



Effects of Perioperative Dronabinol Use in Total Knee Arthroplasty

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PROTOCOL SYNOPSIS

Protocol Title:	Effects of Perioperative Dronabinol Use in Total Knee Arthroplasty
Protocol Number:	2019-1416
Protocol Date:	6/6/2023
Sponsor:	Department of Anesthesiology
Principal Investigator:	Kethy Jules-Elysee, MD
Objective:	The current study will investigate the potential therapeutic benefit of perioperative dronabinol use in patients undergoing unilateral total knee arthroplasty (TKA). With current advanced regional anesthetic techniques and peripheral nerve blocks, pain is generally well controlled following TKA on post operative day (POD) 1. There is a rebound pain that exists, however, on POD2 when these blocks are no longer effective. We aim to study a potential reduction in opioid consumption on POD2 with perioperative dronabinol use in TKA patients.
Study Design:	Randomized Control Clinical Trail
Enrollment:	114
Subject Criteria:	<ol style="list-style-type: none"> 1) Patients aged between 18-70 years old with osteoarthritis scheduled for primary unilateral knee arthroplasty with a participating surgeon. 2) Planned use of regional anesthetic technique during surgery involving infiltration between the popliteal artery and the capsule of the posterior knee (IPACK), adductor canal block (ACB), and PAI 3) Ability to follow study protocol.
Data Collection:	<p>Sources: EPIC, Medical Records, and Patient Reported.</p> <p>Variables: Name, Email, MRN, DOB, Age, Height, Weight, Race, Ethnicity, Gender, BMI, ASA, Co-morbidities, Allergies, Surgeon/Anesthesiologist, Anesthesia events, PONV, Opioid use, Non-opioid analgesic consumption, side effects/adverse events, Patient Satisfaction, length of PACU stay, length of hospital stay, pulse-oximetry data, sleep actigraph data, painOUT questionnaire, DN4 questionnaire, ORSDS, Blinding Assessment, NRS pain scores (on ambulation & at rest)</p>
Statistical Analysis:	<ul style="list-style-type: none"> • Two-sample test • Alpha level: 0.05 (one-sided) • Beta or power level: 80% • Primary outcome: opioid consumption 24-48 hours after anesthesia stop

	<ul style="list-style-type: none"> • Number of groups being compared: 2 • Effect size or change expected between groups: 30% reduction in opioid consumption 24-48 hours after anesthesia stop • Resulting number per group: 50 • Total sample size required: 50 + ~10% to account for attrition = 55, total sample size is 110 with 4 additional patients added to account for unexpected attrition
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1.0 INTRODUCTION

With current emphasis on multimodal analgesia and limiting opioid consumption, the utility of cannabinoids as medications in treatment of acute pain have been relatively unexplored. In addition, the widespread legalization of medical cannabis in several states has led to use of cannabinoids as adjuvants and opioid substitutes for managing pain. While the use of medical cannabis and cannabinoids is supported by strong evidence for the management of chronic pain (1), the literature for use in the acute pain population has been mixed, with limited randomized control trials. A systematic review of European literature by Stevens et al stated that on the basis of seven included RCTs, cannabinoids have no role in the management of acute pain (2). However, the RCTs included had either small sample size, low generalizability, or are outdated, with the most recent study from 2013. Only two studies included in this review used oral medications, though lacked in standardized surgical population, postoperative analgesia, and study power with very small sample size (3, 4). Other meta-analyses have displayed strong animal model, pre-clinical evidence of the cannabinoids and reduced opioid consumption (5). Additionally, literature has shown promise in the lack of addictive and abuse potential in therapeutic use of dronabinol (6). However, clinical studies included in this review were of low- quality evidence and heterogeneous in nature, with mixed surgical populations and varied anesthetic techniques. A recent study by Hickernell et al demonstrated reduced opioid consumption in postoperative TKA and total hip arthroplasty patients receiving dronabinol. These data are promising for the role of cannabinoids in the acute pain population. However, as a retrospective cohort study it lacked randomization and consisted of a varied patient population for both surgical procedure and anesthetic technique. In addition, the reduction in opioid consumption was a consequence of shorter hospital length of stay, with no difference in patient opioid consumption per day (7).

Prior studies by this research team have demonstrated improvements in pain scores, opioid consumption, and patient satisfaction with novel peripheral nerve block techniques (8). With these recent advances in regional anesthesiology at HSS, pain is well controlled in the first 24 hours post operatively. However, these data also revealed that 24-48 hours after block placement, a rebound pain existed as patients in the treatment group had notably increased pain scores and opioid consumption on POD2. There is a need to investigate novel, non-opioid medications to help manage rebound pain, decrease opioid use and increase patient satisfaction. Additionally, there is growing risk of chronic post surgical pain (CPSP) in total knee arthroplasty patients. Recent data has demonstrated a much greater risk of CPSP development in TKA patients than previously reported, and acute post surgical pain has been identified as an independent risk factor for CPSP (15, 16). Aside from improvement in post surgical rebound pain, there is a need to mitigate the acute post surgical pain experience in order to hinder development of CPSP in TKA patients. Patients have expressed willingness to use cannabinoids as a novel therapeutic modality to manage their pain post operatively (9). In addition to potential therapeutic benefit in acute pain, dronabinol is a promising pharmacologic intervention in obstructive sleep apnea treatment. A recent phase II RCT demonstrated reduction in apnea-hypopnea index in OSA patients in the dronabinol treatment group (10). Prior literature has also suggested benefit of dronabinol as an apnea suppressant and respiratory stabilizer in animal models, via stimulation of central cannabinoid receptors (11, 12). Improvements in the qualitative EEG sleep patterns have also been shown following dronabinol therapy in human models (13). The current research team has shown that in the TKA patient, STOP-Bang scores were unrelated to oxygen desaturation episodes post operatively. Additionally, postoperative desaturations were correlated with

longer hospital length of stay in these patients. This increase may have been due to an increased opioid consumption that was demonstrated by these patients on POD1 and POD2 (14). If therapeutic dronabinol can limit opioid consumption, it may attenuate the POD1-POD2 increase in oxygen desaturation events. Therefore, in this study we chose to examine the efficacy of dronabinol, a readily available FDA-approved cannabinoid, in reducing opioid consumption in TKA patients on POD2, when rebound pain is experienced in many patients. The current study can generate new evidence as a randomized control trial, with potential benefit in decreased opioid consumption, pain on POD2, hospital length of stay, as well as improvements in oxygen desaturation episodes.

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2.0 OBJECTIVE(S) OF CLINICAL STUDY

With current regional anesthetic nerve block techniques, post-operative pain is well controlled following TKA on Postoperative Day (POD) 1. However, on POD2 there is typically a rebound pain that exists, especially with patient activity and ambulation. The current study will examine the potential opioid-sparing effect of perioperative dronabinol use in total knee arthroplasty patients on POD2.

Research questions/specific aims:

- a) Does perioperative dronabinol use (starting in the immediate preoperative period (enrollment before 1 PM) , with BID dosing concluding the evening of POD2) affect postoperative opioid consumption 24-48 hours following total knee arthroplasty?
- b) Is there an effect of perioperative dronabinol use in the total knee arthroplasty patient on POD2 pain scores with ambulation?
- c) Will hospital length of stay following total knee arthroplasty be affected in patients who use perioperative dronabinol as compared to control?
- d) Does the use of perioperative dronabinol affect time to reach physical therapy discharge goals in postoperative total knee arthroplasty patients?
- e) Is there a change in number of postoperative oxygen desaturation events in patients following total knee arthroplasty based on perioperative dronabinol use?

3.0 STUDY HYPOTHESES

We hypothesize that patients in the perioperative dronabinol treatment group will have decreased opioid consumption 24-48 hours postoperatively, as well as reductions in all secondary outcomes.

4.0 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Endpoint

Primary Outcome: The primary outcome of the study will be patient opioid consumption 24-48 hours post operatively, defined by total morphine equivalents (MEs). This outcome will be measured throughout the patient hospitalization and conclude at 48 hours postoperatively.

4.1.2 Secondary Endpoints

1. Time to reach discharge physical therapy goals, as defined by the number of hours required to meet the following criteria: stable vital signs during PT, safe independent transfer from bed to standing as well as transfer in and out of seated position, ability to walk 40 feet only with aid of crutch or walker. This outcome will be measured prior to patient discharge.
2. Patient pain with ambulation on POD2, defined by patient reported Numeric Rating Scale (NRS) pain score. Measurements will take place following ambulation on morning of POD1, 2, 7, 90, 180.
3. Patient pain at rest upon PACU arrival, and in the morning of POD1, POD2, and POD7. Measurements will also be taken at POD90 and 180
4. Patient Pain with ambulation during morning PT session on POD1, and POD2
5. Patient opioid consumption at PACU, on POD1, POD2.
6. Hospital length of stay from day of admission to discharge. This outcome will be measured on the day of patient discharge from the hospital.
7. The number of desaturation events. Postoperative oxygen desaturation events will be defined as measured SpO2 of <88% for 20 seconds or longer. This outcome will be measured beginning in the immediate postoperative period on POD0 (in the PACU) and will continue until patient discharge.
8. Cognitive assessment at PACU, on POD1, POD2
9. painOUT score on POD1 and POD2, POD7, POD90, and POD180
10. DN4 questionnaire score on POD1, POD2, POD7, POD90, and POD180
11. ORSDS on POD1 and POD2.
12. Non opioid analgesic consumption (from PACU to POD7). This outcome will be measured on PACU, POD1, POD2, and POD7.
13. NRS Pain and opioid use, POD 90. (Pain at POD 90, or 3 months, is viewed as the onset of chronic pain)

14. Sleep disturbance via actigraphy measurement using the ActiGraph wGT3X-BT activity monitor. Measured as total sleep time, wake after sleep onset, sleep efficiency, number of awakenings from PACU to discharge.

4.2 Study Sites

This study will take place at the main campus of the Hospital for Special Surgery (HSS).

5.0 STUDY POPULATION

5.1 Number of Subjects

114

5.2 Inclusion Criteria

Subjects will be included if:

- Patients ≥ 18 years old with osteoarthritis scheduled for primary unilateral knee arthroplasty with a participating surgeon
- Planned use of regional anesthetic technique during surgery involving infiltration between the popliteal artery and the capsule of the posterior knee (IPACK), adductor canal block (ACB), and PAI
- Ability to follow study protocol

5.3 Exclusion Criteria

Subjects will be excluded from the study if:

- Contraindication to regional or neuraxial anesthetic
- Intended use of general anesthesia
- Intolerance, contraindication, or allergy to any of the study medications or excipients (e.g., sesame oil)
- Patients < 18 or > 70 years of age
- Chronic opioid use (for > 3 months prior to surgery)
- Cannabis/cannabinoid use within the last 3 months
- American Society of Anesthesiology class IV or greater
- Active or history of major mental illness (as defined by the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5). e.g., major depressive disorder, anxiety, bipolar disorder, schizophrenia)
- History of seizures
- Use of antidepressants
- Use of anticonvulsants
- Non-English speakers
- BMI ≥ 40
- Sleep Apnea

6.0 PROCEDURES

6.1 Intraoperative Protocol

Preoperative Holding Area: Study group patients will receive the first dose of dronabinol (5 mg), and control group will receive first non-active placebo dose. Enrollment in the study will

begin no later than 1 PM, ensuring that patients will receive intervention before 1 PM preoperatively and the second BID dose at 10 PM on POD0. BID dosing will continue through the morning of POD2.

Intraoperative: Both groups in the study will receive IV sedation intraoperatively with IV midazolam (2-5 mg) bolus, as well as propofol infusion titrated to patient sedation without respiratory depression and stable hemodynamics. Anti-emetics of ondansetron 4 mg IV and dexamethasone 10 mg IV will be administered, along with 20 mg IV famotidine for GI prophylaxis. Ketorolac (15mg-30 mg) will be dosed intraoperatively, though held if patient baseline creatinine ≥ 2 . Intraoperative ketamine (20mg-50mg) will also be administered by the treating anesthesiologist, with dosage based on clinical judgment.

All patients will receive a neuraxial anesthetic with 60 mg of 1.5% Mepivacaine dosed in the spinal.

All patients will receive both adductor canal and IPACK peripheral nerve blocks. Adductor canal blocks will be performed with 15 mL of 0.25% bupivacaine mixed with 2 mg of preservative free dexamethasone, and IPACK blocks will be performed with 25 mL of 0.25% bupivacaine.

"All patients will receive both a deep and superficial component of periarticular injection (PAI). The deep injections will consist of Cefazolin 500mg per 10 ml with Sodium Chloride 0.9% 22 ml, Bupivacaine-Epinephrine PF (marcaine w/EPI) 150mg, methylprednisolone acetate (DEPO-MEDROL) 40mg. The superficial injection will consist of bupivacaine 0.5% 20 mL with Sodium Chloride 0.9% 20 mL. If there are contradictions to DEPO-MEDROL, patients may receive deep injections that do not contain DEPO-MEDROL."

Post-anesthesia Care Unit:

Patients will receive a pain regimen consisting of:

- Acetaminophen- intravenous, for 15 Minutes, every 6 hours for 1 Doses, For 1 Dose, followed by PO q6
- Ketorolac 15-30 mg IV q6 x4 doses, dosed appropriately
- Oxycodone immediate release 5 mg PO q4 PRN for NRS pain score 0-6
- Oxycodone immediate release 10 mg PO q4 PRN for NRS pain score 7-10
- Hydromorphone 0.5 mg, IV Push, every 5 min PRN Starting S For 2 Doses, Breakthrough Pain, in PACU, Starting S, For 2 Doses, PACU (only)
- IV opioid dosing Patient controlled Analgesia for salvage therapy (NRS>6 for >2 hours)

Floor Care:

- Continue acetaminophen
- Meloxicam 7.5-15mg PO daily to start after ketorolac dosing is completed
- Oxycodone immediate release 5 mg PO q4 PRN for NRS pain score 0-6
- Oxycodone immediate release 10 mg PO q4 PRN for NRS pain score 7-10

6.2 Data Collection

The following data will be collected:

Pre-operative/Baseline

- Name
- Email
- MRN
- DOB
- Age
- Height
- Weight
- Race
- Ethnicity
- BMI
- ASA
- Co-morbidities
- Allergies

Surgical procedure (Intra-operative)

- Surgeon/Anesthesiologist
- Surgery/Anesthesia events

Post-Operative Day 0 (POD 0)

- NRS Pain Scores (on ambulation & at rest)
- Opioid consumption
- Non-opioid analgesic consumption
- Cognitive assessment/subjective drug effects/adverse events
- Continuous O2 saturation (Masimo)
- Sleep actigraphy

Post-Operative Day 1 (POD 1)

- NRS Pain Scores (on ambulation & at rest)
- Opioid consumption
- Non-opioid analgesic consumption
- Cognitive assessment/subjective drug effects/adverse events
- Continuous O2 saturation (Masimo)
- Sleep actigraphy
- painOUT questionnaire
- DN4 questionnaire
- ORSDS

Post-Operative Day 2 (POD 2)

- NRS Pain Scores (on ambulation & at rest)
- Opioid consumption
- Non-opioid analgesic consumption
- Cognitive assessment/subjective drug effects/adverse events
- Continuous O2 saturation (Masimo)
- Sleep actigraphy
- painOUT questionnaire
- DN4 questionnaire
- ORSDS

Discharge

- Blinding assessment

Post-Operative Day 7 (POD 7)

- Blinding assessment
- NRS pain scores (on ambulation & at rest)
- Opioid consumption
- Non opioid analgesic consumption
- painOUT questionnaire
- DN4 questionnaire

Post-Operative Day 90 (POD 90)

- NRS pain scores (on ambulation & at rest)
- Opioid consumption
- painOUT questionnaire
- DN4 questionnaire

Post-Operative Day 180 (POD 180)

- NRS pain scores (on ambulation & at rest)
- painOUT questionnaire
- DN4 questionnaire

7.0 STATISTICAL ANALYSIS

1. **Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):** two-sample t-test
2. **Interim analysis planned?** No.
3. **Alpha level:** 0.05
4. **Beta or power level:** 80%
5. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):** Opioid consumption 24–48 h after anesthesia stop, Control group= 65.7 ± 40 , Treatment group= 45.99 ± 28 (Kim 2018)
6. **Number of groups being compared (use 1 for paired analysis within the same subjects):** 2
7. **Effect size or change expected between groups:** 30% reduction in Opioid consumption 24–48 h after anesthesia stop
8. **Resulting number per group:** 50
9. **Total sample size required:** $50 + \sim 10\%$ to account for attrition = 55, total sample size 110 with 4 additional patients added to account for unexpected attrition

The primary outcome (Opioid consumption 24–48 hours after anesthesia stop) will be compared between the groups using a two-sample t-test or Wilcoxon rank-sum test, depending upon the distribution of the data.

Secondary outcomes (listed above, Section II Q11.) measured once per patient will be analyzed by t-test or Wilcoxon rank-sum test (continuous data) and χ^2 or Fisher's exact test (categorical data). Outcomes measured multiple times per patient (e.g., NRS Pain Scores, Cognitive assessment/Subjective drug effects/Adverse events, Continuous O2 saturation monitoring, painOUT, ORSDS, Opioid Consumption) will be analyzed using regression based on a generalized estimating equation approach.

Balance on demographics and baseline characteristics will be assessed by calculating standardized differences (difference in means or proportions divided by the pooled standard deviation) between groups. An absolute value of 0.2 or greater will be interpreted as more imbalance than would be expected by chance (Austin 2009).

All analyses will be performed on an intention-to-treat basis.

For pulse-oximetry data, we will use Masimo Trace™ software to collect and visualize data:
<http://www.masimo.com/products/analytics/trace/>

For actigraphy data, activity monitors will be collected on the day of discharge. Raw actigraphy data will be extracted and analyzed using CenterPoint Study Admin System software.

8.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report.