# IV meloxicam for pain management post TJA: a prospective randomized trial

NCT05291598

IRB number 20211214

3/30/22

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1) **Protocol Title**

IV meloxicam for pain management post TJA: a prospective randomized trial

2) **Objectives***

The purpose of this project was to determine if a change in patient reported pain, nausea and vomiting after total knee and hip arthroplasty could be observed with the substitution of IV

meloxicam for ketorolac in the current established peri-operative pain protocol and if these changes lead to a decrease in opioid consumption (in morphine equivalents).

## 3) **Background***

Orthopaedic surgery is associated with high levels of post-operative pain. Failure to manage patients' pain can impair overall recovery, increase length of stay in the hospital, increase risk for mortality, and diminishes patient quality of life. Currently, guidelines strongly encourage the use of multimodal analgesia with minimized use of opioids.

We have previously investigated the topic of enhanced recovery after surgery (ERAS) analgesia protocols at our institution, demonstrating the benefits of multimodal pain management after total knee arthroplasty.

Historically, the limited options for pain management following orthopaedic surgery led to an over reliance of opioids with little understanding of the repercussions of such drugs. The potentially devastating effects of sustained opioid use are much better understood evoking tremendous hesitation surrounding the prescription of this class of drugs. Currently, they are recommended to be administered at the lowest possible dose or even avoid entirely in combination with other non-opioid analgesia comprising multiple mechanism of action.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been demonstrated to be effective in reducing post-operative pain as well as having anti-inflammatory properties which improve recovery time and systemic inflammation as well as limiting opioid consumption and thus the adverse effects related to opioids. NSAIDs however have very important adverse effects themselves such as gastrointestinal bleeding, renal azotemia and hematological complications. The risks and benefits of this class of drugs are based on their effects on the cyclooxygenase 1 (COX 1) and cyclooxygenase 2 enzymes (COX 2).

Meloxicam is a selective, non-exclusive, COX 2 inhibitor. This unique mechanism of action relatively spares the gut lining promoting constitutively active COX 1 enzyme, translating to reduced complications from gastrointestinal bleeding compared with non-selective NSAIDs. Its novel long lasting IV formulation further differentiates this drug from the other drugs of its class and has been evaluated in several phase 2 and phase 3 post-operative pain studies. Thus, meloxicam has emerged as an exciting potential alternative/addition to the surgical pain management protocol.

## 4) **Inclusion and Exclusion Criteria***

Inclusion criteria-
1- Patients over the age of 18,
2- Patients undergoing primary total knee or primary total hip replacement at the University of Miami Hospital,
3- Patients that have capacity to provide medical consent

Exclusion criteria-
1- All patients under the age of 18
2-Prisoners, diabetics, increased risk of bleeding, pregnant women. Women planning on becoming pregnant in the next year, and women who think they might be pregnant, or women who become pregnant during the study period will be removed from the study.
3- Patients with prior surgery or history of infection on the joint of interest.
4-Patients with an estimated glomerular filtration rate (eGFR) <50 ml/min
5-Patients on dialysis or renal transplant.
6- Patients on steroid preoperatively.
7-Allergy to sulfas
8-Inability to provide medical consent.
9-Any condition that, in the opinion of the investigator, would compromise the well-being of the patient or the study or prevent the patient from meeting or performing study requirements will exclude the participant.

## 5) **Procedures Involved***

Study design: All patients who fulfill inclusion criteria, undergoing total joint arthroplasty will be randomized to one of two groups to be given the standard orthopaedic joint replacement protocol plus either meloxicam 30 mg IV push pre-op 2 hours before primary incision* **or** ketorolac 15 mg IV push intra-operatively, followed by 15 mg IV push every 6 hours scheduled for 2 doses. Cases will be assigned randomly in a 1:1 fashion. A computer program such as Microsoft Excel will be employed for the randomization process.
***(*meloxicam 30mg IV push pre-op timing may be subject to change depending on results from interim analysis)***

***Standard orthopaedic joint replacement protocol at our institution includes:***

***1. Dexamethasone***
***2- Tylenol***
***3- Lyrica***
***4- Celebrex***
***5-Meloxicam (PO)***
***6-Oxycodone***

Patients will be assessed routinely once every hour by the circulating nurse for the duration of their care in the hospital. Should a patient receive ambulatory care and depart from the hospital before 24 hours have elapsed, they will be contact via telephone for assessment.

## Study Design

The primary outcome of this project is in the treatment of pain around the immediate post-operative time after total joint replacement surgery. This study is building off former FDA approved

prospective clinical trials. As a parallel experimental/ interventional study design, patients will be randomized to either the control group (institution specific joint replacement pain protocol) or the intervention group (receiving the IV meloxicam). Patients and providers will be both be blinded to eliminate bias in a 1:1 randomization process matching intervention group patients with control group patients. A *priori* power analysis was conducted with a = 0.05, b = 0.8, and mean difference of 1.3. The analysis yielded a need for 85 patients in each arm and was based upon prior studies. We aim to enroll 200 patients that will see the intervention through to completion.

## 6) **Study Endpoints***

- *Primary endpoint – difference in pain scores at time points 2 hours and 24 hours after primary total hip and knee arthroplasty for each group. The numeric pain rating scale will be used- a higher pain score would indicate higher pain levels. It is scaled from 0-10*
- *Secondary endpoint - (1) Total opioid consumption in the immediate post-operative period (2 hours and 24 hours), (2) differences in patient nausea scores and vomiting scores (2 hours and 24 hours), (3) duration of hospital stays (hours, nights, and same day discharges), (4) Differences in changes in creatinine levels for patients during routine labs.*

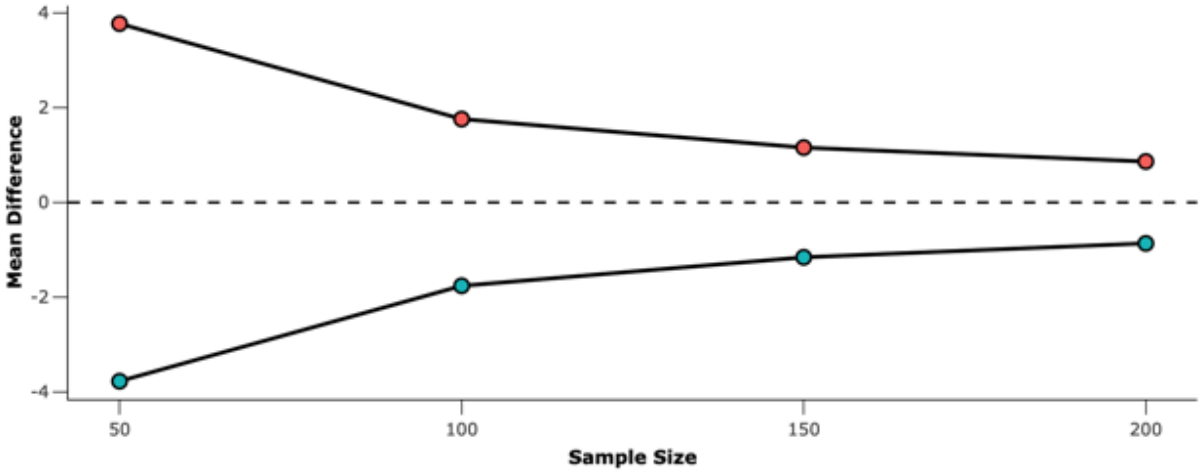
## 7) **Data Management and Statistical Analysis**

We will perform a superiority test and examine the mean pain score differences at time points 2 hours and 24 hours after surgery as our primary outcome. A Mann Whitney U will be performed to compare the means. Secondary outcomes include postop nausea and vomiting scores with a modified likert scale (2 hours and 24 hours), morphine equivalents received (2 hours and 24 hours), length of stay (hours, nights, and number of same day discharges), and differences in creatinine changes (baseline preoperative to highest creatinine on routine postoperative labs while hospitalized). We will compare these scores between groups Mann Whitney U or Fisher's exact test.

*INTERIM ANALYSIS:*

We plan to analyze this trial for futility by employing the O'Brien and Fleming method of interim analysis. Specifically, we will analyze our groups at interims n = 25 and n = 50 (total 50 and 100, respectively) for futility using appropriate boundaries for the mean difference. Should the mean difference exceed the boundary, the trial will conclude concluding significance between the

groups; conversely, should the mean difference be below the boundary, the trial will terminate with futility.




## 8) Risks/Benefits

This study is a prospective cohort study that will collect private, identifiable information about human subjects. The main risk is to subjects' confidentiality should an individual outside of the study team access the study data.

There is no direct benefit to subjects. This research might lead to the benefit of others should the analysis of the data lead to better selection of surgical candidates and possible interventions to reduce adverse outcomes.

## 9) Adverse Events / Serious Adverse Events

Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research will be recorded 6 weeks post-operatively.

## 10) Setting

Single center study - University of Miami Hospital

## 11) Recruitment Methods

After IRB approval is achieved recruitment will start.

Subjects will be recruited at the clinics of participating physicians, by the attending surgeon performing the surgeries. All recruitment will be performed in the private clinics of the

attending surgeons. Consent for surgery and explanation of the surgical procedures to the patients is a routine process that occurs in clinics. Explanation about the study as well as the enrollment process and consent will be performed after patient has consented to undergo total joint replacement. Any patient who attends these clinics and is a candidate for a Total Hip or Total Knee Arthroplasty and meets the inclusion and exclusion criteria will be approached about the study. If patients consent they will be included in the study. Patients will have from the moment they are informed about the study until they undergo the procedure to decide if they want to participate. For those patients, they can telephone call the research coordinator who contact information will be made available, at any time during that period to decide.

There will be neither advertisements for this study nor any method to encourage participation from the local populations.
Participants will not receive monetary compensation for participation.

## 12) **Consent Process**

Patients will be first evaluated for appropriate capacity to provide consent. Upon thorough explanation of the project verbally and subsequent permission at the time of the surgical consult, patient information will be recorded for participation.

The consent process will take place in the private clinics of the primary investigator. As patients are identified in the participating clinics, a member of the study team will obtain an informed consent for participation in the study. For those patients who do not speak English, consent will be obtained in the appropriate the language. We will be following the *SOP: Informed Consent Process for Research (HRP-090).* All consent forms will be available in English. The principal investigator is fluent in Spanish and will be obtaining consents in Spanish when appropriate, in cases where co-investigators do not speak Spanish, the HIPAA compliant interpretation services available in clinic will be used for obtaining consents for the research study.