Effect of Cannabidiol Oil on Postoperative Pain After Ureteroscopy for Urinary Calculi

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IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at [redacted]

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
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Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
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General Study Information

Principal Investigator: Karen Stern, M.D.

Study Title: **Effect of cannabidiol oil on postoperative pain after ureteroscopy for urinary calculi.**

Protocol version number and date: Version 2, 16Oct2020

Research Question and Aims

Hypothesis: Cannabidiol (CBD) oil reduces the level of postoperative pain and usage of rescue opioids following ureteroscopy for stone disease

Aims, purpose, or objectives:

Aim 1. To determine if CBD oil has any effect on decreasing postoperative pain control following ureteroscopy for urinary stone disease. We will test the hypothesis that patients randomized to CBD oil will have significantly decreased postoperative pain compared to those randomized to the control medication (placebo). We will measure patient self-reported pain intensity scores (primary outcome) utilizing the 100-mm continuous visual analog scale (VAS). We also will measure ureteral stent related morbidity using the validated ureteric stent symptom questionnaire (USSQ).

Aim 2. To determine if CBD oil has any effect in decreasing the amount of postoperative opioids (commonly used drug) used by patients after undergoing ureteroscopy for urinary stone disease. We will test the hypothesis that patients randomized to CBD oil will have decreased usage of postoperative opioids given as a rescue

medication compared to those randomized to the control condition also given opioids as a rescue medication. We will analyze number of use, the cumulative and per day usage of analgesic opioid medication.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Ureteroscopy is one of the mainstays of the surgical management of upper urinary tract calculi. In most cases, a ureteral stent is left postoperatively which unfortunately can lead to significant morbidity and discomfort for the patient.[1] More than 80% of patients with a stent post-ureteroscopy report pain that interferes with their daily activities.[1] It is common for providers, and typical protocol at our institution, to prescribe opioids post-operatively for pain control.

In the past 15 years the number of opioid medication prescriptions in the United States has quadrupled. According to the CDC more than 47,600 people died from opioid overdoses in 2017, with one in three of those from prescription opioids.[3] Currently, Arizona has one of the highest age-adjusted rates of drug overdose deaths in the country.[3] Rates of death from overdose in Arizona was also shown to be increasing in recent years. Given the dramatic increase in opioid medication prescriptions in the United States, there has been a significant move towards finding alternative medications to manage patients' pain.

There are numerous biologically active compounds derived from Cannabis sativa, including the main phytocannabinoids tetrahydrocannabinol (THC) and cannabindiol (CBD)[4,5]. THC is the psychoactive cannabinoid derived from the flowers and leaves of the marijuana plant with intoxicating effects through the CB1 receptor. CBD is the main component of oil derived from the flowers and leaves of the hemp plant. It has a more complex mechanism of action than THC and has been shown to reduce inflammation, anxiety, and seizures[4]. Federal and state laws permit the growth and sale of hemp products, including CBD oil, provided the THC content does not exceed 0.3% of the dry weight[5]. Products with a THC content not exceeding 0.3% of the dry weight should not have the psychoactive effects known with THC and therefore theoretically have less risk of misuse or diversion and better safety profile than narcotics[5].

CBD oil has been purified as an oral solution as the drug Epidiolex. It received FDA approval for the treatment of rare seizure disorders in 2018 (FDA approval). Preclinical data have shown promise for the use in chronic pain with anti-inflammatory, antinociceptive and in the treatment of addiction[5]. It has not been studied in the postoperative or postureteroscopy setting.

There is a significant amount of research studying the role of cannabinoids in chronic pain management, however very little research has been done on post-operative pain management with cannabinoids.[6] Specifically within urology, cannabinoids have been shown to be effective in chronic pelvic pain syndrome/chronic prostatitis and help bladder dysfunction in multiple sclerosis patients.[7,8] Cannabinoid receptors (CB1 and CB2) are present in the bladder, testis, prostate, and vas deferens.[9] Endogenous cannabinoids interaction with these receptors is involved in the regulation of smooth muscle contractility.[9] Alpha-receptor antagonists have been found to decrease ureteral stent discomfort by decreasing smooth muscle contractility in the ureter.[10] Theoretically, agonized cannabinoid receptors, if also present in the ureter, as they are in a significant portion of the urinary tract, could also decrease smooth muscle contractility and decrease stent related discomfort. Preclinical data have shown promise for the use in chronic pain with anti-inflammatory, antinociceptive and in the treatment of addiction[5]. There is a gap in the literature to date regarding the use of CBD oil in post-ureteroscopy pain management, and post-surgery in general, but with increasing criticism on opioid prescribing practice, it is an arena that warrants investigation. Therefore, we propose a novel double blind randomized controlled study to compare pain control and safety with CBD oil and oxycodone (opioid) in the post-operative setting after ureteroscopy for urinary calculi.

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Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol.*

This study is designed as a prospective, placebo-controlled, double blind randomized controlled trial. In a blinded fashion, half of the patients will receive the trial drug and half (the control group) will receive the placebo. Both groups will also receive a script for a rescue medication, a commonly used opioid.

The medicinal products will be packaged, and labeled so as to be unidentifiable by the patient. The patient will receive the trial drug or a placebo. Packaging will consist of a syringe labeled with the dosing and administration schedule for both drugs. Drug safety sheets will be provided as part of the package.

Trial medication will be stored by the study pharmacy in a locked and labeled drawer for this particular study until they are dispensed to the patients. Records of allocation and dispensation will be kept by the pharmacy.

The dosage of trial medication will be 20 mg daily.

Patients will receive a prescription for an opioid per usual post-ureteroscopy protocol. For this study patients will receive a prescription for oxycodone 5 mg, 12 tabs. Instructions will consist of instructing the patient to take the medication as needed – 1 tab per mouth every 6 hours as needed for pain, for a maximum of 3 days.

Common adverse reactions to CBD oil include somnolence, decreased appetite, and diarrhea. In addition, elevated liver function tests (LFTs) were noted in patients treated with a different CBD oil product, Epidiolex, which is FDA approved for pediatric seizures associated with Lennox-Gastaut syndrome For Epidiolex, the FDA recommends pre-treatment LFTs drawn. These should be repeated after 1 month and 3 months of treatment[11], which will be significantly outside out treatment window of 3 days.

Patients will be asked to refrain from drinking any alcohol or consuming marijuana-based products during the study period.

Identification and enrollment of patients

Patients will undergo standard consultation for treatment options for urinary stones. Patients electing to undergo ureteroscopy for upper tract urinary stone disease will be identified and considered for enrollment during preoperative counseling in the urology clinic. Those who satisfy the inclusion and exclusion criteria will then be approached for inclusion into the study. Background, significance, risks, benefits, and alternatives will be discussed in detail and all questions will be answered before signing the consent form. A copy of the research consent form with all of the above information will be given to the patients and the signed original consent form will be kept in the urology department as detailed in the Data Collection and Handling section.

Randomization and allocation

Patients will be randomized to one of two groups – trial medication or placebo. Randomization schedule will be generated by the study statistician. Block randomization will be used to ensure temporal balance**.** Once patients have consented to being included in the study, they will be assigned a sequential study number, which will be passed onto the pharmacy study contact at the appropriate site to assign randomization allocation. They will then dispense encapsulated trial medication based on that allocation.

Blinding

This is designed to be a double blinded, placebo controlled trial in which neither the patient nor the clinical team is aware of the group allocation. The medications will be packaged inside a syringe. The medication will be dispensed to the patient with a label that describes both medications, strengths, and administration schedule. The clinical team will be blinded to the allocation and will only receive the dispensed drug from the pharmacy contact and then bring it to the discharging nurse in the recovery room for inclusion with other discharge material.

Preoperative and perioperative procedures

- Patient will undergo standard preoperative procedures including baseline blood work (CBC, BMP, and LFTs), imaging, and medical clearance as required.
- The procedure itself will be performed per standard practice of the surgeon, including choice of instruments, manner of fragmentation, and postoperative management of patient with regards to follow up appointments, stent placement and removal.

Postoperative procedures

- The study pharmacy will disguise the appropriate drug into an unlabeled generic container and dispense the prescription with appropriate instructions.
- In the recovery room, the patient will fill out a 100mm pain visual analog scale sheet which will be kept in the study drawer in the urology department.
- The patient will then be given a packet of materials for data collection along with the syringe with the blinded medication with full administration instructions and safety leaflet.
- The patient will fill out the data sheets for pain scale, trial, rescue and other medication usage, and adverse events on a daily basis for three days. The patient will also fill out the Ureteric Stent Symptoms Questionnaire (USSQ) on postoperative days 1 and 3.
- Patient will then mail the data sheets to the urology department using a provided stamped-addressed envelope or hand in the data sheets at their postoperative appointment.
- The patient will be required to bring all unused trial medication to the postoperative appointment, which will then be returned to the pharmacy staff.

Rescue medication protocol

- Patients will be prescribed an opioid pain medication per the typical protocol of the operating surgeon (12 tabs of oxycodone 5 mg). This can be taken at the patient's discretion for increased pain.
- All usage of opioids will be recorded by the patient on the daily data sheet.

- Given that the presence of the stent itself can be a significant factor in the pain and discomfort for patients undergoing URS, we will also allow for patients to be prescribed oxybutynin, tamsulosin and/or phenazopyridine at the discretion of the clinical team. These two medications, along with tamsulosin (given to patients routinely following URS) are very commonly used to mitigate stent pain in post-URS patients. Use of all adjunct medications will be recorded by the patient on the daily data sheet.

Emergency situation procedures
Participants will be given a patient card, which will have the study title, investigational medication product details, participant identification number and contact details for clinical study team members for business and after hours. If a patient has pain which is not controlled despite use of trial and rescue medications, then patient will have the option to call into the surgeon's office (during business hours) or the after-hours call number, which is usually directed to the resident on call. The patient will give the trial information on the patient card to the resident returning the call. Treatment plan at that point will be developed by the resident in conjunction with on call staff as per usual protocol. This may include medications prescribed over the phone, scheduling office visits as well as emergency room visits.

Subject withdrawal
Participants will remain on the trial unless they choose to withdraw or they no longer meet the inclusion and exclusion criteria.

Outcome measures
The primary outcome measure will be the pain score given by patients on the 100mm continuous visual analog scale (VAS). The VAS is an easy to use instrument for evaluating pain severity. It provides reproducible results that do not differ with age, gender or cause of pain. It is sensitive to treatment effects and data derived from it can be analyzed with standard parametric statistical techniques. Each day, patients will record their maximum and average pain scores. Surveys to record the pain scores and rescue drug (oxycodone) administration will be handed to the patient on day of surgery as well as emailed out via an external REDCap database. We will combine the results from each study and compare the primary outcome between the two groups (i.e. control group and CBD oil group) in two ways: 1. overall, and 2. on a per day basis.
Secondary outcomes

- We will compare the number of use, the cumulative and per day usage of analgesic opioid medication between the two groups.
- Usage of other medications, either self-administered, or prescribed will be compared
- The rate of adverse clinical events defined as the rate of adverse drug reactions, rate of unscheduled phone calls, emergency room visits, hospital admissions, and clinic visits will be compared between the two groups. Collection of adverse events will be done by a combination of patient self-report on data sheets and data gathering from electronic medical record to search for evidence of phone calls, emergency room visits, hospital admissions, clinic visit notes.
- Comparison of ureteral stent symptom questionnaire (USSQ) scores on postoperative days 1 and 3.

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Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 90

Subject population (children, adults, groups): Adults treated at Mayo Clinic, Arizona for kidney stones with ureteroscopy.

Inclusion Criteria:

- Patients who are diagnosed with kidney or ureteral stones confirmed on imaging (CT of the abdomen and pelvis) and who elect for definitive treatment via ureteroscopy at two sites within a tertiary care institution
- Age 18-75
- Patients of either gender
- Patients of all ethnic backgrounds
- Capable of giving informed consent
- Capable and willing to fulfill the requirements of the study

Exclusion Criteria:

- History of chronic pain
- Chronic use of opioid or other pain medication (>12 weeks)
- Known allergy to CBD oil or other cannabinoids
- Known or suspected pregnancy
- Inability to give informed consent or unable to meet requirements of the study for any reason
- Bilateral ureteroscopy
- Current marijuana, cannabidiol (CBD), or dronabinol use
- Liver disease/cirrhosis
- Current treatment of seizures with clobazam, valproate, or other antiepileptic medications

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: __0___ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____0_____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
Volume per blood draw: __0___ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____0_____

Prospective collection of biological specimens other than blood: _____None_____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☐ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples
- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol.*

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

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Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Endpoints
Primary: The primary outcome measure will be the pain score given by patients on the 100mm continuous visual analog scale (VAS).

Secondary:

- We will compare the number of use, the cumulative and per day usage of analgesic opioid medication between the two groups.
- Usage of other medications, either self-administered, or prescribed will be compared
- The rate of adverse clinical events defined as the rate of adverse drug reactions, rate of unscheduled phone calls, emergency room visits, hospital admissions, and clinic visits will be compared between the two groups. Collection of adverse events will be done by a combination of patient self-report on data sheets and data gathering from electronic medical record to search for evidence of phone calls, emergency room visits, hospital admissions, clinic visit notes.
- Comparison of ureteral stent symptom questionnaire (USSQ) scores on postoperative days 1 and 3.

Power Statement:

Previous work looked at pain scores after ureteroscopy for upper urinary tract calculi.[10,11] From these, and an ongoing study at the Cleveland Clinic, we estimated the mean Visual Analog Scale (VAS) score in the control group when the rescue medication is used to be 3.5 with a standard deviation of 2.5. We assume patient in the experiment group (CBD oil) will have a lower pain score and the placebo group has at least 40% higher pain score before use of the rescue medication. We assume alpha (Type I error) equals to 0.05, power (1 - Type II error) 0.80 and the standard deviation of the pain score is 2.5 for each group. Using two-sided t-test, the sample size estimations under different scenarios are listed in the table below. At Mayo Clinic Arizona we perform over 700 surgical cases for stone disease each year, so patient accrual should be amenable to completion in 12 months.

Pain score in treatment group	Pain score in placebo group	Effect size (difference/SD)	Required sample size for each group	Total sample size
2.0	3.5	0.6	45	90
2.25	3.5	0.5	64	128
2.5	3.5	0.4	100	200
2.75	3.5	0.3	176	352

Data Analysis Plan:

All the study data will be summarized by descriptive statistics. We anticipate the baseline characteristics between study groups will be comparable due to randomization. The point estimate and 95% confidence interval (CI) of the primary and secondary outcomes (pain score and USSQ scores) will be reported and compared by the two-sample t-test. If there is imbalance in the baseline characteristics between groups, we will fit a regression model to adjust for the possible confounding effect. The use of analgesic opioid medication (number of use, cumulative and per day usage) will be reported and compared by the two-sample t-test or Chi-square test. All the adverse events observed during the study period will be reported and summarized by frequency count and percentages.

References

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