Title: Effect of Topical Chylobinoid Cream on Pain and Function Scores for Hallux Disorders: A Randomized Controlled Trial

Purpose: The purpose of this study is to compare the change in pain scores in patients with hallux rigidus and hallux valgus who are treated with topical cannabidiol cream vs. placebo.

Hypothesis: Patients treated with topical 1.5% chylobinoid cream (chylobinoid is approximately 85% magnesium-cannabidiolic acid or Mg-CBDa, 5% CBD, 5% other cannabinoids, and naturally occurring plant lipids in a neutral emollient) will show improvement in hallux pain compared to those patients treated with placebo.

Background:
Conditions affecting the first metatarsophalangeal (MTP) joint are highly prevalent and make up a significant portion of orthopedic foot and ankle clinic visits. Hallux rigidus, Latin for "stiff toe," is the term for osteoarthritis of the first MTP joint. It is the most common form of foot arthritis, and incidence continues to rise as the population ages.[1] Hallux valgus is a common foot deformity characterized by chronic subluxation of the first MTP joint, with lateral deviation of the proximal phalanx and medial deviation of the first metatarsal. These conditions represent a large portion of chronic forefoot disorders.

Both of these chronic conditions are associated with pain, inflammation, functional impairment, and corresponding radiographic changes. While operative interventions exist, nonoperative modalities are the mainstay of treatment for most patients. Options include shoe wear modification, manual and physical therapy, intraarticular injection of corticosteroids or sodium hyaluronate, oral nonsteroidal anti-inflammatories, and foot orthoses. Oral anti-inflammatories are some of the most effective non-operative strategies, but unfortunately are associated with major adverse side effects and are contraindicated in many patients. Although these medications do not alter the underlying deformity, they are an important, cost-effective, and clinically validated tools in the management of hallux valgus and hallux rigidus. Oral non-steroidal anti-inflammatories (NSAIDs) are contraindicated in many patients with certain gastrointestinal, renal, or cardiac disease.

The endocannabinoid system has been shown to play an important role in inflammatory regulation, and pain perception.[2] Cannabidiol (CBD) is a component of the cannabis plant that is responsible for the signaling mechanism of cannabinoid receptions involved in a variety of pain pathways. CBD has been found to suppress progression of arthritis by suppressing the inflammatory cytokine pathway involved in osteoarthritis.[3] It has been found to reduce synovitis and decrease progression and pain secondary to osteoarthritis. Philpott et al. assessed pain behavior and joint afferent mechanosensitivity in rats with collagen-induced osteoarthritis of the knee. They found that CBD infusion decreased joint inflammation, inhibited mechanosensitivity of joint nociceptors, and improved hind limb weight bearing and limb withdrawal threshold.[2] Transdermal CBD was found to reduce joint swelling, immune cell infiltration, and synovial thickening in a dose-

dependent manner in rats with induced knee arthritis.[4] This and other studies show preliminary evidence that CBD is a safe, effective way to improve pain and functional impairment associated with osteoarthritis.[5,6]

CBD and its more active form, CBDA, have been studied since the 1960s, and different formulations and administrations have been shown to treat a wide variety of pathology. In the 1970s, publications on the compound increased after research found antiepileptic effects with systemic administration. Recent studies have focused on anti-inflammatory and antioxidative effects after both IV and topical administration. Studies have evaluated oral CBD for pain in patients with kidney disease, multiple sclerosis, spinal cord injury, brachial plexus injury, and limb amputation.[7–10] CBD has been found to decrease generalized pain and increase function after short term.

Topical use for orthopedic disorders has yet to be studied, although the available literature shows that topical CBD application has therapeutic potential for relief of arthritis pain-related behaviors and inflammation without evidence side effects. More recently, a topical chylobinoid cream formulation has become available for study. Chylobinoid describes a chylomicron-like complex extracted from raw hemp flower utilizing a proprietary mineral infusion process developed by Synthonics, Inc. that consists of approximately 85% magnesium-cannabidiolic acid or Mg-CBDa, 5% CBD, 5% other cannabinoids, and naturally occurring plant lipids.

This study would be the first prospective randomized controlled trial to evaluate the use of topical chylobinoid cream in the treatment of hallux rigidus and hallux valgus. It has the potential to improve pain and function for patients who suffer from moderate to severe hallux pain, with low cost and minimal side effects. Additionally, it may significantly reduce the concurrent need for narcotics, NSAIDs, corticosteroids and other oral/topical analgesic remedies.

Study design: Prospective randomized controlled trial

Inclusion criteria:
- Patients with new diagnosis of hallux rigidus and hallux valgus
- VAS pain score of 4 or higher
- Age > 18 years
- Patient provides informed consent

Exclusion criteria:
- Previous operative procedure to the first metatarsal for treatment of hallux valgus or hallux rigidus
- VAS pain score at presentation less than 4
- Concomitant hallux valgus and hallux rigidus on the ipsilateral side
- Allergy to CBD, CBDa or any other ingredient contained in the topical cream
- Pregnant patients
- Non-English speaking patients

- Patient is incarcerated, incapacitated, or otherwise unable to provide appropriate informed consent

Patients and protocols:
Patients will be recruited from the practices of a fellowship trained Orthopedic Foot and Ankle surgeon at Rush University Medical Center. Patients with a new diagnosis of hallux valgus or hallux rigidus without prior operative intervention on the first metatarsal will be approached for enrollment in the study. Pre-treatment VAS pain scores and the Foot Function Index (FFI) are collected as a routine question on new patient questionnaires. Patient's with a VAS pain score of < 4 will be excluded. The goal of the intervention is to improve pain, and patient's with minimal pain at presentation have a little possibility of showing therapeutic response.

Enrolled patients will be randomized to receive chylobinoid cream vs. placebo cream (neutral emollient containing no active agent) for topical treatment of hallux rigidus or hallux valgus. Patients and treating physician will be blinded to the intervention. Patients will not be charged nor will their insurance be billed for cost of the chylobinoid cream or placebo cream. Patients will be instructed to apply the topical cream as needed for pain for a total duration of four weeks. This topical treatment will be combined with other commonly employed conservative modalities, including physical therapy and orthotics as clinically indicated. Patient's will receive the FFI survey via email weekly for a total of 4 weeks after treatment initiation. Patient's will be instructed to keep track of daily VAS pain scores in a pain journal for the four weeks of treatment.

Patient's will attend their regularly scheduled four weeks follow up clinic visit. Post-treatment VAS pain score will be collected at that visit, along with their daily pain journal. Patients will fill out a brief survey regarding their experience with the treatment. The remaining chylobinoid cream will be collected from patients and weighed in order to assess the amount of product used during the four-week study period. The difference in pre and post-treatment VAS score and FFI will be determined between the chylobinoid and placebo groups.

Sample Size:
Power analysis was preformed using a retrospective review of internal patients with new hallux rigidus and hallux valgus diagnoses. VAS scores at the time of presentation were determined. VAS score at presentation for hallux rigidus was 6.74 with standard deviation of 1.7. VAS score at presentation for hallux valgus was 6.45 with standard deviation of 1.68. A clinically significant improvement in VAS pain score was defined as a 2-point decrease. Power analysis based on 80% power and alpha of .05 for detection of a 2-point decrease in VAS score determined the study would require 12 patients with hallux rigidus per group (24 total) and 12 patients with hallux valgus per group (24 total). In order to account for 20% loss to follow up, a total of 28 patients will be enrolled for each hallux rigidus and hallux valgus group (56 total patients for the entire study).

Demographics/patient specifics:
Age, sex, medical co-morbidities, weight, height, pre-treatment pain scores, BMI

Primary outcome measure: Post-treatment VAS score averaged daily over 4 weeks.

Secondary outcome measures:

1. Pre- to post-treatment difference in VAS score
2. Pre- to post-treatment difference in FFI
3. Post-treatment FFI at different time points (1, 2, 3, and 4 weeks post treatment)
4. Adherence to treatment
5. Amount of Chylobinoid cream vs. Placebo cream used during the study period
6. Do you believe you received the treatment or placebo? (4 weeks)
7. Did the cream we gave you help with your pain? (4 weeks)

Procedures for maintaining confidentiality:
A breach of confidentiality and/or privacy is a risk of this study. To prevent this, all collected data will be stored electronically in password-protected files to protect patient identity and information. All information will be collected and reviewed by the research team only. Data will be maintained on a password-protected computer that will be accessible only to the study team. No patient identifiers will be maintained in the database.

References:

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