NCT04388111

Title: Intraosseous Morphine Administration during Primary Total Knee Arthroplasty: A Randomized Control Trial

Version Date 2/12/2020

PROTOCOL TITLE:

Intraosseous Morphine Administration during Primary Total Knee Arthroplasty: A Randomized Control Trial

PRINCIPAL INVESTIGATOR

Kwan Park, MD
Houston Methodist Hospital / Orthopedics & Sports Medicine

CO-INVESTIGATORS/ COLLABORATORS:

Stephen Incavo, MD / Houston Methodist Hospital / Orthopedics & Sports Medicine
Terry Clyburn, MD / Houston Methodist Hospital / Orthopedics & Sports Medicine
Francesca Taraballi, PhD / Houston Methodist Research Institute / Center for Musculoskeletal Regeneration
Ava Brozovich, MPH / Houston Methodist Research Institute / Texas A&M College of Medicine

SPONSOR / FUNDING AGENCY

Internally Funded

VERSION NUMBER/DATE

Version 3 2/12/2020

REVISION HISTORY

This is revision number as submitted to the IRB.

Revision #	Version Date	Summary of Changes	Consent Change (Yes/No)
1	1/14/2020	Clarified sample collection protocol and reasoning. Also added additional information regarding randomization and updated inclusion/exclusion criteria.	Yes

2	1/28/2020	Clarified statistical plan for research study including power analysis and made blood draw language consistent.	Yes
3	//2020	Extended post-operative surveys out to 1 year post-op. Added a baseline blood draw after induction of anesthesia. Also added standardization of tourniquet pressures across providers set to 275 mmHG (within SOC). Lastly, added two references to support the standardization of tourniquet pressures across all study patients across all 3 providers.	Yes
4	3/12/2020	Study design changes: Allowing morphine in PACU/post op and not allowing Toradol (Ketorolac) or Celecoxib in PACU/post op. Clarified that post-op blood draws will only be done on Dr. Incavo's 1st and 2nd case patients to ensure adequate processing availability by the research team. Study blinding will now be double-blind instead of single-blind. Changed the timings of the blood draws in order to better capture the variable of interest (baseline, 15 minutes after tourniquet is released, and 10 hours post-op). Lastly, the research team removed the gathering of bone & soft tissue samples from this study.	
5	5/8/2020	Updated exclusion criteria to include patient must be able to get general and spinal anesthesia.	
6	10/9/2020	Increased BMI cutoff from 35 to 38 for inclusion/exclusion criteria. Added exclusion criteria for same-day discharge patients.	

1. Purpose of the Study / Objectives

The purpose of this study is to determine if IO morphine decreases pain, inflammatory markers, and post-operative opioid use in total knee arthroplasty (TKA) patients.

- Aim 1: IO morphine will significantly reduce patient pain in the post-operative period after primary TKA.
    - Sub aim: IO morphine will cause significantly higher levels of morphine within the joint compared to current standard of care.
- Aim 2: IO morphine will decrease systemic inflammatory markers in the post-operative period after primary TKA.
- Aim 3: IO morphine will result in significantly less post-operative oral opioid use, and achieve superior outcomes such as increased range of motion (ROM).

2. Background

Following total knee arthroplasty (TKA), orthopedic surgeons must provide medication to control postoperative pain. Pain can be due to inflammation caused from tissue trauma, or nerve injury. [1] Traditionally, opioids have been used as the sole pain management medication. Opiates reduce pain levels because they bind to opioid receptors inside and outside of the central nervous system. However, because the underlying physiology of pain is both neurogenic and inflammatory, the medications given should be multimodal. For example, cycylooxygnase-2-specific anti-inflammatory agents that are given pre-operatively, inhibit prostaglandin synthesis, and therefore decrease inflammation and pain in the immediate post-operative period.

Prior studies have explored if tissue or intra-articular injections with pain medications have effects on post-operative pain levels. Compared to patients with no intra-operative pain medication injection, patients that had intra-articular or soft tissue injections of a combination of bupivacaine, epinephrine, and morphine, had significant better pain control in the immediate post-operative period.[2] Other studies have demonstrated that after receiving intra-articular injections, the need for post-operative narcotics decreased. [3-5]

Though there are studies that have proven a beneficial effect of intra-operative medications, there have also been multiple studies that did not detect any difference in pain ratings in the immediate post-operative period. [6 7] Therefore, it is still widely debated among orthopedic surgeons if intra-articular injections of pain medications reduces pain, decrease inflammation, and reduced use of opioids in the post-operative period.

Though studies have examined the effect of intra-articular morphine injection on pain, they have not determined if the level of morphine in the bone is higher compared to levels obtained intravenously. In addition, studies have not demonstrated if morphine has an effect on the inflammatory environment post-operatively. However, following cardiopulmonary bypass surgery, it was determined that morphine decreases the inflammatory response after surgery. Levels of a variety of inflammatory cytokines (IL-6, IL-8, CD11a, CD11b, CD11c, and CD18) were decreased among the patients that received morphine compared to patients that did not.[8]

In addition oral opioids have many side effects including somnolence, depression of the brainstems control of the respiratory drive, urinary retention, nausea and vomiting, constipation, and ileus. In addition, as orthopedic surgery is progressing, patients are being discharged from the hospital 12-24 hours after surgery. This dramatic reduction in hospital stay makes it imperative to find a long lasting pain medication in the immediate post-operative period.

3. Study Design

This study is a double-blind randomized controlled trial with two arms. The control group will receive an intraossoeus (IO) injection of antibiotics as per Dr. Incavo's, Dr. Park's, and Dr. Clyburn's standard of care for primary TKA patients. The experimental group will receive an IO injection of antibiotics mixed with 10 mg of morphine. A research coordinator on the study team will inform the circulator nurse present in the OR during the study patient's case about which group (morphine or no morphine) the patient is in. The circulator nurse will then be instructed to place morphine into the surgical field during the mixing process of the intraosseous solution without notifying the surgeon to ensure the double blind. Patient's post-operative pain levels, pain medication consumption, side effects to pain medications, and range of motion will be recorded for 14 days following surgery.

Patient outcomes will also include pain levels, post-operative pain medication use, and post-operative ROM.

The anticipated total number of participants is 84 with 42 patients being in each group. The maximum number of subjects who will be enrolled is 84 patients (i.e. give consent to participate) at this site.

Participants will be randomized into either the control group or the experimental group by an excel-based software program.

Inclusion Criteria

- Patient gives informed consent to participate in the study
- Patient is undergoing a primary total knee arthroplasty.
- Age > 18 and <80 years old.

Exclusion criteria

- Patient lacks the capacity to consent to the research project (study will not utilize LAR signatures during the informed consent process)
- Weigh < 100 pounds
- BMI > 38
- Pregnancy or suspected pregnancy
- Past medical history of opioid addiction.
- Established hypersensitivity (ie allergy) to morphine.
- Acute or chronic liver disease for example cirrhosis.
- Use of any narcotics 5 days before surgery (opioids, hydrocodone, morphine, hydromorphone, fentanyl, etc).
- Undergoing bilateral total knee replacement, revision total knee arthroplasty, or any additional procedure outside of a primary total knee arthroplasty.
- Unable to get general and spinal anesthesia.
- Same-day discharge on day of surgery.

We will access the following data from medical records (Epic) including PHI:

- MRN, date of surgery, age, gender, past medical history, height, weight, BMI, laterality, pre-operative ROM, pre-operative pain VAS, intra-operative tourniquet pressure, procedure duration, and medications received during hospital stay.

Post-operatively we will ask study patients in both groups to complete a post-op symptom journal that will collect the following information in the interim before the patient's standard 2 week post op appointment with Dr. Incavo, Dr. Park, or Dr. Clyburn:

- Record daily pain levels using a validated pain scale for 14 days post op.
- Record daily pain medication use for days 14 post-op.
- Record daily nausea levels using a validated scale as well as recording bowel movements and any instances of emesis for 7 days post op.

Additionally, the tourniquet pressure intra-op will be standardized to 275 mmHg across all 3 providers on the research team (Drs. Park, Clyburn, and Incavo). This falls within the normal standard of care for all 3 providers for their total knee arthroplasty patients. However, it has been shown in the literature that tourniquet pressure can influence acute post-operative muscle quality including increased pro-inflammatory cytokines.[12-13] Therefore, to limit outside factors on post-operative inflammatory marker levels as well as post-operative rehabilitative outcomes the research team will use the same tourniquet pressure for all study patients. This does not reflect an elevation in risk for study patients since 275 mmHg falls within range of standard of care for total knee arthroplasty patients for all 3 providers.

Baseline and Post-op Blood Samples:

Systemic sample – Blood draws will only be done with Dr. Stephen Incavo's patients that decide to participate in the study if they are the first or second case of the day. Three blood draws will be taken in these patients including just after induction of anesthesia, 15 minutes after the tourniquet is released, and 10 hours post op. The 10hr post-op blood draw timing will be based on the timing of the intraosseous injection. Serum samples will be used to measure inflammatory cytokines IL-6 and IL-8, and expression of CD11a, CD11b, CD11c, and CD18 as well as the systemic level of morphine present in the blood. Only these specific study patients will be having blood draws done due to the 10 hr post-op draw needing to be processed within 30 minutes of the draw. Blood samples will be collected in EDTA glass tubes by Houston Methodist nursing staff or a qualified member of the research team (eg. physician, fellow, or resident). Up to 10 ml of blood will be collected per time point.

For our primary outcome variable of VAS recorded pain, power analysis was performed using JMP statistics software utilizing data extracted from prior work done on the average VAS-Pain scores for TKA patients. [11]

The statistical model for this investigation to be utilized in this investigation is a 2(Treatment) x 2(Time-point) mixed model analysis of covariance with repeated measures, co-varied on pre-operative VAS scores recorded on the day of surgery. Although there will be several days of VAS recorded out to 14-days post-surgery, the statistical question for pairwise comparisons will be to determine (1) how pain recorded on each subsequent day compares back to initial baseline (pre-operative) values within each group (treatment vs control) and (2) how each group compares to each other at the same measurement time-point. Therefore, each subsequent day will be modeled separately against the baseline value.

From the reference cited above, the 3-day average VAS score immediately following TKA was 3.2 cm (standard deviation, 2.0cm). The minimum detectable change (MDC) to detect will be set at 1.6cm as described in the literature. [11]

The primary hypotheses of the study is that the treatment group will experience a reduction in post-operative pain compared to the control group. Based on the previous literature listed above, for a power analysis of 2 groups across 2 time-points, to detect a MDC of 1.6cm at a statistical

power of 0.9 (α=0.05), we will require a total of 35 patients per group (total of 140 observations). To account for a potential patient dropout rate of ~20%, we will aim to recruit 42 patients per group for a total of 84 patients.

The aforementioned statistical analysis will be performed at the end of each year to evaluate the efficacy of the intervention and to identify potential outliers in the data or any possible errors in data entry. Yearly analysis using the same statistical modeling will also be performed for our secondary outcome measures (tissue biomarkers) in order to prevent potential tissue sample and biochemical reagent degradation over time and to confirm the accuracy of the tissue analysis procedure performed.

Additionally, the study will stop recruiting if adverse effects is significantly different between the two treatment groups, or greater than the previously specified risks listed within the informed consent and protocol or if a new unanticipated adverse effect is discovered. Recruitment will be suspended if there are 5 similar adverse events in a row. The most serious risks include respiratory depression, apnea, circulatory depression, respiratory arrest, shock, and cardiac arrest. These risks are <1% of the population. More frequent adverse effects include sedation, lightheadedness, dizziness, nausea, vomiting, and constipation. Patients will be monitored for these side effects in the immediate post-operative period.

Study Intervention

This study is evaluating whether a 10mg intraosseous injection of morphine will help reduce inflammatory markers following surgery as well as reduce pain and pain medication use in patients undergoing primary total knee arthroplasty when compared with patients receiving the current standard of care for primary total knee arthroplasty. In the post-operative period study patients will have their post-operative opioid consumptions monitored while in the hospital and for 14 days following their surgery. Study patients will not be allowed Ketorolac or Celecoxib (Toradol), both non-steroidal anti-inflammatorys (NSAIDs), in the PACU / post-operative period following their total knee replacement. This is being done because the research team wishes to standardize the post-operative care protocols across all 3 providers participating in the study since not all prescribe NSAIDs in the post-operative period following TKA. Additionally, there is no method for NSAIDs like Ketorolac or Celecoxib to be converted into morphine equivalence scores and thus would prevent accurate quantification of pain relief provided in the post-operative period.

Should the patient suffer any side-effects from the IO morphine injection they will have all of the necessary care provided to them. This study will require the patient to consent to a number of study-related items including that do not fall under their usual standard of care:

- Filling out study surveys (PROMIS Global Health SF v1.1 and KOOS JR) at pre-op, 2 weeks post op, 8 weeks post op, and 1 year post-op. The surveys will be sent through RedCap.
- Blood draws to measure systemic levels of inflammatory cytokines right after induction of anesthesia, 15 minutes post tourniquet release, and 10 hours post op. This sample will be collected by a qualified Houston Methodist nurse or qualified member of the research team (ie physician/fellow/resident).

- Filling out a symptom journal for 2 weeks post op that will record pain, pain medication use, nausea (including emesis), and bowel movements.
- Lastly, patient range of motion will be recorded from their physical therapist' progress notes and at 2 week post-operative follow-up appointment.

This study will note require the patient to attend any additional study visits. The expected amount of time the patient for the patient to complete all study related items including filling out the symptom journal and answered pre/post-op surveys is approximately 90 minutes. The patient will participate in the study for a total of 52 weeks. The anticipated duration to enroll all study subjects is 18 months. The estimated date for the investigators to complete primary analyses is 2.5 years following the initiation of the study.

4. Drugs, Biologics, Devices

Morphine is approved by the FDA and it will be administered intraosseously. This method of administration has been shown to provide a similar pharmoco-kinetic profile when compared to IV morphine.[9] Intraosseous morphine injection in primary total knee arthroplasty is not considered standard of care as it is not known if it helps with post-operative pain.

The most serious side effects of morphine include respiratory depression, apnea, circulatory depression, respiratory arrest, shock, and cardiac arrest. More common adverse effects include sedation, lightheadedness, dizziness, nausea, vomiting, and constipation. Patients will be monitored in the post-operative period for these side effects prior to discharge.

5. Data Privacy / Confidentiality

Houston Methodist policies for handling Protected Health Information will be followed including all requirements for physical and electronic data security, use of encrypted devices, and utilizing HM password protected servers. All data for this study will be complete, accurate, original, and legible. All physical study related data such as the symptom journal will be stored in a locked office cabinet of a qualified member of the research team. All electronic data such as the surveys sent from Houston Methodist's RedCap system (KOOS JR & PROMIS Global Health) will be password protected and only accessible by members of the research team. The data for this study will be maintained indefinitely. Any data that is published as a result of this study will be completely de-identified including the removal of any PHI.

The only PHI being used by the research team for this study are dates including discharge dates and birth date (to determine age at time of surgery) as well as MRNs. The use of identifiable data is necessary for the research team to confirm past medical history of morphine allergy, acute or chronic liver disease, or opioid addiction to ensure only qualified patients are recruited into the study. No PHI will ever be disclosed beyond Houston Methodist. This data will be stored along with other data recorded from Epic on password protected servers accessible only to qualified members of the research team.

Identifier (or parts of)	Recorded	Disclosed	Comment
Names	Yes	No	Recorded prior to any recruitment method (phone or email). Needed so that qualified members of the research team can properly address the patient over phone or email to inform them about the study.
All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and elements of dates (including year) indicative of such age	Yes	No	Recording birth date to determine age at time of surgery. Recording surgery date as well as the discharge date.
Phone numbers; Fax numbers	Yes	No	For recruitment purposes. However the informed consent for this study will only take place in person with a qualified member of the research team. Also needed to remind a patient to bring their symptom journal to their standard 2 week post op appointment with Dr. Incavo, Dr. Park, or Dr. Clyburn..
Email address	Yes	No	Needed to email Houston Methodist RedCap surveys to study patients or remind a study patient to bring their symptom journal to their standard 2 week post op appointment with Dr. Incavo, Dr. Park, or Dr. Clyburn.
Medical record numbers	Yes	No	Necessary to confirm past medical history.

6. Study Population

see pages 3-4 section 3 of this protocol.

Patients will be approached if they are undergoing TKA at Houston Methodist Hospital. Study coordinator, Thomas Sullivan, or other qualified member of the research team (qualified to give informed consent) will determine if patients are eligible, and then consent the patient during their pre-operative visit.

7. Screening and Recruitment [S R]

The research team requests a waiver of authorization for preparatory for research. It would not be practical to conduct this research study without preliminary screening of potential study patients. Without the waiver the research team would have to request fan authorization to view PHI from every patient of Dr. Incavo, Dr. Park, and Dr. Clyburn to determine if they could be a possible candidate for the research study. There is no risk related to this waiver of authorization. Data safety practices of all PHI have been described in the section 6 on page 6 of this protocol.

Potential study patients will be identified by the research team prior to their surgery date by looking at Dr. Incavo's, Dr. Park's, and Dr. Clyburn's surgery schedule searching for primary total knee arthroplasty surgeries. The potential study patient's medical records will then be viewed in Epic to identify and confirm inclusion and exclusion criteria including morphine allergy, pregnancy status, past medical history, type of surgery, weight, and BMI. If the patient meets the initial criteria to participate in the study then a qualified member of the research team will email or call the patient to inform them about the study and determine if they are interested in possibly participating. Alternatively, the recruitment process may also take place at in clinic (6445 Main Street Houston, Texas 77030 or at the Houston Methodist Pin Oak 5505 West Loop South Houston, TX 77081) after the patient's visit with Dr. Incavo, Dr. Park, or Dr. Clyburn. In either scenario, meaning phone/email/or in person recruitment, potential study patients will be screened for inclusion and exclusion criteria prior to the informed consent. The informed consent will take place in person with a qualified member of the research team where the patient will be informed about all aspects of the research study to determine if they wish to participate. The screening document as well as the email/telephone call recruitment templates will be included in the IRB application.

Sensitive information such as history of morphine addiction will be asked during the screening process. Should a patient admit to that history and consequently be excluded from the study the screening document will immediately be disposed of in a HIPAA bin to later be shredded. Any data from that patient prior to inclusion in the study will be deleted except for their name and "EXCLUDED FROM PARTICIPATION" in the dataset. It is important to note that screening data will not be collected from email and will only be done either in person or over the phone.

8. Withdrawal of Subjects

Patients may be withdrawn from the study if it is discovered that they have any of the exclusion criteria that was not previously identified during the recruitment and screening process. If this is the case the patient will be informed of their removal from the study and the reason why they were removed from the study.

If a study patient has an allergic/negative reaction to the IO morphine injection that the event will be reported immediately to the IRB and the patient will be removed from the study.

9. Provisions to Protect the Privacy Interests of Subjects

If a patient has indicated on their electronic medical record in Epic that they do not want to participate in research or share any of their personal information that request will be honored and they will not be included in this research study.

10. Risks to Subjects

Risk to Morphine:
Most serious risks include respiratory depression, apnea, circulatory depression, respiratory arrest, shock, and cardiac arrest. These risks are <1% of the population. More frequent adverse effects include sedation, lightheadedness, dizziness, nausea, vomiting, and constipation. Patients will be monitored for these side effects in the immediate post-operative period.

Possible loss of confidentiality is a risk.

No additional risk is associated for collection of samples. During TKA in current standard of care, the tibia is reamed to place the prosthetic. The bone marrow that is removed during this step will be collected instead of thrown away. In addition, cuts made to the tibia and femur to appropriately fit the prosthetic result in bone being thrown away. This bone will instead be collected for research purposes.

All PHI except MRN will be taken off any record associated with the subjects' tissue before it is studied. A code number will be assigned to the tissue. No information will be released that will let others know who the subjects are. The data will be kept on a secure password protected, hospital server and will be deleted after the study is complete.

11. Potential Benefits

Study patients in the IO morphine group of this research study may experience less pain, consume less pain medication, and achieve a greater range of motion following their primary total knee arthroplasty when compared to patients receiving the standard of care.

12. Financial and Economic Issues

There will be no monetary cost to the subject to participate in this research study. Any research related cost, including the IO morphine injection, will be covered by the research study. The patient/the patient's insurance will be responsible for all costs associated with their surgery and

subsequent rehabilitation following surgery. Additionally, there will be no compensation provided to the study patient for participating in this study.

13. Data Safety Plan

The study will be monitored by clinicians involved in the study. Interim analysis will be performed yearly.

14. Informed Consent Documentation and Process

Required for all protocol types including Sponsored trials. Provide local information.

The initial identification and screening process are described on pages 7-8 section 8 of this protocol. Following screening, patients will meet with a qualified member of the research team to explain all aspects of the study and answer any questions that the patient may have. Then, should the patient agree to participate in the study, both the patient and the member of the research team will sign the informed consent. The patient will be encouraged to take a copy of the informed consent for their records should they have any additional questions at a later time.

15. Waiver of Informed Consent and /or Authorization

There will be no waiver of informed consent for this study. The research team requested a waiver for “Preparatory for research” in “section 8 on pages 7-8” of this protocol.

16. References

1. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anaesth.* 2001;48(10):1000-1010.

2. Lombardi AV, Jr., Berend KR, Mallory TH, Dodds KL, Adams JB. Soft tissue and intra-articular injection of bupivacaine, epinephrine, and morphine has a beneficial effect after total knee arthroplasty. *Clin Orthop Relat Res.* 2004(428):125-130.

3. Badner NH, Bourne RB, Rorabeck CH, MacDonald SJ, Doyle JA. Intra-articular injection of bupivacaine in knee-replacement operations. Results of use for analgesia and for preemptive blockade. *J Bone Joint Surg Am.* 1996;78(5):734-738.

4. Badner NH, Bourne RB, Rorabeck CH, Doyle JA. Addition of morphine to intra-articular bupivacaine does not improve analgesia following knee joint replacement. *Reg Anesth.* 1997;22(4):347-350.

5. Mauerhan DR, Campbell M, Miller JS, Mokris JG, Gregory A, Kiebzak GM. Intra-articular morphine and/or bupivacaine in the management of pain after total knee arthroplasty. *J Arthroplasty.* 1997;12(5):546-552.

6. Ritter MA, Koehler M, Keating EM, Faris PM, Meding JB. Intra-articular morphine and/or bupivacaine after total knee replacement. *J Bone Joint Surg Br.* 1999;81(2):301-303.

7. Klasen JA, Opitz SA, Melzer C, Thiel A, Hempelmann G. Intraarticular, epidural, and intravenous analgesia after total knee arthroplasty. *Acta Anaesthesiol Scand.* 1999;43(10):1021-1026.

8. Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS. The effects of morphine and fentanyl on the inflammatory response to cardiopulmonary bypass in patients undergoing elective coronary artery bypass graft surgery. *Anesth Analg.* 2007;104(6):1334-1342, table of contents.

9. Von Hoff DD, Kuhn Pharm JG, Burris HA, Miller LJ. Does intraosseous equal intravenous? A pharmacokinetic study. Am J Emerg Med. 2008;26(1):31–8. doi: 10.1016/j.ajem.2007.03.024.

10. Lakra, Akshay, et al. 2019. "Early Postoperative Pain Predicts 2-Year Functional Outcomes Following Knee Arthroplasty." *The journal of knee surgery* (2019).

11. How much pain is significant? Defining the minimal clinically important difference for the visual analog scale for pain after total joint arthroplasty." *The Journal of arthroplasty* 33.7 (2018): S71-S75.

12. Mayer C, Franz A, Harmsen JF, et al. Soft-tissue damage during total knee arthroplasty: Focus on tourniquet-induced metabolic and ionic muscle impairment. *J Orthop*. 2017;14(3):347–353. Published 2017 Jun 24. doi:10.1016/j.jor.2017.06.015

13. Zhang W, Li N, Chen S, Tan Y, Al-Aidaros M, Chen L. The effects of a tourniquet used in total knee arthroplasty: a meta-analysis. *J Orthop Surg Res*. 2014;9(1):13. Published 2014 Mar 6. doi:10.1186/1749-799X-9-13