Effects of cannabidiol (CBD) oral solution in patients undergoing bilateral total knee arthroplasty: a randomized, controlled, parallel, triple blind, pilot study

FUNDER: Department of Anesthesiology

PROTOCOL NO.: 2019-1688

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PROTOCOL SYNOPSIS

Protocol Title:	Effects of cannabidiol (CBD) oral solution in patients undergoing bilateral total knee arthroplasty: a randomized, controlled, parallel, triple blind, pilot study
Protocol Number:	2019-1688
Protocol Date:	12/5/2025
Sponsor:	Department of Anesthesiology
Principal Investigator:	Alexandra Sideris, PhD
Products:	Epidiolex
Objective:	A pilot study to investigate whether cannabidiol (CBD) oral solution (Epidiolex®) is associated with minimal opioid use and adequate analgesia in patients undergoing bilateral total knee arthroplasty (BTKA)
Study Design:	Randomized Controlled Clinical Trial
Enrollment:	37
Subject Criteria:	Inclusion criteria: • age 18 to 75 years of age • Patients scheduled for same-day bilateral total knee replacements with participating surgeons • American Society of Anesthesiologists (ASA) Physical Status 1 or 2 Exclusion criteria: • ASA 3 and higher • Weight less than 40kg • Planned use of general anesthesia • Contraindication to major components of study protocol • Cannabis or cannabinoid use within the past 3 months (recreational and/or medical) • Use or ingestion of hemp seeds or hemp oil in any form within the past 30 days • Chronic opioid use (>3 months) • Coumadin use • Current use of SSRIs or SNRIs • History of substance abuse or dependence • Active or history of major psychiatric illness • Severe cardiovascular disorder • Severe hepatic or renal insufficiency (transaminase levels above ULN)

	• History of epilepsy • Diagnosis of rheumatic disease, autoimmune disease, or immunodeficiency (e.g. rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, multiple sclerosis, etc.) • Use of valproate or clobazam • Known or suspected hypersensitivity, allergy, or contraindication to cannabinoids or any of the excipients in the study medications (i.e. sesame oil, sucralose, strawberry flavor) • Active use of steroids - oral steroids upon admission • Stress dose steroids • Non-English speakers • Planned discharge to home without caregiver(s)
Study Duration:	• November 2022 – January 2025
Data Collection:	**Sources**: Medical Record (Epic), Patient Report, ActiGraph, Patient blood **Variable**: Name, MRN, DOB, Date of Surgery, Race, Ethnicity, Gender, Height, Weight, BMI, pre-op pain medication use, co-morbidities, allergies, phone number, ASA, procedure/surgery details, anesthesia details, tourniquet time & pressure, NRS pain scores at rest/with movement, Brief Pain Inventory – short form, Hospital Anxiety and Depression Scale, Leeds Sleep Evaluation Questionnaire, Opioid-Related Symptom Distress Scale, opioid and non-opioid analgesic use, Bang Blinding Index assessment, side effects/adverse events, ActiGraph data, PT milestones, Range of Motion, Length of Stay, Interleukin-6 levels, cannabidiol and metabolite levels
Statistical Analysis:	1. **Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):** Descriptive statistics will be presented for each group. Dunnett's test (2 pairwise comparisons, one between each of the 2 CBD dosing groups and control) will be used for any comparisons. 2. **Interim analysis planned?** No. 3. **Alpha level:** --- 4. **Beta or power level:** --- 5. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):** --- 6. **Number of groups being compared (use 1 for paired analysis within the same subjects): 3** 7. **Effect size or change expected between groups:** --- 8. **Resulting number per group:** 12

	9. **Total sample size required: (**N=12 placebo (Ora-Sweet SF); N=12 400mg Epidiolex; N=12 800mg Epidiolex)

1.0 INTRODUCTION

Cannabidiol (CBD) is a non-intoxicating phytocannabinoid that has therapeutic potential for several indications, including pain[1]. Studies using animal models of acute and chronic pain demonstrate that CBD relieves hyperalgesia and edema associated with inflammation,[2-5] and reduces allodynia and anxiety associated with nerve injury.[6,7] CBD has a complex pharmacological profile, distinct from delta-9-tetrahydrocannabinol (THC). CBD has a low affinity for the cannabinoid 1 and 2 receptors, which likely explains why this cannabinoid does not produce a "high." CBD activates serotonin (5-HT1a), glycine (a1, a3), and vanilloid receptors, and inhibits the activity of fatty acid amide hydrolase (FAAH) and the novel cannabinoid receptor, GPR55.[1] These targets are important because they are all involved in modulating pain behaviors. Most importantly, CBD itself is not addictive[8,9] and is actually being investigated as a treatment for drug and alcohol abuse.[10,11]

Until recently, marijuana and any of its extracts, including CBD, were classified by the DEA as Schedule I - a designation that has significantly impeded research. In June 2018, Epidiolex®, an oral solution of purified CBD (≥99%, and < 0.1% THC), was the first cannabis-derived medication to be approved by the FDA. It is indicated for the treatment of refractory seizures associated with Lennox Gastaut and Dravet syndromes. The DEA has reclassified Epidiolex® to Schedule V, effectively lifting the regulatory barrier that has hindered the rigorous study of CBD in the past. As of 2020, Epidiolex is no longer a schedule V controlled substance, but still requires a prescription.

Due to several legislative changes across the United States, consumers have access to a wide variety of marijuana and hemp-based products. According to publicly available registry data, pain is the most common qualifying condition in state medical marijuana programs.[12] In a cross-sectional study of CBD users, the top three medical conditions for use were chronic pain, arthritis/joint pain, and anxiety.[13] CBD products are being marketed and used for pain, but an evidence base for this indication, supported by RCTs, is lacking. CBD preparations, oftentimes with questionable cannabinoid content,[14,15] are sold widely, but retailers are facing increased scrutiny from federal[15,16] and local[17] governments. More research is needed on the effects of cannabis derivates and their mechanisms of action in different patient populations, particularly those who suffer from pain. With the FDA approval and DEA rescheduling of Epidiolex®, we now have the historic opportunity to study the purported analgesic and opioid-sparing effects of a legal, well-regulated cannabinoid preparation that is devoid of euphoric and addictive properties. No studies have been published on the analgesic and anti-inflammatory effects of pure CBD in humans.

Conducting this pilot study will provide preliminary information that will be used to design future studies targeting pain and opioid use in orthopedic patients following surgery. Bilateral Total Knee Arthroplasty (BTKA) patients are ideal to use for this pilot study because they stay in the hospital for several days and data can be collected in a monitored setting. In addition to collecting data on opioid consumption and pain levels, we will collect blood samples to estimate levels of the inflammatory marker IL-6 in plasma on POD1 and peak CBD concentrations within six hours of Epidiolex® administration. Though *in vitro* and animal models indicate that cannabidiol is a potent anti-inflammatory compound that inhibits the release of pro-inflammatory cytokines like

IL-6,[18,19] no studies have measured levels of inflammatory cytokines in patients taking CBD. This research team has previously demonstrated that IL-6 is significantly upregulated in the blood of patients 24 hours after BTKA.[20,21] We seek to obtain estimates of IL-6 levels in the plasma from patients given Epidiolex in order to help design future studies addressing CBD's mechanism of action. Regarding pharmacokinetics, the only existing literature on Epidiolex® comes from healthy volunteers[22,23] and pediatric patients with seizures.[24] CBD levels are affected by high-fat meals[22] and other lipophilic compounds such as Intralipid®.[25] Because there is a paucity of data on CBD pharmacokinetics,[26] additional studies in different patient populations, including surgical patients, are needed to develop dosing algorithms.[27]

2.0 OBJECTIVE OF CLINICAL STUDY

In light of the opioid epidemic and evidence suggesting that cannabis may be opioid-sparing, we are in a unique position to conduct a novel, high-impact study that would set the stage for future RCTs examining the effects of a nonintoxicating and nonaddictive cannabinoid in an orthopedic patient population. Epidiolex®, an oral cannabidiol (CBD) solution, is the first ever cannabis-derived medication to be approved by the Food & Drug Administration. No studies have been published using CBD for the management of pain in humans. Our aim is to conduct a pilot study using a placebo (Ora-Sweet® SF), 400mg and 800mg Epidiolex® to gather data on its effects on patients undergoing bilateral total knee arthroplasty (BTKA). We will be estimating whether Epidiolex® is associated with minimal opioid use and adequate analgesia. We will also assess its tolerability, pharmacokinetics, and effects on inflammatory markers in the perioperative setting.

3.0 STUDY HYPOTHESES

This is a pilot study with the primary aims of gathering data on the opioid requirements, pain scores, serum inflammatory markers in patients receiving cannabidiol oral solution and the pharmacokinetics of two different doses of CBD administered perioperatively. The hypothesis is that CBD will be associated with less opioid consumption, and lower pain scores.

4.0 STUDY DESIGN

4.1 Study Duration

November 2022 – January 2025

4.2 Endpoints

4.2.1 Primary Endpoint

- The primary outcome of the study will be cumulative opioid use in the first 72h post operatively, in morphine equivalents (MEs). This outcome will be

measured throughout the patient's hospitalization and conclude 72h post operatively (i.e. 72h after surgery end). (PCA push will be calculated separately and in total opioid use.)

4.2.2 Secondary Endpoints

- **Pharmacokinetics of perioperative CBD** (0, 1, 2, 3, 4, 6 hrs after administration on POD0)
- **Levels of plasma Inflammatory marker (IL-6)** at baseline POD0 and POD1 (24 hrs after incision start)
- **Pain at rest / with movement** – NRS pain on POD 0 (pre-op and upon PACU arrival), in the morning of POD1, POD2, POD3, POD4, POD7, and at 3 months
- **Severity of Pain and Impact on Functioning** – Brief Pain Inventory short form on POD 0 (pre-op), POD1, POD2, POD3, POD4, POD7, and at 3 months
- **Incidence of adverse events** – allergic reactions, pyrexia, somnolence, GI problems (upset stomach, diarrhea), dry mouth, escalation of post-op opioid requirement
- **Scores on Opioid-related Symptom Distress Scale** (ORSDS) on POD1, POD2, POD3, POD4, POD7, and at 3 months
- **Anxiety levels** - Hospital Anxiety and Depression Scale (HADS) pre-op-POD0, POD1, POD2, POD3, POD4, POD7, 3 months
- **Cumulative inpatient analgesic use (non-opioid)** POD0, POD1, POD2, POD3
- **Opioid & non-opioid analgesic consumption** from discharge to POD7 and at 3 months
- **Hospital LOS**
- **Blinding assessment on POD4**
- **Time to reach discharge physical therapy goals, and range of motion**.
- **Sleep quality and duration–** assessed by actigraphy using the ActiGraph wGT3X-BT activity monitor (morning of POD1, POD2, POD3) and the Leeds sleep evaluation questionnaire - patient reported outcome (Pre-op, POD1, POD2, POD3, POD4, POD7, 3 months)

4.3 Study Sites

HSS Main Campus, Other (MSKCC)

5.0 STUDY POPULATION

5.1 Number of Subjects

37

5.2 Inclusion Criteria

Subjects of either gender will be included if they:

1. age 18 to 75 years of age
2. Patients scheduled for same-day bilateral total knee replacements with participating surgeons
3. American Society of Anesthesiologists (ASA) Physical Status 1 or 2

5.3 Exclusion Criteria

Subjects will be excluded from the study if they:

1. ASA 3 and higher
2. Weight less than 40kg
3. Planned use of general anesthesia
4. Contraindication to major components of study protocol
5. Cannabis or cannabinoid use within the past 3 months (recreational and/or medical)
6. Use or ingestion of hemp seeds or hemp oil in any form within the past 30 days
7. Chronic opioid use (>3 months)
8. Coumadin use
9. Current use of SSRIs or SNRIs
10. History of substance abuse or dependence
11. Active or history of major psychiatric illness
12. Severe cardiovascular disorder
13. Severe hepatic or renal insufficiency (transaminase levels above ULN)
14. History of epilepsy
15. Diagnosis of rheumatic disease, autoimmune disease, or immunodeficiency (e.g. rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, multiple sclerosis, etc.)
16. Use of valproate or clobazam
17. Known or suspected hypersensitivity, allergy, or contraindication to cannabinoids or any of the excipients in the study medications (i.e. sesame oil, sucralose, strawberry flavor)
18. Active use of steroids - oral steroids upon admission
19. Stress dose steroids
20. Non-English speakers
21. Planned discharge to home without caregiver(s)

5.4 Randomization

A total of 36 patients will be randomized 1:1:1 on the day of surgery to receive either placebo, 400mg or 800mg Epidiolex®

6.0 PROCEDURES

6.1 Surgical Procedure

Bilateral total knee arthroplasty (BTKA)

6.2 Medical Record Requirements

Using EPIC, research staff will review the patient's medical history to determine eligibility to participate in the study.

6.3 Data Collection

The following data will be collected:

Pre-operative/Baseline: Name, MRN, DOB, Race, Ethnicity, Gender, Height, Weight, BMI, pre-op pain medication use, co-morbidities, allergies, phone number, ASA, NRS pain scores at rest/with movement, Brief Pain Inventory – short form, Hospital Anxiety and Depression Scale, Leeds Sleep Evaluation Questionnaire, Interleukin-6 levels, cannabidiol and metabolite levels

Surgical procedure: date of surgery**,** procedure/surgery details, anesthesia details, tourniquet time & pressure

Follow-up visits (PACU, Post-operative day (POD) 1,2,3,4,7 and Post-operative month 3): NRS pain scores at rest/with movement, Brief Pain Inventory – short form, Hospital Anxiety and Depression Scale, Leeds Sleep Evaluation Questionnaire, Opioid-Related Symptom Distress Scale, opioid and non-opioid analgesic use, Bang Blinding Index assessment, side effects/adverse events, ActiGraph data, PT milestones, Range of Motion, Length of Stay, Interleukin-6 levels, cannabidiol and metabolite levels

7.0 STATISTICAL ANALYSIS

1. **Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):** Descriptive statistics will be presented for each group. Dunnett's test (2 pairwise comparisons, one between each of the 2 CBD dosing groups and control) will be used for any comparisons.
2. **Interim analysis planned?** No.
3. **Alpha level:** ---
4. **Beta or power level:** ---
5. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):** ---
6. **Number of groups being compared (use 1 for paired analysis within the same subjects): 3**
7. **Effect size or change expected between groups:** ---
8. **Resulting number per group:** 12
9. **Total sample size required: (**N=12 placebo (Ora-Sweet SF); N=12 400mg Epidiolex; N=12 800mg Epidiolex)

8.0 ADVERSE EVENT ASSESSMENT

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

9.0 REFERENCES

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