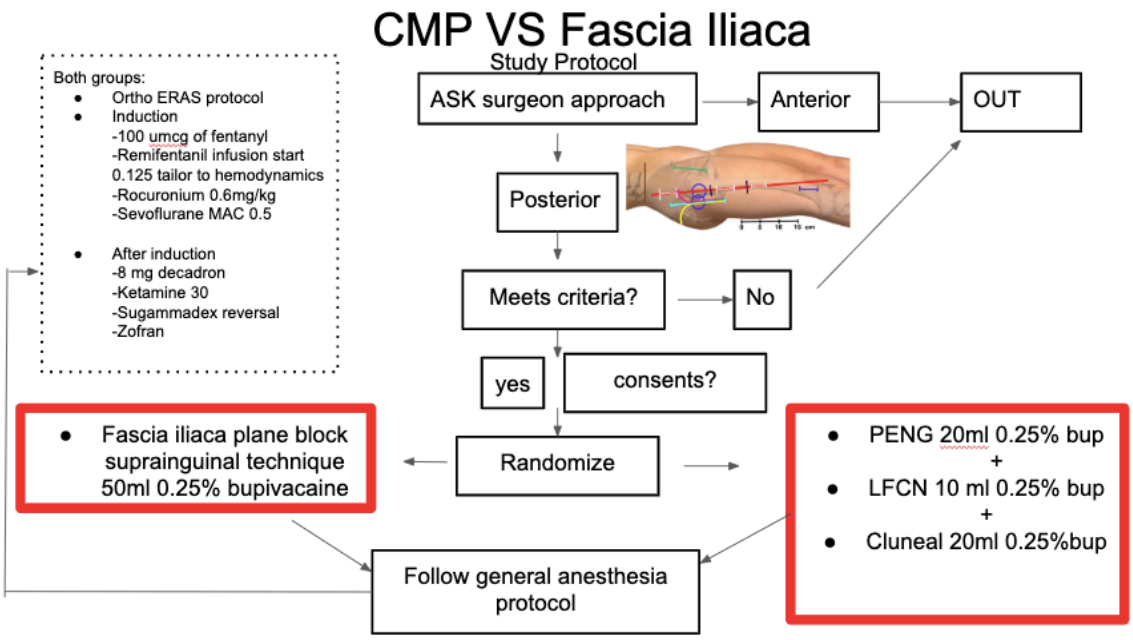
Another goal of the study is to test the null hypothesis that there is no difference in the average Numeric Rating Scale (NRS) pain score between the two cohorts at 24 hours. With 19 patients assigned to each cohort for a total of 38 patients, the trial has 80% power to detect an average difference of at least 1.9 NRS points when the common within-group standard deviation is also 2.0 NRS points. As before, this computation assumes the criterion for significance (alpha) is 0.05 and that the test will be 2-tailed, meaning an effect in either direction will be interpreted.

In this study, summary statistics will be used to describe all quantitative measures using mean and standard deviation (if normally distributed) or median with interquartile range (if non-normally distributed). Summary frequencies will be provided as valid counts and percentages for all nominal and ordinal patient characteristics. These summary measures will be stratified by treatment assignment.

For the primary aim, an independent samples t-test will be used to compare the morphine equivalent dose between the two cohorts at 24 hours post-procedure. For this comparison, the normal distribution assumption of morphine equivalents will be assessed using QQ plots and outliers will be assessed using box-plots. The homogeneity assumption will be assessed using Levene's test.

For the secondary aim, NRS scores are repeated every hour and patients may contribute multiple NRS scores to the analysis. A linear mixed-effects model will be used to compare the change in NRS scores between treatment groups over time. In this model, random intercepts will be allowed for each patient to account for their correlated NRS observations, and an interaction term will be allowed to estimate the difference in NRS slopes over time between the two cohorts. If the interaction term is not significant, it will be removed from the model to compare the overall average NRS score between the two groups while holding elapsed time constant. In linear-mixed effects models, the random intercept for each patient and the residual error term are assumed to be independent of each other and of the treatment effect. We will use residual plots and QQ plots to assess these model assumptions. All analyses will be completed using SAS version 9.4 (Cary, NC).

IX. Appendix A



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