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1. Project Title

Randomized, Controlled Cross-over Comparison of Cannabidiol to Oral Opioid for Postoperative Photorefractive Keratectomy Pain Control

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3. Abstract:

Photorefractive Keratectomy (PRK) is a commonly performed corneal refractive surgery for the correction of refractive errors. The procedure is less popular than Laser In-Situ Keratomileusis (LASIK) due to increased post-operative pain and discomfort associated with PRK, but some patients and surgeons increasingly prefer PRK for its superior safety profile in select patients.

Surgeons prescribe topical and oral medications to promote healing and reduce post-operative discomfort after PRK, with additional topical anesthetics and/or oral narcotics for break-through pain. Oral narcotic agents are typically opioid-acetaminophen combinations. Current evidence, however, demonstrates that opioid use is associated with unfavorable side-effects and that legitimate opioid prescriptions have fueled the current opioid addiction crisis. A safe, effective means of post-operative pain ibcontrol is needed, and alternatives to opioid medication are worth consideration.

We propose a crossover randomized paired-eye controlled trial to compare post-PRK pain control with a CBD chemovar to codeine/acetaminophen. Patients will receive PRK in each eye sequentially, using the CBD chemovar or codeine/acetaminophen for one eye and the other treatment for the fellow eye two weeks later. This crossover paired-eye design allows for robust self-control. Masking treatments will not be possible given the different appearance and dosing regimen of treatments. Surgical and post-operative parameters will be standardized between the two arms.

Medication use, pain levels and potential side effects will be collected. Primary outcome measures will be change from baseline in daily pain intensity on the pain rating scale to postoperative day 4 and responses between the study medication and the opioid/acetaminophen combination medication. Secondary measures will be surgical, refractive error, and patient reported outcomes noted at 1 and 3 months postoperatively. Final refractive error determinations will not be determined until 6 months postoperatively for patients having greater than 6D of myopia preoperatively.

4. Background:

Photorefractive keratectomy (PRK) is a common corneal refractive surgery with a superior safety profile compared to Laser In-Situ Keratomileusis (LASIK) for some patients but has increased post-operative pain and discomfort, frequently requiring opioids for post-operative pain control. Published evidence suggests that hemp-based cannabidiols (CBD) may be a suitable pain-control alternative, and we propose this study to evaluate the efficacy and safety of oral CBD for reduction of PRK post-operative pain compared to opioid-acetaminophen combinations.

PRK is a commonly performed corneal refractive surgery for the correction of myopia, hyperopia and astigmatism. The procedure is not as popular as LASIK due to the increase in post-operative pain and discomfort associated with PRK.[1-4] Many patients and surgeons choose PRK for a perceived enhanced safety profile over LASIK. PRK has recently gained popularity with some surgeons as a safer procedure than LASIK in select patients with predisposing conditions which may lead to increased post-operative complications such as dry eye, ectasia, and flap dislocation. A safe, effective means of post-operative pain control is needed.

Refractive surgeons employ a host of topical and oral medications to promote healing and to reduce post-operative discomfort after PRK. Topical antibiotics, non-steroidal, steroidal anti-inflammatory and rewetting drops are typically used. Oral non-steroidal medications are employed for pain control in a fraction of patients as well.[5,6] For break-through pain, patients are often prescribed topical anesthetics and/or oral narcotics.

Attempts to optimize the specific constituent components of this combination approach have been documented in the medical literature. Variability in efficacy and side effects with many components has been reported. Several types of bandage contact lens materials have been shown to offer varying rates of healing and patient post-operative comfort, with senofilcon A offering lowest pain reports.[7-11] Topical nonsteroidal [12-23] and topical anesthetic [24-26] medications have been demonstrated to be effective for pain control but offer the potential for delayed healing.[27,28] Application of cold packs after surgery has been shown to reduce post-PRK pain as well.[29-33] Concerns for affected sensorium which can limit activities of daily living and the potential for abuse with narcotics has led some refractive surgeons instead to use oral gabapentinoids for post-operative pain management, but with limited success.[34-37]

Combination approaches including a bandage contact lens, topical anesthetic, and topical nonsteroidal drops with oral narcotic medication for breakthrough pain has been shown to be more efficacious in addressing pain following PRK surgery.[38-40]

Combination codeine/acetaminophen, hydrocodone/acetaminophen and oxycodone/acetaminophen are commonly used oral narcotic/analgesic combination medication for post-PRK pain.[41] Use of transdermal fentanyl patches has been reported as well.[42] Some evidence suggests codeine/acetaminophen may be better for post-PRK pain control than oxycodone containing combinations.[43] However, opioid use has been associated with unfavorable side effects and social impacts. Unfavorable side effects including gastrointestinal and sensorium changes in patients taking a hydrocodone/acetaminophen combination have been reported.[44-46] Current evidence suggests that legitimate opioid prescriptions for injury or surgery have fueled the current opioid addiction crisis.[47, 48] The most common route for first exposure to opioids for persons who end up with opioid addiction is a legitimate prescription for an injury.[49] Over 25% of select patient populations who were prescribed opioid medications for

acute pain have been reported to still be using them at one year.[50] Alternative treatments are worth consideration.

Published evidence suggests hemp-based cannabidiol (CBD) with or without tetrahydrocannabidiol (THC) may be a suitable post-surgical opioid pain control alternative.[51, 52] CBD products with lower THC content may be preferable to higher THC-containing products associated with impaired cognition. Additionally Capano et al. treated a series of 131 patients taking more than 50 daily baseline morphine equivalents with a low-THC oral CBD chemical variant and found 53.2% of patients were able to reduce opioid medication use and had improved quality of life measures.[53] Laboratory data also indicate that topically applied CBD can reduce nociceptive pain responses in a superficial ocular injury model suggesting CBD sensitive pain-regulatory pathways in the cornea.[54] If the selected chemovar is clinically helpful for patients otherwise requiring an average of 50 morphine equivalents daily, we expect the intervention to be effective in our patient population typically well-managed with up to 18 morphine equivalents per day.

A paucity of data exists evaluating the efficacy of alternative anxiolytic and pain modulating treatments including CBD containing products to control post-PRK pain. Based on demonstrated success in other pain control applications as well as evidence of CBD sensitive corneal pathways, we postulate that CBD treatment perioperatively may be a suitable method for post-PRK pain control. An alternative low-THC CBD-based agent, if found to be effective for pain control, could decrease potential for opioid abuse, opioid-related complications and inherently decrease administrative burden for both prescribing and dispensing post-operative medications.

5. Specific Aims:

We will compare the safety and efficacy of a low-THC, oral CBD chemovar to oral codeine-acetaminophen for controlling post-operative PRK pain.

6. Research Plan:

Once a patient been evaluated, has been informed of the risks and benefits of the procedures, their cost and has decided on PRK, then the study will be introduced to the patient to determine their interest in participation.

Up to fifty patients will be enrolled in the study with the goal of Thirty-five total patients completing the study and will include otherwise healthy patients with myopia meeting criteria for PRK without contraindications to any of the study medications. Patients will undergo PRK in each eye sequentially, separated by two weeks. Half of the patients will receive the CBD chemovar for pain control during the first surgery, and half will initially receive codeine/acetaminophen. Both arms will then cross over to the other pain-control treatment during the second surgery for the fellow eye two weeks later.

For the eye to be treated with the narcotic medication, patients will be prescribed 12 tablets of codeine/acetaminophen (30mg/300mg) for break-through pain. Patients will be counseled that these medications may be taken as needed up to once every 4 hours (up to 18 morphine equivalents daily), that use will preclude driving and, and that this medication may result in unfavorable side-effects including gastro-intestinal symptoms. Chemovars of CBD delivered via smoking and/or vaping were not considered for this study for the concern that eluted vapors may impede healing of the ocular surface. Sublingual tinctures were deemed to be potentially less reliable for precise dosing using a dropper, especially in subjects with impaired visual acuity in the immediate post-operative period.

For the eye to be treated with the CBD chemovar, patients will be prescribed 20 CBD gummies (50mg) and instructed to use 2 of the chemovars (50mg total each dose) beginning the morning of the procedure and continuing twice daily through the evening dose on post-operative day (POD) 4. The CBD chemovar selected for this study is a full spectrum CBD gummy provided by SunFlora which contains 50mg of CBD with less than 0.3% THC by weight. This product is readily available for direct consumer purchase without administrative encumbrances associated with higher level THC chemovars. The cannabinoid profile is verified by an independent laboratory using a host of chromatography techniques. The analysis includes screening for heavy metals, toxins, industrial chemicals, microbiological and pesticide contamination. CBD used for this study will all be selected from the same lot to reduce variability. A similar strength CBD product has been used in a published clinical study[53] in 131 patients without reported adverse events which should increase the likelihood of tolerability in our patient population. Some evidence suggests that as many as 10 million adults in the US consume supplement-grade CBD products daily with limited adverse effects reported.[54] Patients will be counseled that use of this product will preclude driving until they experience how the product affects them, and that this medication may result in unfavorable side-effects including sleepiness, decreased appetite, diarrhea, liver enzyme elevations, fatigue, malaise, rash, insomnia, sleep problems and infections.

The investigators will pursue investigational new drug approval for this CBD chemovar prior to treating patients.

Inclusion/exclusion criteria to ensure safety of study subjects:

Inclusion criteria will be healthy adult patients except for myopia with suitable health for photorefractive keratectomy.

Exclusion criteria will include pregnancy or lactating within the preceding 6 months of the procedure (female and male subjects will be counseled to practice acceptable methods of birth control until completing all study medications), concomitant use of amiodarone, isotretinoin, or sumatriptan. Female patients will be pregnancy tested on the day of each planned procedure. Other exclusion criteria include a history of poorly controlled diabetes, HIV (Human Immunodeficiency Virus) or other immune and collagen vascular disorders, glaucoma, herpetic eye disease (including simplex and Zoster), or corneal ectasia or dystrophy. Additional exclusion criteria include subjects with any history of seizure disorder, family history of seizure disorders, or head trauma, any history of liver disease or use of medications associated with liver dysfunction, any history of renal disease, or any history of cardiovascular disease, history of peptic ulcer disease, gastrointestinal hemorrhage and/or history of NSAID-related gastrointestinal adverse events. Subjects with a personal history of opioid misuse, abuse, or addiction will also be excluded from the study.

There is some evidence that prolonged, high dose CBD use (Epidiolex) has resulted in elevated transaminases. The fraction of patients experiencing CBD-associated liver injury in the literature are mostly children at 10mg/kg/day to 20mg/kg/day dosing with an equivalent total dose of 700 to 1400mg per day for a 70kg adult. Transaminase elevations have been reported in approximately 16% of patients after 90 days of use.[56] This is the equivalent of 63,000mg cumulative dose for a 70kg adult. Approximately 2/3 of the patients with elevated transaminases were taking concomitant valproate.[55] There is a very low likelihood of liver injury to adult subjects in this study taking 10 doses of 50mg of supplement-grade CBD for 500mg total exposure which is the equivalent of less than 1 day recommended dosing of Epidiolex. As listed above, any history of liver disease or use of medications associated with liver dysfunction is an exclusion criterion.

Surgical and post-surgical procedures:

All other surgical and post-operative parameters will be standardized between the two arms. All patients will undergo comprehensive medical history and eye exams including manifest and cycloplegic refractions, ocular dominance, wavefront analysis, corneal topography, corneal tomography, pachymetry, autorefraction, keratometry and iDesign aberrometry. Treatment plans with satisfactory quality infinity-calibrated iDesign profiles will be nomogram adjusted in minus cylinder by age as per center routine. After ensuring all manufacturer recommended laser daily calibrations have been completed, all surgeries will be performed by the same experienced surgeon (WAS). Epithelial debridement will be completed with an Amoil's brush with a hyperopic head. Ablations will be performed with the VISX S4 (Johnson & Johnson) excimer laser using pupil tracking and iris registration when available. Patients will be coached to maintain fixation on the centration beam during ablations and recentering joystick maneuvers will be used as necessary to maximize pupil centration within the reticle overlay. Mitomycin C 0.02% will be applied in all cases for 20 seconds per 50 microns of ablation and irrigated with 15cc of room-temperature balanced salt solution. The mitomycin 0.02% sterile solution used in this protocol is supplied by Fagron Sterile Services (FDA Registered 503B Outsourcing Facility) NDC 71266-8475-03. The label indicates: Sterile Mitomycin Solution 0.02% (0.2 mg per 1 mL preservative-free, single-dose syringe) Each mL contains: Mitomycin 0.2 mg, Mannitol USP 0.4 mg, Water (HCl or NaOH for pH adjustment) For Ophthalmic Use Only (Not For IV Use) Storage: 2-8°C (36-46°F); Protect from Light

Post-operatively, a senofilcon A bandage contact lens (Acuvue Oasys) will be used in the operative eye. Moxifloxacin 0.5%, ketorolac 0.5%, fluorometholone 0.1%, and preservative free rewetting drops, (Refresh Plus--carboxymethylcellulose sodium 0.5%) will be used in all patients 4 times daily as per routine. Patients will be prescribed ibuprofen 800mg orally three times daily for constitutive use for the first 48 hours postoperatively to reduce pain and inflammation. All patients will be counseled to apply ice packs to their closed eyelids through a cloth or towel for approximately 15 minutes per hour while awake for the first 48 hours. Female patients of reproductive age will be given a pregnancy test prior to enrollment.

Patients will be randomly assigned to either the oral CBD first or oral codeine/acetaminophen first treatment arms in a 1:1 ratio using a random number generator from Microsoft Excel. Patients will be assigned consecutive study identification numbers as they are enrolled. Identification numbers will be apportioned to each arm using the Excel randomization generator before the first patient is enrolled. Masking study patients from which

medication they are using will not be possible given the different appearance and dosing regimen of the two pain control agents.

Patients will complete a pain diary to record pain levels on each POD starting on the evening of POD0 through re-evaluation and collection of data sheets on POD7. The diary will also contain subjective medication side effect descriptions and intensity. Patients will be provided with emergency contact information to contact the clinic and/or on-call personnel if they are concerned they are experiencing an adverse reaction to the procedure or one of the study medications. A medical review of symptoms will be performed at the follow up examination to assess the potential for adverse reactions to the procedure or any of the study medications.

Opioid-based medication used by patients will be tabulated on the POD7 visit and unused medications will be disposed of in an RxDestroyer device in a witnessed fashion and witness forms will be entered into patients' records in accordance with UF Health ambulatory clinic policies as specified in the Patient Supplied Controlled Substance Destruction and Recordkeeping Protocol.

Patients will be given electronic versions of a Microsoft Forms survey tool to collect responses to selected questions from the Patient Reported Outcomes with LASIK (PROWL), NEI Refractive Error Quality of Life-42, Work Productivity and Activity Impairment and Ocular Surface Disease Index questionnaires.

PRK Study Schedule of Events

DATE	ITEM	NOTES
Presurgery	Preopoerative Assessment	Potential Enrollment Date
1st Surgery	Surgery of 1st Eye	Randomized to single pain medication
Postop Day 7	Postop Eval	Collection of diary, postoperative assessment of 1st surgery
2nd Surgery (2 weeks after 1st)	Surgery of Fellow Eye	Other pain medication
Postop Day 7	Postop Eval	Collection of diary, postoperative assessment of 2nd surgery
1 Month Assessment	Postop Eval	Weeks 3-5 after 1st surgery, evaluation for haze, outcomes assessment
3 Month Assessment	Postop Eval	Weeks 10-14 after 1st surgery, outcomes/complication assessment
6 month assessment	Postop Eval	Weeks 24-28 after 1st surgery (only if >6D myopia preop)

Safety Monitoring and Stopping Criteria:

Baseline assessments will include a brief physical exam with vital signs and a thorough medical and psychiatric history, including a review of past medical history, concomitant medications, inclusion/exclusion criteria, and potential contraindications.

Follow-up visits will include monitoring for adverse events as listed above including reassessment of vital signs and review of patient symptom diaries.

Subjects contacting the clinic and/or emergency on-call personnel between scheduled visits will be assessed via telephone for potential adverse events. If a potential adverse event is suspected, the subject will be recommended to stop the study medication and will be prescribed an alternative pain medication pro re nata.

7. Possible Discomforts and Risks:

Normal discomforts and risks associated with PRK for myopia may be experienced by patients. Patients will be receiving a pain medication for each of the surgical eyes. One pain medication is the acetaminophen/codeine product used for all PRK patients were Refractive Center standard protocol. The other eye will be treated with the CBD product. It is possible that subjects could experience less pain control with one or the other interventions. Based on clinical practice, most patients having bilateral surgery report more pain than those having single eye surgery. If a subject in this study has less pain control with one of the study agents, this pain level is likely to be lower than that experienced by routine patients having both eyes treated simultaneously.

Other discomforts and risks are similar to those experienced by patients having PRK for myopia not involved in the research study. These can include intra-procedure anxiety and discomfort, post-operative pain, irritation, tearing, blurred vision, double vision, potential loss of vision and need for additional procedures.

Study subjects will need to have each eye treated sequentially approximately 2 weeks apart. This will result in them having to convalesce twice from the procedure and attend additional clinic visits than if having routine simultaneous bilateral surgery. Study subjects will also be required to complete postoperative questionnaires after each eyes' surgery.

Study medication risks are as mentioned above. For the opioid combination medication, use will preclude driving and use has been associated with sleepiness, fatigue, nausea/vomiting, constipation, itching, and potential for abuse. For the CBD product, use may be associated with somnolence, sedation, decreased appetite, diarrhea, liver enzyme elevations, fatigue, malaise, rash, insomnia, sleep problems and infections.

8. **Possible Benefits**:

Benefits of the study could be to identify an alternative pain control regimen satisfactory for post-PRK pain that could reduce the need for opioid prescriptions.

9. Conflict of Interest:

The investigators have no financial interests related to the study. The study is funded by a grant from the Consortium for Medical Marijuana Clinical Outcomes Research.

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