Title: Postoperative Pain management in Patients Undergoing IMN Fixation After Closed Tibial and Femoral Fractures

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Postoperative Pain Management in Patients Undergoing Intramedullary Nail (IMN) Fixation After Tibial and Femoral Fractures.

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Research Questions:

1. Is the co-administration of intravenous ketorolac and oral acetaminophen an effective alternative for post-operative pain management in patients with tibial and femoral shaft fractures who undergo intramedullary nailing?

Hypothesis & Scientific Aim:

We believe that the perioperative co-administration of intravenous ketorolac and oral acetaminophen diminishes opioid consumption, provides adequate pain control, and has more tolerable side effects in patients who undergo intramedullary nailing for tibial and femoral shaft fractures, when compared to patients taking opioid medications for pain control.

We will design an alternate pain control protocol composed of intravenous ketorolac and oral acetaminophen for patients who undergo intramedullary nailing for tibial and femoral shaft fractures to determine its efficacy when compared to pain control with intravenous morphine and oral oxycodone combined with acetaminophen.

Background/Significance :

Acute pain after a surgical procedure may occur secondary to trauma from the procedure itself or from procedure-related complications [1]. Appropriate perioperative acute pain management is an important phase of patients' recovery since the undertreatment can lead

to adverse outcomes such as: thromboembolic and pulmonary complications, additional time spent in an intensive care unit or hospital, hospital readmission for further pain management, needless suffering, impairment of health-related quality of life, and development of chronic pain [1]. Furthermore, its overtreatment with opioid medications is associated with an increased risk of thromboembolic, infectious and gastrointestinal complications as well as increased length of hospital stay, cost of care and risk of opioid addiction [2]. Opioid addiction has led to a nationwide public health emergency in which approximately 115 American patients die daily from an overdose[3].

The effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on fracture healing has been a controversial topic in the orthopedic scientific community for many years. These medications are an effective, and safe analgesic alternative drug that are commonly used in fracture management worldwide.[11] However, many physicians in the United States prefer to prescribe opioids over NSAIDs in patients with long bone fractures.[11]

Since orthopaedic surgeons in the United States are the third leading prescribers of opioid medications, it is crucial to identify other alternatives for opioid based pain management protocols.[11] The possibility of a non-opioid pain management protocol may decrease the orthopaedic surgeon's impact on the ongoing opioid epidemic.

Perioperative administration of IV ibuprofen 800mg every 6 hours has been shown to effectively decrease opioid requirements and pain intensity, while demonstrating minimal tolerable side effects after abdominal surgery and elective orthopedic procedures [7–9]. Gürkan et al. showed in a clinical trial that patients who received IV ibuprofen 800mg every 6 hours had significantly lower pain intensity measurements after total hip replacement. In the same way, Gupta et al., combined the same dose of ibuprofen with IV acetaminophen 1000mg every 6 hours, showing significant pain improvement on the third postoperative day of patients who underwent total hip or knee arthroplasty [6]

The authors of this study believe that the use of the pain management protocols used in Total Knee Arthroplasty (TKA) can be effectively used as an alternative for patients undergoing intramedullary nailing for femur and tibia shaft fractures. This arises from the idea that TKA are considered among the most painful orthopaedic procedures. Wylde et al. demonstrated that on postoperative day 1, 58% of TKA patients indicated to have moderate-severe pain, which only decreased to 43% by postoperative day 3.[14]

Additionally, studies have shown that patients undergoing TKA, experienced more acute postoperative pain than Total Hip Replacement (THR) patients.[13]

Throughout this trial, we wish to determine whether oral acetaminophen and intravenous ketorolac are viable alternatives to opioid medication regimens for the pain management of Hispanic patients who undergo intramedullary nailing of tibial and femoral shaft fractures.

Methodology and Study Design:

Study Design

A prospective, single blind, randomized control trial will be designed to evaluate the efficacy of NSAIDs and acetaminophen in post-operative pain control on Hispanic patients undergoing intramedullary nailing of tibia and femur shaft fractures at University District Hospital of the University of Puerto Rico at San Juan, PR. All consecutive cases (during a 12 month period) from the orthopedic trauma service of the University of Puerto Rico Orthopaedic Surgery Residency program, will be included. We will limit the enrollment to 150 patients.

The study cohort will be composed of patients who underwent intramedullary nailing of tibial and femoral shaft fractures at our institution. The sub-groups will be created based on pain control protocol (opioid vs non-opioid).There will be 2 aleatory assigned study groups.

Group 1 will be composed of patients receiving the following standard pain control protocol: ketorolac 30 mg IV every 6 hours for patients younger than 70 years vs ketorolac 15mg IV every 6 hours for patients older than 70 years, first dose will be administered 30 minutes preoperatively. An additional 1000mg of acetaminophen PO will be administered every 6 hours simultaneously regardless of the age group. Patients who determine pain to be unbearable and wish to opt out of the non-opioid group will receive may do so. The case will then be analyzed on an individual basis by the PI, Dr. Lojo, who will analyze your specific case and tailor the pain management for the individual patient.

Group 2 will be composed of patients receiving the following pain control protocol: morphine 0.1 mg per kg IV every 6 hours with an additional oxycodone combined with acetaminophen 2 tabs PO every 6 hours.

The randomization method will be simple randomization. An unblinded research assistant will use an online random list generator (http://randomization.com/)[12] in order to randomize the subjects in a 1:1 ratio to receive either an opioid or non-opioid based regimen. Informed written consent from all participants will be obtained.

Inclusion Criteria:

The target population is: female and male patients older than 18 years of age undergoing intramedullary nailing of tibial and femoral shaft fractures and classified as ASA I/ASA II as per the American Society of Anesthesiologists physical status classification system.

Exclusion criteria:

Patients with (1) a history of recent use of opioids; (2) allergy or hypersensitivity to NSAID; (3) impaired renal, cardiac, or hepatic function; (4) history of gastrointestinal bleeding; (5) history of substance abuse; (6) polytraumatized; (7) younger than 18 years of age; (8) unable to consent; (9) Pregnant Women; (10) Mentally Incompetent; will be excluded from the study.

Variables

Variables such as sociodemographic, past medical history, diagnosis/fracture type, highest educational level, allergies, history of illicit drug use, and pain intensity measurement using a Visual Analogue Scale for pain (VAS) score; will be obtained for all patients. VAS score is a previously validated questionnaire. Post-operatively the first questionnaire will be given 12 hour postoperatively and during subsequent twelve hours intervals until discharge. We will also record secondary variables such as time to GI motility, time to weight bearing of affected limb, resumption of ambulation, and length of hospital stay. Each assessment will take about 15 minutes, and the authors of this study estimate that the entire time per patient will be 60 minutes. The time intervals for the data collection chosen for this project was based on previous studies performed in our institution.

Each patient will be provided with all the necessary information of the risk and benefits involved in this study and their intention to participate (Statement of Purpose and Justification). Previous authorization from the MSC - IRB office will be obtained before starting the research study.

Risk and Benefits:

This study presents minimum risks for the patients. A possible risk would be a probable feeling of uncomfortableness due to the time it takes for the patient to complete the VAS instrument for pain intensity. If the pain becomes overwhelming patients may choose to opt out of the treatment group and have the PI (Dr. Lojo) analyze the individual case and tailor the pain medication to their needs. Patients will not be receiving a direct benefit, such as a reward, before and after the study. However, the information obtained during this study will help improve future doctor-patient interactions hence improving patient satisfaction. Risks and benefits will be explained to the patient prior to performing the study.

Analytic Plan:

Data analysis will be performed and expressed using frequency and percentages for categorical variables and means with standard deviation for quantitative data. In addition, comparisons between data will be assessed with the chi-square test and student's t-test or analysis of variance (ANOVA) for categorical and quantitative variables, respectively. Statistical significance will be considered for p-values ≤ 0.05.

The patients participating in the study will be assigned a sequential identification number (1, 2, 3, etc.) on a password protected Google Sheet (GS1), only the study's PI, Dr. Lojo, and study coordinator, Dr. Olivellas will have access to this sheet. This will be done in order to preserve confidentiality and avoid the use of identification using the medical record number. Once the data is retrieved in the form of questionnaires, it will be recorded on a separate password protected Google Sheet (GS2) which will only have the sequential identification numbers (not the medical record numbers) it will be de-identified. The master key to this code will be securely placed in a locked file in the research office at the Orthopedic Surgery Section office (9th floor) at the Medical Sciences Building. Only the PI, Co-PI, study coordinator, and medical students affiliated with the Orthopaedic Surgery department who have met the CITI requirements will have access to GS2. All statistical analyses will be performed with de-identified data. All data will be stored in a secured and encrypted hard disk to which outside personnel has no access. Once the study is completed, all electronic files will be stored for two additional years. Afterward, these electronic documents will be permanently deleted from all authorized devices by the study coordinator.

Limitations:

Since the VAS for pain is a subjective measurement for the evaluation of pain, there is an inherent probability for under or over appreciation. In addition, the population selected may represent convenience bias due to its location on the northeast side of Puerto Rico.

Vulnerable Populations

Hospitalized patients, Patients age 18-20 years old, Patients older than 65 years of age.

Consent Process:

Upon admission to the in patient orthopaedic ward at the University District Hospital, patients will be approached with the opportunity to participate in the study. Patients will be approached by Dr. Tresgallo, Dr. Hess, Dr, Olivellas, Dr. Rullan, or Dr. Pinci, who will have a conversation about the risks, and benefits of the study, and its contribution to the medical field. Any questions that may arise will be answered at this time. Furthermore, the patients will be asked to explain the study in order to verify understanding. In the case of patients who fall within 18-20 years old, the investigators will have a conversation, and verify understanding from both the parents or guardians and patients. Finally, informed consent and assent forms will be taken and singed. Each participant, and parent or guardians in the case of 18-20 years of age, will be instructed on the ability to resign from this study at any time.

Privacy and Confidentiality:

References:

1. American Society of Anesthesiologists. Practice Guidelines for Acute Pain Management in the. *Anesthesiology*. 2012;116(2):248-273. doi:10.1097/ALN.0b013e31823c1030
2. Cozowicz C, Olson A, Poeran J, et al. Opioid prescription levels and postoperative outcomes in orthopedic surgery. *Pain*. 2017;158(12):2422-2430. doi:10.1097/j.pain.0000000000001047
3. Understanding the Epidemic | Drug Overdose | CDC Injury Center. https://www.cdc.gov/drugoverdose/epidemic/index.html. Accessed September 30, 2019.

4. Nadarajah V, Glazier E, Miller K, et al. Evaluation of Preoperative Pain Using PROMIS Pain Interference in Knee Surgery Patients. *J Knee Surg*. 2019;1(212). doi:10.1055/s-0039-1688769

5. Chou R, Gordon DB, De Leon-Casasola OA, et al. Management of postoperative pain: A clinical practice guideline from the American pain society, the American society of regional anesthesia and pain medicine, and the American society of anesthesiologists' committee on regional anesthesia, executive commi. *J Pain*. 2016;17(2):131-157. doi:10.1016/j.jpain.2015.12.008

6. Gupta A, Abubaker H, Demas E, Ahrendtsen L. A randomized trial comparing the safety and efficacy of intravenous ibuprofen versus ibuprofen and acetaminophen in knee or hip arthroplasty. *Pain Physician*. 2016;19(6):349-356.

7. Gago Martínez A, Escontrela Rodriguez B, Planas Roca A, Martínez Ruiz A. Intravenous ibuprofen for treatment of post-operative pain: A multicenter, double blind, placebo-controlled, randomized clinical trial. *PLoS One*. 2016;11(5):1-16. doi:10.1371/journal.pone.0154004

8. Singla N, Rock A, Pavliv L. Pre-Operatively_2010.Pdf. 2010:1284-1293.

9. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo- controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clin Ther*. 2009;31(9):1922-1935. doi:10.1016/j.clinthera.2009.08.026

10. Gürkan Y, Yörükoğlu HU, Işık E, Kuş A. The effect of ibuprofen on postoperative opioid consumption following total hip replacement surgery. *Turkish J Anaesthesiol Reanim*. 2019;47(1):31-34. doi:10.5152/TJAR.2018.48265

11. Fader L, Whitaker J, Lopez M, et al. Tibia fractures and NSAIDs. Does it make a difference? A multicenter retrospective study. *Injury*. 2018;49(12):2290-2294. doi:10.1016/j.injury.2018.09.024

12. Dallal G. *Randomization. com*. Available online at: http://www.randomization.com/. (2003).

13. T. Thomas, C. Robinson, D. Champion, M. McKell, M. Pell. Prediction and assessment of the severity of postoperative pain and of satisfaction with management. *Pain*. 75 (1998), pp. 177-185

14. V. Wylde, J. Rooker, L. Halliday, A. Blom. Acute postoperative pain at rest after hip and knee arthroplasty: Severity, sensory qualities and impact on sleep. Orthopaedics & Traumatology: Surgery & Research. 2011;97(2):139-144.