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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on ClinicalTrials.gov)

Strengths and limitations of this study

- This is the first human randomized clinical trial to assess the potential therapeutic effects of cannabidiol on pain and inflammation following orthopaedic trauma.
- This trial includes a longitudinal assessment of CBD treatment on pain symptoms and trauma-related outcomes up to three months post-fracture which marks the critical period of transition to chronic pain.
- This study will assess potential interactions between pain mediators, such as opioids, mild traumatic brain injury and sex, and response to CBD treatment. This evaluation will help gain a more comprehensive understanding of the effects of pain mediators on treatment response, as well as the effects of treatment on opioid uptake.
- Therapeutic drug monitoring could be beneficial to account for inter-individual variability as well as to optimize doses.

Introduction

Bone fractures are a prevalent condition affecting individuals of all ages and are the most commonly treated trauma in hospitals (1, 2). In 2019, the estimated annual incidence of new fractures worldwide was 178 million (3). The process of bone healing involves multiple consecutive and interrelated phases including inflammation, repair, and remodeling, which occur in a spatial and temporal series of dynamic processes (4, 5). The skeletal system possesses a remarkable capacity for regeneration. The initial process of bone healing typically occurs over a period of eight weeks (6), while bone remodeling extends for months following a fracture (7).

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1β, IL-6, IL-10) and the tumor necrosis factor (TNF- α) (8). In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) (9). Persistent CNS inflammation plays a key mediating role in central sensitization (10), a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life (10), is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures (11). A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female gender, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture (12-16).

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living (17). In addition, patients with orthopedic trauma report a deterioration in their quality of life up to twelve months following the injury (17, 18). However, pain emerges as the most prominent complaint, with 97% of patients reporting pain after an orthopedic injury (1, 19). Acute pain management is a crucial concern considering that inadequate pain control can lead to prolonged inflammation, which can

perpetuate pain signals and lead to chronic pain (20, 21). Currently, a pharmacological approach is widely recommended to manage acute post-trauma pain. Both non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-inflammatory and analgesic effects (22). Nevertheless, the use of NSAIDs has been associated with delayed bone healing (23, 24) as well as digestive complication and kidney failure (25). As for opioids, in addition to major side effects, they pose a high risk of dependence and tolerance (4, 26). Furthermore, several studies show that opioids inhibit effective bone remodeling (27), increase the risk of pseudarthrosis (28), and heighten the risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central sensitization (26).

Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic pain admissions was observed, leading experts to question the potentially beneficial effects of cannabis on pain (29). Indeed, one study found that 61% of medical cannabis users reported consuming it to alleviate pain (30, 31). However, the medical use of cannabis is limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due to its low affinity with the CB1 receptor (32). It is of particular interest as it is devoid of addictive effects (33, 34) and has an excellent safety profile (35), and its use does not affect daily activities such as driving or working.

CBD is highly lipophilic which facilitate its ability to cross the blood-brain barrier (36). However, the bioavailability of CBD varies greatly according to the method of

administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect, with approximately 5% of the product reaching the bloodstream (37-39). Food consumption as well as nanotech and oil-based formulations of CBD have been shown to increase bioavailability (40). However, compared to smoked CBD, oral administration of CBD presents multiple advantages, including greater control over dosage, ease of administration, and fewer side effects (38).

Mechanisms of action of CBD are complex, not yet fully understood and involve multiple pharmacological targets. Emerging evidence suggests that CBD exerts a number of important effects via its modulating role on several non-cannabinoid receptors and ion channels including those of endogenous neurotransmitters, such as serotonin (41) as well as several types of TRP channels, such as TRPV1 (42), and by modulating the binding affinity of certain G protein-coupled receptors (43). Several in vitro and animal model studies have demonstrated CBD's anti-inflammatory effect, notably by reducing pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, in addition to inhibiting microglial activation (32, 42, 44-51). CBD has also shown analgesic potential in studies using neuropathic and inflammatory pain models. These human and animal studies suggest a reduction in pain, hyperalgesia, and allodynia following treatment with CBD (35, 52-59). CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in several animal and human studies (60-66). In addition, a well-controlled preliminary animal study showed that CBD, but not THC, enhanced the biomechanical properties of healing mid-femoral fractures in rats, supporting a beneficial effect of CBD on bone healing (67).

Epidemiological studies have suggested a reduction in opioid use for pain coinciding with an increased use of medical cannabis (30), a trend also documented in Canada (68). While the interaction between CBD and opioids is not yet fully understood, studies have shown that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors (69). CBD was also shown to potentially enhance the analgesic effects of endogenous and exogenous opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic pain resulted in a reduction in opioid consumption and improvements in overall quality of life (70).

Providing effective pain management for patients with fractures is not only a fundamental right but also offers numerous benefits. It reduces stress, shortens hospitalization time, decreases associated healthcare costs and lowers the risk of developing chronic pain (1). Preventing chronic pain is easier than reversing the sensitization processes that cause it (71), making acute pain control a priority. Given its excellent safety profile (33, 35) coupled with its downregulating effects on microglial and inflammatory activity, the primary neuroinflammatory and pain mechanism, CBD represents an appealing neuroprotective agent for pain-susceptible orthopedic trauma patients.

Study objectives

The primary objective of this study is to evaluate the effects of CBD treatment on self-reported pain in patients following a long bone fracture injury. The second objective is to assess the effect of the CBD treatment on inflammation and patient well-being. Additionally, secondary analyses will look at the possible associations between pain

mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to CBD treatment. The aim is to better identify the effects of these pain mediators on treatment response and the impact of CBD treatment on opioid uptake.

Methods

Study design

This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the effects of two doses (low and moderate) of CBD compared to a placebo on pain and inflammation after a long bone fracture.

Participants

A total of 225 participants aged 18 to 70 will be recruited within one week after their long bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM), one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic patients treated annually.

Inclusion criteria

Subjects meeting the following criteria are eligible for the trial:

- Patients with a long bone fracture of the lower limb (tibia, fibula, femur, metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals, and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one week of the accident
- Participants is between 18 and 70 years of age

- Patients with or without surgical procedures

Exclusion criteria

Patients presenting any of the following characteristics are not eligible for the trial:

- Moderate/severe traumatic brain injury (TBI)
- Diagnosis of any of the following mental disorders as defined by the DSM-5: schizophrenia, intellectual disability, bipolar disorder, major depression, a diagnosed and untreated sleep disorders
- History of alcohol or opioid misuse/abuse
- Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)
- Pregnant or lactating women, women of childbearing potential who are not using medically accepted forms of contraception, or women who are planning on becoming pregnant
- History of adverse reactions to cannabis
- Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the injury
- Patients experiencing on average mild-to-absent pain in the last 24h preceding recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))
- Transport business drivers and heavy machinery operators
- A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)
- Not having French or English as a spoken language
- A weighted MoCA score of less than 24

- Regular cannabis use more than 5 times a week

Recruitment

Recruitment will begin in September 2024. Potential participants will be screened daily by the research team and collaborators. Potentially eligible patients will be approached by a research team member and provided with a consent form. Once the research team has addressed any remaining questions and obtained a signed consent form, the participant will be randomized. See figure 1 for an overview of the study timeline.

Assignment of interventions

Participants will undergo concealed randomization to avoid selection bias. The study pharmacist will randomly assign participants to one of the three treatment groups (low or moderate CBD or placebo) using a 1:1:1 ratio through block randomization, stratified by sex, age and type of fracture (i.e., lower and upper limb). The randomization procedure will be performed a priori by an independent biostatistician. Identical tablets for CBD and placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study pharmacist will be aware of allocation but will have no clinical or interpretive role. Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate allocation concealment. In the event of a serious adverse event or reaction, the allocation list can be retrieved.

Intervention

Patients in the treatment group will receive either a low dose (25 mg) or a moderate dose (50 mg) of CBD self-administered orally as a tablet twice daily with a meal for one month. Patients in the placebo group will receive an identical amount of a matching placebo administered with a meal twice daily for one month.

Investigational product

CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto, Canada). The pharmacokinetic profile of the CBD product has already been established, and efforts to register the product with Health Canada have begun.

Dose justification

A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various conditions (72, 73). The low dose (25 mg) selected for our study is based on initial and ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per day (65). This is also approximately the mean dose of CBD administered in a successful trial of Sativex (THC/CBD) for neuropathic pain (74). Moreover, a higher but relatively moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD doses in this range have shown no statistical difference in intoxication scores in healthy volunteers (75) and doses of up to 800 mg per day for a minimum of 4 weeks showed an excellent safety and tolerability profile (76 , 77) Participants will be advised to ingest the treatment at mealtime, as studies have shown an increased bioavailability of CBD in subjects after eating (78, 79). To achieve our primary goal of mitigating acute pain, a one-

month treatment period has been selected, aligning with the typical evolution of acute pain post-fracture (6).

Study procedure

Upon enrollment in the study, research staff will provide study instructions, collect baseline data (e.g., demographics and clinical characteristics), administer questionnaires and cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines. Patients will report their pain intensity at baseline, and then three times a week throughout the entire one-month treatment duration. Participants will be instructed to complete a daily medication diary for one month to monitor the administration of study product, as well as opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) (80). Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with

anchor words ranging from “no pain” to “worst imaginable pain”. Participants will indicate the intensity of their pain at that moment by placing a mark along the line.

Secondary outcomes

At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers, quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and orthopaedic function outcomes will be collected. In addition, at baseline, participants will be asked to indicate their level of treatment expectation using the Treatment Expectation Questionnaire (TEX-Q-F) (81), a fifteen-question questionnaire, considering the potential modulation of therapeutic effects by patients' expectations of treatment (82, 83). After treatment completion, participants will also be asked to indicate whether they felt they had received active treatment or placebo.

Measures

Demographic and clinical characteristics

The following information will be collected at baseline to characterize participants: age, sex, height, weight, percentage of adipose tissue using an impedance meter scale, occupation, education level, ethnicity, language spoken, pre-morbid medical history (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs, cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and severity, mechanism of injury.

Pain

At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain Inventory short form (BPI-sf) (84), a 9-item self-report questionnaire assessing for the presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief treatment, and pain interference with activities of daily living. In addition, pain will be assessed using the VAS at several time points for comparison: baseline, three times per week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing Scale (85), a 13-item questionnaire evaluated on Likert scales, given the significant contribution of psychological factors in the experience of pain.

Opioid usage

Participants will continue their usual pain care regimen throughout the study. Opioid usage and analgesic will be recorded in a daily medication diary for the initial month and through the number of prescription refills for months two and three. Self-reported opioid use in a diary has been shown to be an accurate assessment of the quantity of opioids consumed (86).

Inflammation

Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1β) and TNF-α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA

plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as per manufacturer recommendation. Simoa is a leader in the quantification of plasma biomarkers with markedly lower detection threshold than traditional ELISA (87).

Cognition

At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain, and that do not require the use of the fractured limb, will be administered: a task assessing information processing speed (Symbol Search from the WAIS-IV Battery), two memory tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test (Elevator counting with distraction and Elevator counting without distraction from the Test of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).

Mild TBI symptoms resolution

Patients who sustained a concomitant mTBI with their fracture will be included in the study. Additional measures will be documented to control for this variable. At 1 and 3-months follow-up, information on mTBI symptoms resolution will be collected for patients diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion Questionnaire (88).

Orthopaedic function

At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA) Questionnaire (89) will be administered. The SMFA includes 34 questions that evaluate patient's function, and 12 questions related to how bothered patients are by their symptoms.

Well-being

At 1 and 3-months follow-ups, various important domains of well-being significantly modulated by pain will be measured including: quality of life using the Short Form (36) Health Survey (90), a 36-item self-report questionnaire for measuring quality of life across 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) (91), a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks. Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms will be assessed using the Beck's Depression Inventory-II (BDI-II) (92) and the Beck's Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up using the PTSD Checklist for DSM-5 (PCL-5) questionnaire (93).

Data management

Data collected will be transcribed from the source documents into the electronic Case Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-Montréal (94) and quality controlled by a second qualified staff member. Data will be

stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

Sample size estimation

A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in the CBD group and expected 20% in the placebo group) has been used extensively to reflect clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect a statistically significant difference in the proportion of patients who reaches 30% pain reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout rate of 20% and a significance level of 5%. These parameters are taken from a successful randomised, placebo-controlled clinical trial using Sativex© in treating 125 neuropathic pain patients (74).

Moreover, considering that the placebo group may ingest more opiates and that the anticipated inter-group effect at one month may be reduced to 20%, a total sample size of 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20% and a significance level of 5%.

Primary outcome

The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the mean VAS pain score at the 1-month follow-up.

Secondary outcomes

For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on VAS pain data collected during treatment will be used to assess CBD treatment success rate relative to placebo at achieving 50% pain intensity reduction during treatment duration. The proportion of patients no longer experiencing significant pain symptoms at the 3-month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for repeated measures with covariables mTBI and orthopedic surgery and treatment as factor will be used to assess between-group treatment effects on total opioids use at both 1 and 3-month follow-ups. The same approach will be used to assess between-group treatment effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

Discontinuation

Participants may withdraw from this research project at any time without giving reasons. Discontinuation of treatment does not imply withdrawal from the trial. The following reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of consent by the participant, failure to pass the selection phase, meeting an exclusion criterion, failure to participate in follow-up, termination of the trial by the investigator,

major protocol deviation incompatible with trial participation, an adverse event or any other condition which, in the opinion of the investigator, would expose the participant to undue risk by continuing the treatment trial, any condition that the investigator considers medically necessary to withdraw the patient from the trial.

Adherence

During the baseline visit, a research team member will conduct an information session to discuss the significance of adhering to the guidelines related to doses, timing of drug administration, the procedure to be followed in case of a missed dose, and the importance of reporting any adverse event. Automatic SMS reminders will be sent to ensure completion of the digital VAS and medication diary. A high protocol adherence is expected given that cannabidiol has limited adverse side effects, and the administration is oral and non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics. For adherence purposes, patients will be instructed to return all treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant will receive financial compensation for costs incurred during their participation in this research study. Participants who withdraw or are withdrawn from the project prior to its completion will receive an amount proportional to the length of their participation.

Safety and serious adverse events

Risks of adverse effects are considered low given the demonstrated excellent safety profile of CBD (33, 35). Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased appetite are the most probable adverse events associated with CBD in adult patients (34).

Participants will be instructed to advise the research team of any adverse events which will be thoroughly monitored and documented. Access to on-duty emergency physicians at HSCM will be provided during the entire treatment duration.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study.

Confidentiality

All data collected in our databases will be stored following a de-identification process. Participants will be identified by a unique identification code, and nominal data will be protected separately. Uncoded data will only be accessible to the principal investigator. No identifying data will be disclosed in any scientific communication or publication.

Ethics and dissemination

Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki. The results will be published in a peer-reviewed journal and presented at local, national, and international conferences.

Author Contributions

DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript. All authors contributed to the revisions of the manuscript.

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Competing interests: None declared.

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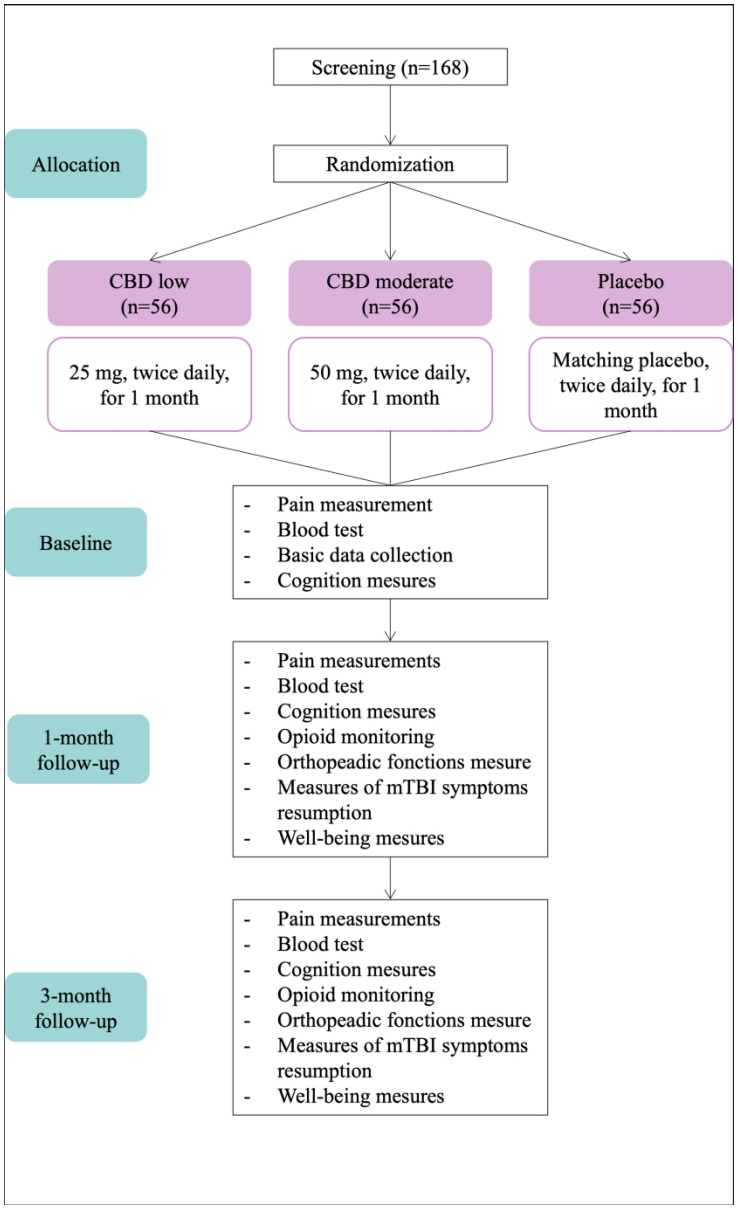

Figure 1 - Study schema

171x281mm (300 x 300 DPI)

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
Secondary outcomes	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X
	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X
	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
Other	Pain Catastrophizing Scale (PCS)		X			
	Treatment Expectation Questionnaire (TEX-Q)		X			
	PTSD Checklist for DSM-5 (PCL-5)		X		X	
	Treatment assignation hypothesis				X	
	Opioid consomption	X	X	X	X	X
	Adverse events			X	X	

Table 1. Schedule of assessment

172x213mm (144 x 144 DPI)

BMJ Open

Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Secondary Subject Heading:	Global health
Keywords:	Clinical Trial, PAIN MANAGEMENT, Orthopedics, Fractures, Bone

Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on ClinicalTrials.gov)

Strengths and limitations of this study

- This is the first human randomized clinical trial to assess the potential therapeutic effects of cannabidiol on pain and inflammation following orthopaedic trauma.
- This trial includes a longitudinal assessment of CBD treatment on pain symptoms and trauma-related outcomes up to three months post-fracture which marks the critical period of transition to chronic pain.
- To help gain a more comprehensive understanding of the effects of pain mediators on treatment response, as well as the effects of treatment on opioid uptake, this study will assess potential interactions between pain mediators, such as opioids, mild traumatic brain injury and sex, and response to CBD treatment.
- One limitation of this study is that therapeutic drug monitoring was not performed, which could have helped account for inter-individual variability and optimize dosing.

Introduction

Bone fractures are a prevalent condition affecting individuals of all ages and are the most commonly treated trauma in hospitals [1, 2]. In 2019, the estimated annual incidence of new fractures worldwide was 178 million [3]. The process of bone healing involves multiple consecutive and interrelated phases including inflammation, repair, and remodeling, which occur in a spatial and temporal series of dynamic processes [4, 5]. The skeletal system possesses a remarkable capacity for regeneration. The initial process of bone healing typically occurs over a period of eight weeks [6], while bone remodeling extends for months following a fracture [7].

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1β, IL-6, IL-10) and the tumor necrosis factor (TNF- α) [8]. In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) [9]. Persistent CNS inflammation plays a key mediating role in central sensitization [10], a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life [10], is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures [11]. A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female sex, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture [12-16].

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living [17]. In addition, patients with orthopedic trauma report a deterioration in their quality of life up to twelve months following the injury [17, 18]. However, pain emerges as the most prominent complaint, with 97% of patients reporting pain after an orthopedic injury [1, 19]. Acute pain management is a crucial concern considering that inadequate pain control can lead to prolonged inflammation, which can

perpetuate pain signals and lead to chronic pain [20, 21]. Currently, a pharmacological approach is widely recommended to manage acute post-trauma pain. Both non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-inflammatory and analgesic effects [22]. Nevertheless, the use of NSAIDs has been associated with delayed bone healing [23, 24] as well as digestive complication and kidney failure [25]. As for opioids, in addition to major side effects, they pose a high risk of dependence and tolerance [4, 26]. Furthermore, several studies show that opioids inhibit effective bone remodeling [27], increase the risk of pseudarthrosis [28], and heighten the risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central sensitization [26].

Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic pain admissions was observed, leading experts to question the potentially beneficial effects of cannabis on pain [29]. Indeed, one study found that 61% of medical cannabis users reported consuming it to alleviate pain [30, 31]. However, the medical use of cannabis is limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due to its low affinity with the CB1 receptor [32]. It is of particular interest as it is devoid of addictive effects [33, 34] and has an excellent safety profile [35], and its use does not affect daily activities such as driving or working.

CBD is highly lipophilic which facilitates its ability to cross the blood-brain barrier [36]. However, the bioavailability of CBD varies greatly according to the method of

administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect, with approximately 5% of the product reaching the bloodstream [37-39]. Food consumption as well as nanotech and oil-based formulations of CBD have been shown to increase bioavailability [40]. However, compared to smoked CBD, oral administration of CBD presents multiple advantages, including greater control over dosage, ease of administration, and fewer side effects [38].

Mechanisms of action of CBD are complex, not yet fully understood and involve multiple pharmacological targets. Emerging evidence suggests that CBD exerts a number of important effects via its modulating role on several non-cannabinoid receptors and ion channels including those of endogenous neurotransmitters, such as serotonin [41] as well as several types of transient receptor potential channels (TRP), such as TRPV1 [42], and by modulating the binding affinity of certain G protein-coupled receptors [43]. Several in vitro and animal model studies have demonstrated CBD's anti-inflammatory effect, notably by reducing pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, in addition to inhibiting microglial activation [32, 42, 44-51]. CBD has also shown analgesic potential in studies using neuropathic and inflammatory pain models. These human and animal studies suggest a reduction in pain, hyperalgesia, and allodynia following treatment with CBD [35, 52-59]. CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in several animal and human studies [60-66]. In addition, a well-controlled preliminary animal study showed that CBD, but not THC, enhanced the biomechanical properties of healing mid-femoral fractures in rats, supporting a beneficial effect of CBD on bone healing [67].

Epidemiological studies have suggested a reduction in opioid use for pain coinciding with an increased use of medical cannabis [30], a trend also documented in Canada [68]. While the interaction between CBD and opioids is not yet fully understood, studies have shown that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors [69]. CBD was also shown to potentially enhance the analgesic effects of endogenous and exogenous opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic pain resulted in a reduction in opioid consumption and improvements in overall quality of life [70].

Providing effective pain management for patients with fractures is not only a fundamental right but also offers numerous benefits. It reduces stress, shortens hospitalization time, decreases associated healthcare costs and lowers the risk of developing chronic pain [1]. Preventing chronic pain is easier than reversing the sensitization processes that cause it [71], making acute pain control a priority. Given its excellent safety profile [33, 35] coupled with its downregulating effects on microglial and inflammatory activity, the primary neuroinflammatory and pain mechanism, CBD represents an appealing neuroprotective agent for pain-susceptible orthopedic trauma patients.

Study objectives

The primary objective of this study is to evaluate the effects of CBD treatment on self-reported pain in patients following a long bone fracture injury. The second objective is to assess the effect of the CBD treatment on inflammation and patient well-being.

Additionally, secondary analyses will look at the possible associations between pain mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to CBD treatment. The aim is to better identify the effects of these pain mediators on treatment response and the impact of CBD treatment on opioid uptake.

Methods

Study design

This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the effects of two doses (low and moderate) of CBD compared to a placebo on pain and inflammation after a long bone fracture.

Participants

A total of 225 participants aged 18 to 70 will be recruited within one week after their long bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM), one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic patients treated annually. The planned age range, targeting a population representative of individuals who frequently experience traumatic fractures, was chosen as it allows for a more homogenous evaluation of fracture healing and pain recovery. Including participants over 70 introduces additional challenges, such as increased comorbidities, chronic diseases, bone fragility, polymedication and increased complications, which could slow the healing process, influence pain perception and complicate result interpretation.

Inclusion criteria

Subjects meeting the following criteria are eligible for the trial:

- Patients with a long bone fracture of the lower limb (tibia, fibula, femur, metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals, and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one week of the accident
- Participants is between 18 and 70 years of age
- Patients with or without surgical procedures

Exclusion criteria

Patients presenting any of the following characteristics are not eligible for the trial:

- Moderate/severe traumatic brain injury (TBI)
- Diagnosis of any of the following mental disorders as defined by the DSM-5: schizophrenia, intellectual disability, bipolar disorder, major depression, a diagnosed and untreated sleep disorders
- History of alcohol or opioid misuse/abuse, as defined by the DSM-5
- Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)
- Pregnant or lactating women, women of childbearing potential who are not using medically accepted forms of contraception (e.g., condoms, oral contraceptive or intrauterine device), or women who are actively planning on becoming pregnant
- History of adverse reactions to cannabis
- Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the injury

- Patients experiencing on average mild-to-absent pain in the last 24h preceding recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))
- Transport business drivers and heavy machinery operators
- A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)
- Not having French or English as a spoken language
- A weighted MoCA score of less than 24
- Regular cannabis use more than 5 times a week

Recruitment

Recruitment will begin in January 2025 and end in January 2027. Potential participants will be screened daily by the research team and collaborators. Potentially eligible patients will be approached by a research team member and provided with a consent form. Once the research team has addressed any remaining questions and obtained a signed consent form, the participant will be randomized. See figure 1 for an overview of the study timeline.

Assignment of interventions

Participants will undergo concealed randomization to avoid selection bias. The study pharmacist will randomly assign participants to one of the three treatment groups (low or moderate CBD or placebo) using a 1:1:1 ratio through block randomization with randomly selected block sizes, stratified by sex, age (i.e., participants aged 45 and under, and those over 45) and type of fracture (i.e., lower and upper limb). The randomization procedure will be performed a priori by an independent biostatistician. Identical tablets for CBD and

placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study pharmacist will be aware of allocation but will have no clinical or interpretive role. Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate allocation concealment. In the event of a serious adverse event or reaction, the allocation list can be retrieved.

Intervention

Patients in the treatment group will receive either a low dose (25 mg per tablet) or a moderate dose (50 mg per tablet) of CBD self-administered orally as a tablet twice daily with a meal for one month. Patients in the placebo group will receive an identical amount of a matching placebo administered with a meal twice daily for one month.

Investigational product

CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto, Canada). The pharmacokinetic profile of the CBD product has already been established, and efforts to register the product with Health Canada have begun.

Dose justification

A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various conditions [72, 73]. The low dose (25 mg) selected for our study is based on initial and ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per day [65]. This is also approximately the mean dose of CBD administered in a successful

trial of Sativex (THC/CBD) for neuropathic pain [74]. Moreover, a higher but relatively moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD doses in this range have shown no statistical difference in intoxication scores in healthy volunteers [75] and doses of up to 800 mg per day for a minimum of 4 weeks showed an excellent safety and tolerability profile [76 , 77]. Participants will be advised to ingest the treatment at mealtime, as studies have shown an increased bioavailability of CBD in subjects after eating [78, 79]. To achieve our primary goal of mitigating acute pain, a one-month treatment period has been selected, aligning with the typical evolution of acute pain post-fracture [6].

Study procedure

Upon enrollment in the study, research staff will provide study instructions, collect baseline data (e.g., demographics and clinical characteristics), administer questionnaires and cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines. Patients will report their pain intensity at baseline, and then three times a week throughout the entire one-month treatment duration. Participants will be instructed to complete a daily medication diary for one month to monitor the administration of study product, as well as opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD

consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Table 1. Schedule of assessment

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
Secondary outcomes	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X
	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X
	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
Other	Pain Catastrophizing Scale (PCS)		X			

	Treatment Expectation Questionnaire (TEX-Q)		X			
	PTSD Checklist for DSM-5 (PCL-5)		X		X	
	Treatment assignation hypothesis				X	
	Opioid consomption	X	X	X	X	X
	Adverse events			X	X	

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) [80]. Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with anchor words ranging from “no pain” to “worst imaginable pain”. Participants will indicate the intensity of their pain at that moment by placing a mark along the line.

Secondary outcomes

At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers, quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and orthopaedic function outcomes will be collected. In addition, at baseline, participants will be asked to indicate their level of treatment expectation using the Treatment Expectation Questionnaire (TEX-Q-F) [81], a fifteen-question questionnaire, considering the potential modulation of therapeutic effects by patients' expectations of treatment [82, 83]. After treatment completion, participants will also be asked to indicate whether they felt they had received active treatment or placebo.

Measures

Demographic and clinical characteristics

The following information will be collected at baseline to characterize participants: age, sex, height, weight, percentage of adipose tissue using an impedance meter scale, occupation, education level, ethnicity, language spoken, pre-morbid medical history (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs, cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and severity, mechanism of injury.

Pain

At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain Inventory short form (BPI-sf) [84], a 9-item self-report questionnaire assessing for the presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief treatment, and pain interference with activities of daily living. In addition, pain will be assessed using the VAS at several time points for comparison: baseline, three times per week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing Scale [85], a 13-item questionnaire evaluated on Likert scales, given the significant contribution of psychological factors in the experience of pain.

Opioid usage

Participants will continue their usual pain care regimen throughout the study. Opioid usage and analgesic will be recorded in a daily medication diary for the initial month and through

the number of prescription refills for months two and three. Self-reported opioid use in a diary has been shown to be an accurate assessment of the quantity of opioids consumed [86].

Inflammation

Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1β) and TNF-α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as per manufacturer recommendation. Simoa is a leader in the quantification of plasma biomarkers with markedly lower detection threshold than traditional ELISA [87].

Cognition

At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain, and that do not require the use of the fractured limb, will be administered: a task assessing information processing speed (Symbol Search from the WAIS-IV Battery), two memory tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test (Elevator counting with distraction and Elevator counting without distraction from the Test of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).

Mild TBI symptoms resolution

Patients who sustained a concomitant mTBI with their fracture will be included in the study. Additional measures will be documented to control for this variable. At 1 and 3-months follow-up, information on mTBI symptoms resolution will be collected for patients diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion Questionnaire [88].

Orthopaedic function

At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA) Questionnaire [89] will be administered. The SMFA includes 34 questions that evaluate patient's function, and 12 questions related to how bothered patients are by their symptoms.

Well-being

At 1 and 3-months follow-ups, various important domains of well-being significantly modulated by pain will be measured including: quality of life using the Short Form (36) Health Survey [90], a 36-item self-report questionnaire for measuring quality of life across 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) [91], a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks. Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms will be assessed using the Beck's Depression Inventory-II (BDI-II) [92] and the Beck's Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms

of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up using the PTSD Checklist for DSM-5 (PCL-5) questionnaire [93].

Data management

Data collected will be transcribed from the source documents into the electronic Case Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-Montréal [94] and quality controlled by a second qualified staff member. Data will be stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

Sample size estimation

A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in the CBD group and expected 20% in the placebo group) has been used extensively to reflect clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect a statistically significant difference in the proportion of patients who reaches 30% pain reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout rate of 20% and a significance level of 5%. These parameters are taken from a successful randomised, placebo-controlled clinical trial using Sativex© in treating 125 neuropathic pain patients [74].

Moreover, considering that the placebo group may ingest more opiates and that the anticipated inter-group effect at one month may be reduced to 20%, a total sample size of 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20% and a significance level of 5%.

Primary outcome

The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the mean VAS pain score at the 1-month follow-up.

Secondary outcomes

For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on VAS pain data collected during treatment will be used to assess CBD treatment success rate relative to placebo at achieving 50% pain intensity reduction during treatment duration. The proportion of patients no longer experiencing significant pain symptoms at the 3-month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for repeated measures with covariables mTBI and orthopedic surgery and treatment as factor will be used to assess between-group treatment effects on total opioids use at both 1 and 3-month follow-ups. The same approach will be used to assess between-group treatment effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

Analyses will be performed on an intention-to-treat (ITT) dataset. The ITT dataset will include all participants randomized in the analysis, whether or not they have completed treatment in order to limit bias and reflect results under real treatment conditions.

Missing data will be reported and justified in the results. The multiple imputation method, which has been recognized in clinical studies involving experimental treatment, will be applied. Additionally, a sensitivity analysis will be performed to assess the impact of missing data on the results.

Discontinuation

Participants may withdraw from this research project at any time without giving reasons. Discontinuation of treatment does not imply withdrawal from the trial. The following reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of consent by the participant, failure to pass the selection phase, meeting an exclusion criterion, failure to participate in follow-up, termination of the trial by the investigator, major protocol deviation incompatible with trial participation, an adverse event or any other condition which, in the opinion of the investigator, would expose the participant to undue risk by continuing the treatment trial, any condition that the investigator considers medically necessary to withdraw the patient from the trial.

Adherence

During the baseline visit, a research team member will conduct an information session to discuss the significance of adhering to the guidelines related to doses, timing of drug

administration, the procedure to be followed in case of a missed dose, and the importance of reporting any adverse event. Automatic SMS reminders will be sent to ensure completion of the digital VAS and medication diary. A high protocol adherence is expected given that cannabidiol has limited adverse side effects, and the administration is oral and non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics[95]. For adherence purposes, patients will be instructed to return all treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant will receive financial compensation for costs incurred during their participation in this research study. Participants who withdraw or are withdrawn from the project prior to its completion will receive an amount proportional to the length of their participation.

Safety and serious adverse events

Risks of adverse effects are considered low given the demonstrated excellent safety profile of CBD [33, 35]. Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased appetite are the most probable adverse events associated with CBD in adult patients [34]. Participants will be instructed to advise the research team of any adverse events which will be thoroughly monitored and documented. Access to on-duty emergency physicians at HSCM will be provided during the entire treatment duration.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study.

Confidentiality

All data collected in our databases will be stored following a de-identification process. Participants will be identified by a unique identification code, and nominal data will be protected separately. Uncoded data will only be accessible to the principal investigator. No identifying data will be disclosed in any scientific communication or publication.

Ethics and dissemination

Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki. The results will be published in a peer-reviewed journal and presented at local, national, and international conferences.

Author Contributions

DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript. All authors contributed to the revisions of the manuscript. LDB is guarantor.

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EmpowerPharm (Ontario, Canada). The study's design, management, analysis, and reporting are entirely independent of the CBD manufacturers.

Competing interests: None declared.

Figure 1. Study Schema. CBD, cannabidiol; mTBI, mild traumatic brain injury.

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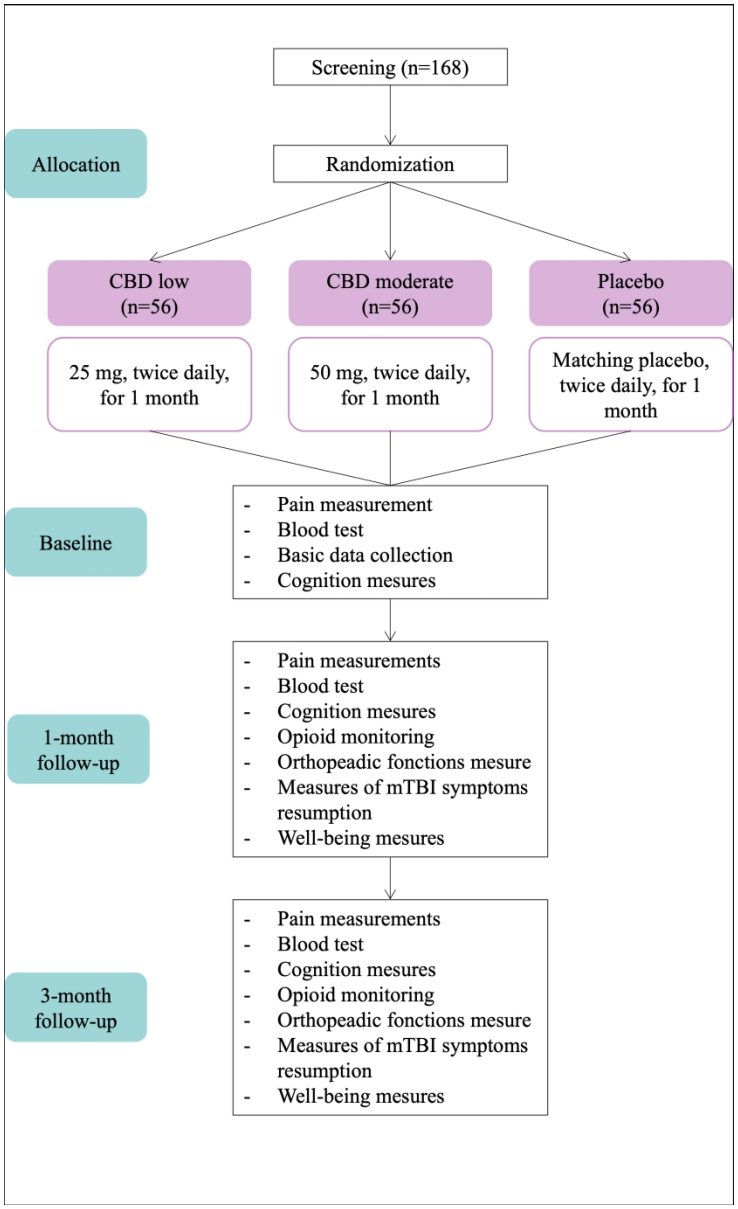

Figure 1 - Study schema

171x281mm (330 x 330 DPI)

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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on ClinicalTrials.gov)

Strengths and limitations of this study

- This study is robust due to its triple-blind randomized, placebo-controlled design, which assesses the effects of two different doses of pharmaceutical-grade CBD.
- The extensive number of measurements allows for a comprehensive assessment of the treatment's impact, not only by evaluating patients' perceived well-being and recovery but also by objectively quantifying CBD's effect on inflammation through inflammatory markers.
- This trial includes a longitudinal assessment of CBD treatment on pain symptoms and trauma-related outcomes up to three months post-fracture, a critical period marking the transition to chronic pain, however, the long-term effects of the treatment will not be assessed.
- One limitation is the exclusion of osteoporotic patients, as well as a potential restriction in the inclusion of women, since those of childbearing age who are not using contraception will have to be excluded due to limited knowledge on the teratogenic effects of CBD.
- One limitation of this study is that therapeutic drug monitoring was not performed, which could have helped account for inter-individual variability and optimize dosing.

Introduction

Bone fractures are a prevalent condition affecting individuals of all ages and are the most commonly treated trauma in hospitals [1, 2]. In 2019, the estimated annual incidence of new fractures worldwide was 178 million [3]. The process of bone healing involves multiple consecutive and interrelated phases including inflammation, repair, and

remodeling, which occur in a spatial and temporal series of dynamic processes [4, 5]. The skeletal system possesses a remarkable capacity for regeneration. The initial process of bone healing typically occurs over a period of eight weeks [6], while bone remodeling extends for months following a fracture [7].

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1β, IL-6, IL-10) and the tumor necrosis factor (TNF- α) [8]. In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) [9]. Persistent CNS inflammation plays a key mediating role in central sensitization [10], a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life [10], is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures [11]. A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female sex, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture [12-16].

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living [17]. In addition, patients with orthopedic trauma report

a deterioration in their quality of life up to twelve months following the injury [17, 18]. However, pain emerges as the most prominent complaint, with 97% of patients reporting pain after an orthopedic injury [1, 19]. Acute pain management is a crucial concern considering that inadequate pain control can lead to prolonged inflammation, which can perpetuate pain signals and lead to chronic pain [20, 21]. Currently, a pharmacological approach is widely recommended to manage acute post-trauma pain. Both non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-inflammatory and analgesic effects [22]. Nevertheless, the use of NSAIDs has been associated with delayed bone healing [23, 24] as well as digestive complication and kidney failure [25]. As for opioids, in addition to major side effects, they pose a high risk of dependence and tolerance [4, 26]. Furthermore, several studies show that opioids inhibit effective bone remodeling [27], increase the risk of pseudarthrosis [28], and heighten the risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central sensitization [26].

Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic pain admissions was observed, leading experts to question the potentially beneficial effects of cannabis on pain [29]. Indeed, one study found that 61% of medical cannabis users reported consuming it to alleviate pain [30, 31]. However, the medical use of cannabis is limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due to its low affinity with the CB1 receptor [32]. It is of particular interest as it is devoid of

addictive effects [33, 34] and has an excellent safety profile [35], and its use does not affect daily activities such as driving or working.

CBD is highly lipophilic which facilitates its ability to cross the blood-brain barrier [36]. However, the bioavailability of CBD varies greatly according to the method of administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect, with approximately 5% of the product reaching the bloodstream [37-39]. Food consumption as well as nanotech and oil-based formulations of CBD have been shown to increase bioavailability [40]. However, compared to smoked CBD, oral administration of CBD presents multiple advantages, including greater control over dosage, ease of administration, and fewer side effects [38].

Mechanisms of action of CBD are complex, not yet fully understood and involve multiple pharmacological targets. Emerging evidence suggests that CBD exerts a number of important effects via its modulating role on several non-cannabinoid receptors and ion channels including those of endogenous neurotransmitters, such as serotonin [41] as well as several types of transient receptor potential channels (TRP), such as TRPV1 [42], and by modulating the binding affinity of certain G protein-coupled receptors [43]. Several in vitro and animal model studies have demonstrated CBD's anti-inflammatory effect, notably by reducing pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, in addition to inhibiting microglial activation [32, 42, 44-51]. CBD has also shown analgesic potential in studies using neuropathic and inflammatory pain models. These human and animal studies suggest a reduction in pain, hyperalgesia, and allodynia following treatment with CBD [35,

52-59]. CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in several animal and human studies [60-66]. In addition, a well-controlled preliminary animal study showed that CBD, but not THC, enhanced the biomechanical properties of healing mid-femoral fractures in rats, supporting a beneficial effect of CBD on bone healing [67].

Epidemiological studies have suggested a reduction in opioid use for pain coinciding with an increased use of medical cannabis [30], a trend also documented in Canada [68]. While the interaction between CBD and opioids is not yet fully understood, studies have shown that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors [69]. CBD was also shown to potentially enhance the analgesic effects of endogenous and exogenous opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic pain resulted in a reduction in opioid consumption and improvements in overall quality of life [70].

Providing effective pain management for patients with fractures is not only a fundamental right but also offers numerous benefits. It reduces stress, shortens hospitalization time, decreases associated healthcare costs and lowers the risk of developing chronic pain [1]. Preventing chronic pain is easier than reversing the sensitization processes that cause it [71], making acute pain control a priority. Given its excellent safety profile [33, 35] coupled with its downregulating effects on microglial and inflammatory activity, the primary neuroinflammatory and pain mechanism, CBD represents an appealing neuroprotective agent for pain-susceptible orthopedic trauma patients.

Study objectives

The primary objective of this study is to evaluate the effects of CBD treatment on self-reported pain in patients following a long bone fracture injury. The second objective is to assess the effect of the CBD treatment on inflammation and patient well-being. Additionally, secondary analyses will look at the possible associations between pain mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to CBD treatment. The aim is to better identify the effects of these pain mediators on treatment response and the impact of CBD treatment on opioid uptake.

Methods

Study design

This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the effects of two doses (low and moderate) of CBD compared to a placebo on pain and inflammation after a long bone fracture.

Participants

A total of 225 participants aged 18 to 70 will be recruited within one week after their long bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM), one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic patients treated annually. The planned age range, targeting a population representative of individuals who frequently experience traumatic fractures, was chosen as it allows for a more homogenous evaluation of fracture healing and pain recovery. Including participants

over 70 introduces additional challenges, such as increased comorbidities, chronic diseases, bone fragility, polymedication and increased complications, which could slow the healing process, influence pain perception and complicate result interpretation.

Inclusion criteria

Subjects meeting the following criteria are eligible for the trial:

- Patients with a long bone fracture of the lower limb (tibia, fibula, femur, metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals, and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one week of the accident
- Participants is between 18 and 70 years of age
- Patients with or without surgical procedures

Exclusion criteria

Patients presenting any of the following characteristics are not eligible for the trial:

- Moderate/severe traumatic brain injury (TBI)
- Diagnosis of any of the following mental disorders as defined by the DSM-5: schizophrenia, intellectual disability, bipolar disorder, major depression, a diagnosed and untreated sleep disorders
- History of alcohol or opioid misuse/abuse, as defined by the DSM-5
- Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)

- Pregnant or lactating women, women of childbearing potential who are not using medically accepted forms of contraception (e.g., condoms, oral contraceptive or intrauterine device), or women who are actively planning on becoming pregnant
- History of adverse reactions to cannabis
- Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the injury
- Patients experiencing on average mild-to-absent pain in the last 24h preceding recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))
- Transport business drivers and heavy machinery operators
- A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)
- Not having French or English as a spoken language
- A weighted MoCA score of less than 24
- Regular cannabis use more than 5 times a week

Recruitment

Recruitment will begin in January 2025 and end in January 2027. Potential participants will be screened daily by the research team and collaborators. Potentially eligible patients will be approached by a research team member and provided with a consent form. Once the research team has addressed any remaining questions and obtained a signed consent form, the participant will be randomized. See figure 1 for an overview of the study timeline.

Assignment of interventions

Participants will undergo concealed randomization to avoid selection bias. The study pharmacist will randomly assign participants to one of the three treatment groups (low or moderate CBD or placebo) using a 1:1:1 ratio through block randomization with randomly selected block sizes (9 and 12), stratified by sex, age (i.e., participants aged 45 and under, and those over 45) and type of fracture (i.e., lower and upper limb). The randomization procedure will be performed a priori by an independent biostatistician. Identical tablets for CBD and placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study pharmacist will be aware of allocation but will have no clinical or interpretive role. Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate allocation concealment. In the event of a serious adverse event or reaction, the allocation list can be retrieved.

Intervention

Patients in the treatment group will receive either a low dose (25 mg per tablet) or a moderate dose (50 mg per tablet) of CBD self-administered orally as a tablet twice daily with a meal for one month. Patients in the placebo group will receive an identical amount of a matching placebo administered with a meal twice daily for one month.

Investigational product

CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto, Canada). The pharmacokinetic profile of the CBD product has already been established, and efforts to register the product with Health Canada have begun.

Dose justification

A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various conditions [72, 73]. The low dose (25 mg) selected for our study is based on initial and ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per day [65]. This is also approximately the mean dose of CBD administered in a successful trial of Sativex (THC/CBD) for neuropathic pain [74]. Moreover, a higher but relatively moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD doses in this range have shown no statistical difference in intoxication scores in healthy volunteers [75] and doses of up to 800 mg per day for a minimum of 4 weeks showed an excellent safety and tolerability profile [76 , 77]. Participants will be advised to ingest the treatment at mealtime, as studies have shown an increased bioavailability of CBD in subjects after eating [78, 79]. To achieve our primary goal of mitigating acute pain, a one-month treatment period has been selected, aligning with the typical evolution of acute pain post-fracture [6].

Study procedure

Upon enrollment in the study, research staff will provide study instructions, collect baseline data (e.g., demographics and clinical characteristics), administer questionnaires and cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines. Patients will report their pain intensity at baseline, and then three times a week throughout the entire one-month treatment duration. Participants will be instructed to complete a daily medication diary for one month to monitor the administration of study product, as well as

opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Table 1. Schedule of assessment

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
Secondary outcomes	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X
	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X

	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
Other	Pain Catastrophizing Scale (PCS)		X			
	Treatment Expectation Questionnaire (TEX-Q)		X			
	PTSD Checklist for DSM-5 (PCL-5)		X		X	
	Treatment assignation hypothesis				X	
	Opioid consomption	X	X	X	X	X
	Adverse events			X	X	

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) [80]. Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with anchor words ranging from "no pain" to "worst imaginable pain". Participants will indicate the intensity of their pain at that moment by placing a mark along the line.

Secondary outcomes

At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers, quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and orthopaedic function outcomes will be collected. In addition, at baseline, participants will

be asked to indicate their level of treatment expectation using the Treatment Expectation Questionnaire (TEX-Q-F) [81], a fifteen-question questionnaire, considering the potential modulation of therapeutic effects by patients' expectations of treatment [82, 83]. After treatment completion, participants will also be asked to indicate whether they felt they had received active treatment or placebo.

Measures

Demographic and clinical characteristics

The following information will be collected at baseline to characterize participants: age, sex, height, weight, percentage of adipose tissue using an impedance meter scale, occupation, education level, ethnicity, language spoken, pre-morbid medical history (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs, cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and severity, mechanism of injury.

Pain

At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain Inventory short form (BPI-sf) [84], a 9-item self-report questionnaire assessing for the presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief treatment, and pain interference with activities of daily living. In addition, pain will be assessed using the VAS at several time points for comparison: baseline, three times per week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing

Scale [85], a 13-item questionnaire evaluated on Likert scales, given the significant contribution of psychological factors in the experience of pain.

Opioid usage

Participants will continue their usual pain care regimen throughout the study. Opioid usage and analgesic will be recorded in a daily medication diary for the initial month and through the number of prescription refills for months two and three. Self-reported opioid use in a diary has been shown to be an accurate assessment of the quantity of opioids consumed [86].

Inflammation

Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1β) and TNF-α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as per manufacturer recommendation. Simoa is a leader in the quantification of plasma biomarkers with markedly lower detection threshold than traditional ELISA [87].

Cognition

At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain, and that do not require the use of the fractured limb, will be administered: a task assessing

information processing speed (Symbol Search from the WAIS-IV Battery), two memory tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test (Elevator counting with distraction and Elevator counting without distraction from the Test of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).

Mild TBI symptoms resolution

Patients who sustained a concomitant mTBI with their fracture will be included in the study. Additional measures will be documented to control for this variable. At 1 and 3-months follow-up, information on mTBI symptoms resolution will be collected for patients diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion Questionnaire [88].

Orthopaedic function

At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA) Questionnaire [89] will be administered. The SMFA includes 34 questions that evaluate patient's function, and 12 questions related to how bothered patients are by their symptoms.

Well-being

At 1 and 3-months follow-ups, various important domains of well-being significantly modulated by pain will be measured including: quality of life using the Short Form (36) Health Survey [90], a 36-item self-report questionnaire for measuring quality of life across 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) [91],

a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks. Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms will be assessed using the Beck's Depression Inventory-II (BDI-II) [92] and the Beck's Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up using the PTSD Checklist for DSM-5 (PCL-5) questionnaire [93].

Data management

Data collected will be transcribed from the source documents into the electronic Case Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-Montréal [94] and quality controlled by a second qualified staff member. Data will be stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

Sample size estimation

A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in the CBD group and expected 20% in the placebo group) has been used extensively to reflect clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample

size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect a statistically significant difference in the proportion of patients who reaches 30% pain reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout rate of 20% and a significance level of 5%. These parameters are taken from a successful randomised, placebo-controlled clinical trial using Sativex© in treating 125 neuropathic pain patients [74].

Moreover, considering that the placebo group may ingest more opiates and that the anticipated inter-group effect at one month may be reduced to 20%, a total sample size of 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20% and a significance level of 5%.

Primary outcome

The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the mean VAS pain score at the 1-month follow-up.

Secondary outcomes

For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on VAS pain data collected during treatment will be used to assess CBD treatment success rate relative to placebo at achieving 50% pain intensity reduction during treatment duration. The proportion of patients no longer experiencing significant pain symptoms at the 3-month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for

repeated measures with covariables mTBI and orthopedic surgery and treatment as factor will be used to assess between-group treatment effects on total opioids use at both 1 and 3-month follow-ups. The same approach will be used to assess between-group treatment effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

Analyses will be performed on an intention-to-treat (ITT) dataset. The ITT dataset will include all participants randomized in the analysis, whether or not they have completed treatment in order to limit bias and reflect results under real treatment conditions.

Missing data will be reported and justified in the results. The multiple imputation method, which has been recognized in clinical studies involving experimental treatment, will be applied. Additionally, a sensitivity analysis will be performed to assess the impact of missing data on the results.

Discontinuation

Participants may withdraw from this research project at any time without giving reasons. Discontinuation of treatment does not imply withdrawal from the trial. The following reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of consent by the participant, failure to pass the selection phase, meeting an exclusion criterion, failure to participate in follow-up, termination of the trial by the investigator, major protocol deviation incompatible with trial participation, an adverse event or any other condition which, in the opinion of the investigator, would expose the participant to

undue risk by continuing the treatment trial, any condition that the investigator considers medically necessary to withdraw the patient from the trial.

Adherence

During the baseline visit, a research team member will conduct an information session to discuss the significance of adhering to the guidelines related to doses, timing of drug administration, the procedure to be followed in case of a missed dose, and the importance of reporting any adverse event. Automatic SMS reminders will be sent to ensure completion of the digital VAS and medication diary. A high protocol adherence is expected given that cannabidiol has limited adverse side effects, and the administration is oral and non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics[95]. For adherence purposes, patients will be instructed to return all treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant will receive financial compensation for costs incurred during their participation in this research study. Participants who withdraw or are withdrawn from the project prior to its completion will receive an amount proportional to the length of their participation.

Safety and serious adverse events

Risks of adverse effects are considered low given the demonstrated excellent safety profile of CBD [33, 35]. Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased appetite are the most probable adverse events associated with CBD in adult patients [34]. Participants will be instructed to advise the research team of any adverse events which will

be thoroughly monitored and documented. Access to on-duty emergency physicians at HSCM will be provided during the entire treatment duration.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study.

Confidentiality

All data collected in our databases will be stored following a de-identification process. Participants will be identified by a unique identification code, and nominal data will be protected separately. Uncoded data will only be accessible to the principal investigator. No identifying data will be disclosed in any scientific communication or publication.

Ethics and dissemination

Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki. The results will be published in a peer-reviewed journal and presented at local, national, and international conferences.

Author Contributions

DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript. All authors contributed to the revisions of the manuscript. LDB is guarantor.

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Competing interests: None declared.

Figure 1. Study Schema. CBD, cannabidiol; mTBI, mild traumatic brain injury.

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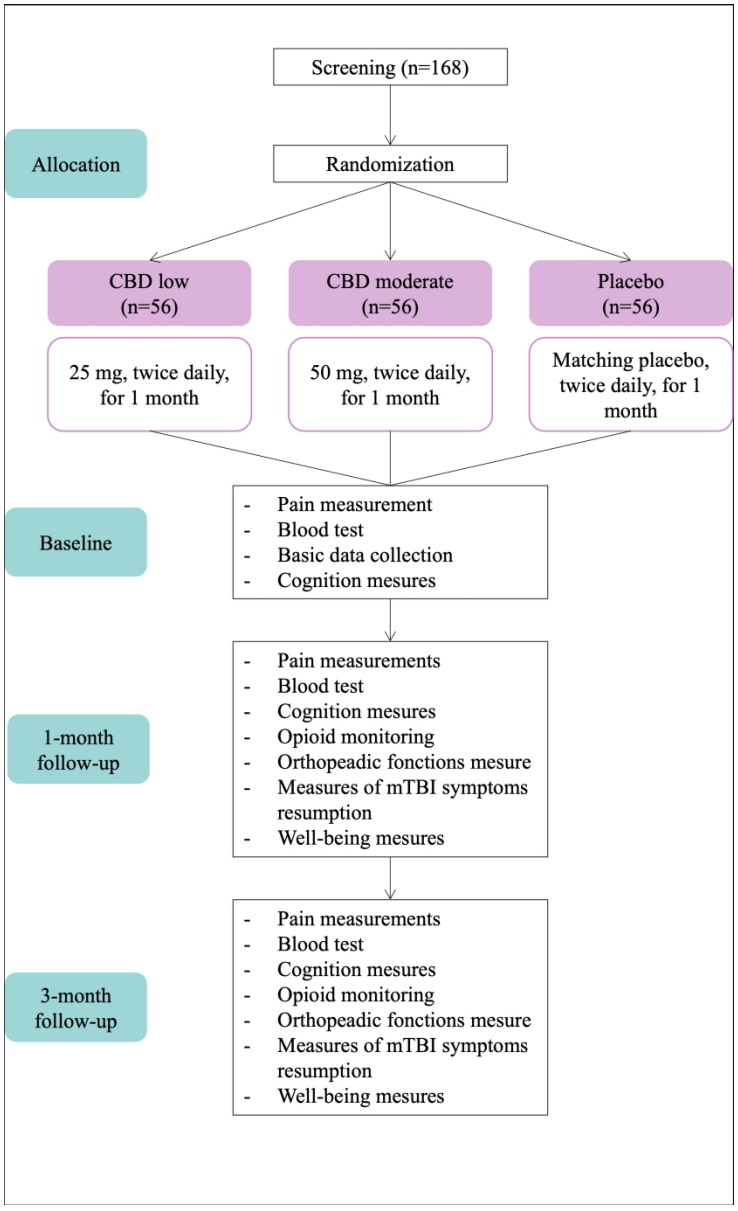

Figure 1 - Study schema

171x281mm (330 x 330 DPI)

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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Impact of an acute 1-month cannabidiol treatment on pain and inflammation after a long bone fracture: a triple-blind randomized, placebo controlled, clinical trial protocol

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Abstract

Introduction. Acute pain levels following orthopedic injury (e.g., fracture) is a predictor of the onset of chronic pain, which affects nearly 50% of fracture patients and impairs functional recovery. Among current pharmacological treatments for acute pain, non-steroidal anti-inflammatory drugs have been associated with delayed bone healing, while opioids inhibit effective bone remodeling, increase the risk of pseudarthrosis, and carry a high risk of addiction. In light of this, the development of new pain treatments is essential.

Cannabidiol (CBD), a non-addictive and non-psychotropic cannabis component stands out as a potential therapeutic agent, given its analgesic and anti-inflammatory properties as well as its potential benefits for bone healing. This randomized controlled trial aims to investigate the effect of acute CBD treatment, compared to placebo, on patients' self-reported pain, inflammation and well-being following a fracture injury.

Methods and analysis. This is a triple-blind, randomized, placebo-controlled clinical trial. A total of 225 adults aged 18 to 70 years, who have suffered a long bone fracture and were treated at the Hôpital du Sacré-Coeur de Montréal, will be randomly assigned within one week to one of three treatment arms (25 mg or 50 mg of CBD or placebo) for one month. The primary outcome will be difference in the pain score between groups at one-month follow-up. Secondary outcomes will include measures of persistent pain, inflammation, opioid usage, quality of life, sleep quality, depression, anxiety, cognition and orthopaedic function. Data will be collected at baseline, 1- and 3-month follow-ups.

Ethics and dissemination. This study obtained a Health Canada license for use of cannabis products. It has also been approved by Health Canada and the Research Ethics Board of the CIUSSS du Nord-de-l'Île-de-Montréal (Project ID 2025-2105). The findings will be published in a peer-reviewed journal and presented at local, national, and international conferences. The trial's results will be made publicly available on the clinicaltrials.gov database.

Trial registration number: NCT06448923 (registered on ClinicalTrials.gov)

Strengths and limitations of this study

- This study is robust due to its triple-blind randomized, placebo-controlled design, which assesses the effects of two different doses of pharmaceutical-grade CBD.
- The extensive number of measurements allows for a comprehensive assessment of the treatment's impact, not only by evaluating patients' perceived well-being and recovery but also by objectively quantifying CBD's effect on inflammation through inflammatory markers.
- This trial includes a longitudinal assessment of CBD treatment on pain symptoms and trauma-related outcomes up to three months post-fracture, a critical period marking the transition to chronic pain, however, the long-term effects of the treatment will not be assessed.
- A limitation is the exclusion of osteoporotic patients, as well as a potential restriction in the inclusion of women, since those of childbearing age who are not using contraception will have to be excluded due to limited knowledge on the teratogenic effects of CBD.
- Another limitation of this study is that therapeutic drug monitoring was not performed, which could have helped account for inter-individual variability and optimize dosing.

Introduction

Bone fractures are a prevalent condition affecting individuals of all ages and are the most commonly treated trauma in hospitals [1, 2]. In 2019, the estimated annual incidence of new fractures worldwide was 178 million [3]. The process of bone healing involves multiple consecutive and interrelated phases including inflammation, repair, and

remodeling, which occur in a spatial and temporal series of dynamic processes [4, 5]. The skeletal system possesses a remarkable capacity for regeneration. The initial process of bone healing typically occurs over a period of eight weeks [6], while bone remodeling extends for months following a fracture [7].

Independent of body location, traumatic injury sets off an acute non-specific immune response characterized by the release of pro-inflammatory cytokines such as interleukins (IL-1β, IL-6, IL-10) and the tumor necrosis factor (TNF- α) [8]. In addition, systemic acute inflammation after bone fracture promotes the sustained release of cytokines disrupting the blood-brain barrier, thereby allowing toxic intruders such as pro-inflammatory cytokines to invade/migrate to the central nervous system (CNS) [9]. Persistent CNS inflammation plays a key mediating role in central sensitization [10], a maladaptive plasticity process driven by an increased response to nociceptive inputs, involved in pain persistence and chronicity. Chronic pain, a condition associated with delayed functional recovery, sleep disturbances, mental health disorders, and poorer quality of life [10], is highly prevalent 3-6 months after trauma, affecting 30-50% of individuals with bone fractures [11]. A number of variables have been identified as potential predictors of chronic pain after trauma, including pain intensity at three months post-accident, female sex, poor sleep, levels of anxiety and depression, and the concomitant occurrence of traumatic brain injury (TBI) or peripheral nerve injury at the time of fracture [12-16].

Following a fracture, patients frequently report a range of symptoms, including increased fatigue and motor impairment, which can exert a significant impact on their ability to perform activities of daily living [17]. In addition, patients with orthopedic trauma report

a deterioration in their quality of life up to twelve months following the injury [17, 18]. However, pain emerges as the most prominent complaint, with 97% of patients reporting pain after an orthopedic injury [1, 19]. Acute pain management is a crucial concern considering that inadequate pain control can lead to prolonged inflammation, which can perpetuate pain signals and lead to chronic pain [20, 21]. Currently, a pharmacological approach is widely recommended to manage acute post-trauma pain. Both non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are frequently prescribed for their anti-inflammatory and analgesic effects [22]. Nevertheless, the use of NSAIDs has been associated with delayed bone healing [23, 24] as well as digestive complication and kidney failure [25]. As for opioids, in addition to major side effects, they pose a high risk of dependence and tolerance [4, 26]. Furthermore, several studies show that opioids inhibit effective bone remodeling [27], increase the risk of pseudarthrosis [28], and heighten the risk of hyperalgesia, i.e. a paradoxical increase in pain sensitivity due to central sensitization [26].

Interestingly, following the legalization of cannabis in Colorado, a reduction in chronic pain admissions was observed, leading experts to question the potentially beneficial effects of cannabis on pain [29]. Indeed, one study found that 61% of medical cannabis users reported consuming it to alleviate pain [30, 31]. However, the medical use of cannabis is limited due to the undesirable psychotropic and addictive effects of tetrahydrocannabinol (THC). Cannabidiol (CBD), an organic component of cannabis, is non-psychoactive due to its low affinity with the CB1 receptor [32]. It is of particular interest as it is devoid of

addictive effects [33, 34] and has an excellent safety profile [35], and its use does not affect daily activities such as driving or working.

CBD is highly lipophilic which facilitates its ability to cross the blood-brain barrier [36]. However, the bioavailability of CBD varies greatly according to the method of administration. The bioavailability of oral CBD is lower due to the hepatic first-pass effect, with approximately 5% of the product reaching the bloodstream [37-39]. Food consumption as well as nanotech and oil-based formulations of CBD have been shown to increase bioavailability [40]. However, compared to smoked CBD, oral administration of CBD presents multiple advantages, including greater control over dosage, ease of administration, and fewer side effects [38].

Mechanisms of action of CBD are complex, not yet fully understood and involve multiple pharmacological targets. Emerging evidence suggests that CBD exerts a number of important effects via its modulating role on several non-cannabinoid receptors and ion channels including those of endogenous neurotransmitters, such as serotonin [41] as well as several types of transient receptor potential channels (TRP), such as TRPV1 [42], and by modulating the binding affinity of certain G protein-coupled receptors [43]. Several in vitro and animal model studies have demonstrated CBD's anti-inflammatory effect, notably by reducing pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, in addition to inhibiting microglial activation [32, 42, 44-51]. CBD has also shown analgesic potential in studies using neuropathic and inflammatory pain models. These human and animal studies suggest a reduction in pain, hyperalgesia, and allodynia following treatment with CBD [35,

52-59]. CBD is alleged to possess anxiolytic and anti-depressant properties, as shown in several animal and human studies [60-66]. In addition, a well-controlled preliminary animal study showed that CBD, but not THC, enhanced the biomechanical properties of healing mid-femoral fractures in rats, supporting a beneficial effect of CBD on bone healing [67].

Epidemiological studies have suggested a reduction in opioid use for pain coinciding with an increased use of medical cannabis [30], a trend also documented in Canada [68]. While the interaction between CBD and opioids is not yet fully understood, studies have shown that CBD acts as an allosteric modulator of the mu- and delta-opioid receptors [69]. CBD was also shown to potentially enhance the analgesic effects of endogenous and exogenous opioids. In one study, the use of CBD as a co-analgesic treatment for patients with chronic pain resulted in a reduction in opioid consumption and improvements in overall quality of life [70].

Providing effective pain management for patients with fractures is not only a fundamental right but also offers numerous benefits. It reduces stress, shortens hospitalization time, decreases associated healthcare costs and lowers the risk of developing chronic pain [1]. Preventing chronic pain is easier than reversing the sensitization processes that cause it [71], making acute pain control a priority. Given its excellent safety profile [33, 35] coupled with its downregulating effects on microglial and inflammatory activity, the primary neuroinflammatory and pain mechanism, CBD represents an appealing neuroprotective agent for pain-susceptible orthopedic trauma patients.

Study objectives

The primary objective of this study is to evaluate the effects of CBD treatment on self-reported pain in patients following a long bone fracture injury. The second objective is to assess the effect of the CBD treatment on inflammation and patient well-being. Additionally, secondary analyses will look at the possible associations between pain mediators (such as opioids, sex, and mild traumatic brain injury (mTBI)) and response to CBD treatment. The aim is to better identify the effects of these pain mediators on treatment response and the impact of CBD treatment on opioid uptake.

Methods

Study design

This is a randomized, placebo controlled, triple-blind 1-month clinical trial evaluating the effects of two doses (low and moderate) of CBD compared to a placebo on pain and inflammation after a long bone fracture.

Participants

A total of 225 participants aged 18 to 70 will be recruited within one week after their long bone fracture injury and consultation to the Hôpital du Sacré-Coeur de Montréal (HSCM), one of the largest Level 1 trauma centres in Canada with approximately 3,500 orthopedic patients treated annually. The planned age range, targeting a population representative of individuals who frequently experience traumatic fractures, was chosen as it allows for a more homogenous evaluation of fracture healing and pain recovery. Including participants

over 70 introduces additional challenges, such as increased comorbidities, chronic diseases, bone fragility, polymedication and increased complications, which could slow the healing process, influence pain perception and complicate result interpretation.

Inclusion criteria

Subjects meeting the following criteria are eligible for the trial:

- Patients with a long bone fracture of the lower limb (tibia, fibula, femur, metatarsals, and phalanges) or the upper limb (humerus, radius, ulna, metacarpals, and phalanges) treated to Hôpital du Sacré-Coeur de Montréal (HSCM) within one week of the accident
- Participants is between 18 and 70 years of age
- Patients with or without surgical procedures

Exclusion criteria

Patients presenting any of the following characteristics are not eligible for the trial:

- Moderate/severe traumatic brain injury (TBI)
- Diagnosis of any of the following mental disorders as defined by the DSM-5: schizophrenia, intellectual disability, bipolar disorder, major depression, a diagnosed and untreated sleep disorders
- History of alcohol or opioid misuse/abuse, as defined by the DSM-5
- Evidence of severe renal (stage 4 or 5) or hepatic impairment (Child B or C)

- Pregnant or lactating women, women of childbearing potential who are not using medically accepted forms of contraception (e.g., condoms, oral contraceptive or intrauterine device), or women who are actively planning on becoming pregnant
- History of adverse reactions to cannabis
- Patients taking warfarin, sildenafil, valproate or under opioids treatment prior to the injury
- Patients experiencing on average mild-to-absent pain in the last 24h preceding recruitment (as per a score <30 on a 0-100mm Visual Analogue Scale (VAS))
- Transport business drivers and heavy machinery operators
- A diagnosis of chronic pain, bone pathology (e.g., osteoporosis) or chronic inflammatory disease (e.g., rheumatoid arthritis, arthritis, psoriasis)
- Not having French or English as a spoken language
- A weighted MoCA score of less than 24
- Regular cannabis use more than 5 times a week

Recruitment

Recruitment will begin in January 2025 and end in January 2027. Potential participants will be screened daily by the research team and collaborators. Potentially eligible patients will be approached by a research team member and provided with a consent form. Once the research team has addressed any remaining questions and obtained a signed consent form, the participant will be randomized. See figure 1 for an overview of the study timeline.

Assignment of interventions

Participants will undergo concealed randomization to avoid selection bias. The study pharmacist will randomly assign participants to one of the three treatment groups (low or moderate CBD or placebo) using a 1:1:1 ratio through block randomization with randomly selected block sizes (9 and 12), stratified by sex, age (i.e., participants aged 45 and under, and those over 45) and type of fracture (i.e., lower and upper limb). Block randomization with randomly selected block sizes (9 and 12) was chosen to minimize selection bias and maintain the blinding of investigators and other project members by ensuring the unpredictability of block assignments. Given that there are three groups, a block size of 9 results in a distribution of 3 patients per group, whereas a block size of 12 allocates 4 patients in each group. The randomization procedure will be performed a priori by an independent biostatistician. Identical tablets for CBD and placebo will ensure blinding of clinicians, researchers, patients, families, and biostatistician to avoid unequal co-interventions, ascertainment bias, and analytic bias. The study pharmacist will be aware of allocation but will have no clinical or interpretive role. Assignments will be kept in sequentially numbered, sealed envelopes to ensure adequate allocation concealment. In the event of a serious adverse event or reaction, the allocation list can be retrieved.

Intervention

Patients in the treatment group will receive either a low dose (25 mg per tablet) or a moderate dose (50 mg per tablet) of CBD self-administered orally as a tablet twice daily with a meal for one month. Patients in the placebo group will receive an identical amount of a matching placebo administered with a meal twice daily for one month.

Investigational product

CBD tablets, along with matching placebos, will be supplied by EmpowerPharm (Toronto, Canada). The pharmacokinetic profile of the CBD product has already been established, and efforts to register the product with Health Canada have begun.

Dose justification

A wide range of CBD doses ranging from <1 to 50mg/kg has been used in various conditions [72, 73]. The low dose (25 mg) selected for our study is based on initial and ongoing studies of CBD in chronic pain which used a mean dose of 22.5mg and 20mg per day [65]. This is also approximately the mean dose of CBD administered in a successful trial of Sativex (THC/CBD) for neuropathic pain [74]. Moreover, a higher but relatively moderate dose of CBD (50 mg) will be evaluated to assess dose-response effect. CBD doses in this range have shown no statistical difference in intoxication scores in healthy volunteers [75] and doses of up to 800 mg per day for a minimum of 4 weeks showed an excellent safety and tolerability profile [76 , 77]. Participants will be advised to ingest the treatment at mealtime, as studies have shown an increased bioavailability of CBD in subjects after eating [78, 79]. To achieve our primary goal of mitigating acute pain, a one-month treatment period has been selected, aligning with the typical evolution of acute pain post-fracture [6].

Study procedure

Upon enrollment in the study, research staff will provide study instructions, collect baseline data (e.g., demographics and clinical characteristics), administer questionnaires and

cognitive tests, and collect blood samples for quantification of pro-inflammatory cytokines. Patients will report their pain intensity at baseline, and then three times a week throughout the entire one-month treatment duration. Participants will be instructed to complete a daily medication diary for one month to monitor the administration of study product, as well as opioid, drugs, or other analgesic medication use. This data will be collected via questionnaires sent by e-mail or SMS message from the RedCap secure database. At 24h following treatment completion (one-month follow-up) and at the 3-month follow-up, participants will be evaluated at the research laboratory to collect measures of pain intensity and related outcomes including opioids intake, inflammation, cognition, orthopedic function and indicators of overall well-being. Participants will have to abstain from CBD consumption from the end of treatment until the last follow-up visit. See Table 1 for a detailed schedule of assessments.

Table 1. Schedule of assessment

Domain	Mesure	Screening	Baseline	During Treatment	1-month follow-up	3-month follow-up
Eligibility	Demographic questionnaire	X	X			
	Consent form	X				
	Medical history	X				
	MoCA	X				
	Medication	X	X	X	X	X
Primary outcome	Visual Analog Scale	X	X	X	X	X
Secondary outcomes	Brief Pain Inventory short form (BPI-sf)				X	X
	Blood sample - Inflammation markers		X		X	X
	Cognition		X		X	X

	Rivermead TBI symptoms				X	X
	Short Musculoskeletal Function Assessment (SMFA)				X	X
	Short Form Health Survey				X	X
	Pittsburgh Sleep Quality Index (PSQI)				X	X
	Beck's Depression Inventory-II		X		X	X
	Beck's Anxiety Inventory		X		X	X
Other	Pain Catastrophizing Scale (PCS)		X			
	Treatment Expectation Questionnaire (TEX-Q)		X			
	PTSD Checklist for DSM-5 (PCL-5)		X		X	
	Treatment assignation hypothesis				X	
	Opioid consomption	X	X	X	X	X
	Adverse events			X	X	

Primary outcome

The main outcome is the difference between groups in the mean pain intensity score at one-month follow-up, as measured by the visual analog scale (VAS) [80]. Pain intensity on the VAS will be gathered 24h following treatment completion. The VAS is a 100mm line with anchor words ranging from "no pain" to "worst imaginable pain". Participants will indicate the intensity of their pain at that moment by placing a mark along the line.

Secondary outcomes

At 1 and 3-month follow-ups, persistent pain, opioid consumption, inflammation markers, quality of life, sleep quality, depression, anxiety, cognition, mTBI symptom resolution, and orthopaedic function outcomes will be collected. In addition, at baseline, participants will be asked to indicate their level of treatment expectation using the Treatment Expectation Questionnaire (TEX-Q-F) [81], a fifteen-question questionnaire, considering the potential modulation of therapeutic effects by patients' expectations of treatment [82, 83]. After treatment completion, participants will also be asked to indicate whether they felt they had received active treatment or placebo.

Measures

Demographic and clinical characteristics

The following information will be collected at baseline to characterize participants: age, sex, height, weight, percentage of adipose tissue using an impedance meter scale, occupation, education level, ethnicity, language spoken, pre-morbid medical history (including psychological health history), pre-morbid substance use (e.g., alcohol, drugs, cigarettes, medications), recreational cannabis use, history of brain trauma, injury type and severity, mechanism of injury.

Pain

At 1- and 3-month follow-up, persistent pain will be assessed using the Brief Pain Inventory short form (BPI-sf) [84], a 9-item self-report questionnaire assessing for the presence, intensity, and location(s) of pain, as well as perceived efficacy of pain relief treatment, and pain interference with activities of daily living. In addition, pain will be

assessed using the VAS at several time points for comparison: baseline, three times per week during treatment, 24h after the end of treatment and at the 3-month follow-up. Pain catastrophizing will also be assessed during the initial visit using the Pain Catastrophizing Scale [85], a 13-item questionnaire evaluated on Likert scales, given the significant contribution of psychological factors in the experience of pain.

Opioid usage

Participants will continue their usual pain care regimen throughout the study. Opioid usage and analgesic will be recorded in a daily medication diary for the initial month and through the number of prescription refills for months two and three. Self-reported opioid use in a diary has been shown to be an accurate assessment of the quantity of opioids consumed [86].

Inflammation

Blood levels of pro-inflammatory cytokines including interleukins (IL-6, IL-10, IL-1β) and TNF-α will be collected at baseline and at the 1 and 3-month follow-up sessions. To assess cytokine levels, blood samples will be separated in buffy coat, serum and plasma, and stored at -80 °C in polypropylene tubes on average 1-2h after the blood draw. EDTA plasma will be tested with cutting-edge ultra-sensitive Quanterix ImmunoAssay Analyzer Simoa HD-X to quantify biomarkers using the Cor-Plex-Cytokine-10-Plex assay panel as per manufacturer recommendation. Simoa is a leader in the quantification of plasma biomarkers with markedly lower detection threshold than traditional ELISA [87].

Cognition

At baseline, 1 and 3-months follow-ups, neuropsychological tests highly sensitive to pain, and that do not require the use of the fractured limb, will be administered: a task assessing information processing speed (Symbol Search from the WAIS-IV Battery), two memory tests (California Verbal Learning Test and Digit Span from the WAIS-IV battery), two executive function tests (D-KEFS Color-Word and Verbal Fluency), and an attention test (Elevator counting with distraction and Elevator counting without distraction from the Test of Everyday Attention battery) (see Lezac et al., 1995 for test descriptions).

Mild TBI symptoms resolution

Patients who sustained a concomitant mTBI with their fracture will be included in the study. Additional measures will be documented to control for this variable. At 1 and 3-months follow-up, information on mTBI symptoms resolution will be collected for patients diagnosed with a mTBI concomitant to the fracture using the Rivermead Post-Concussion Questionnaire [88].

Orthopaedic function

At 1 and 3-months follow-ups, the Short Musculoskeletal Function Assessment (SMFA) Questionnaire [89] will be administered. The SMFA includes 34 questions that evaluate patient's function, and 12 questions related to how bothered patients are by their symptoms.

Well-being

At 1 and 3-months follow-ups, various important domains of well-being significantly modulated by pain will be measured including: quality of life using the Short Form (36) Health Survey [90], a 36-item self-report questionnaire for measuring quality of life across 9 domains; sleep quality and quantity using the Pittsburgh Sleep Quality Index (PSQI) [91], a self-report questionnaire that assesses sleep quality and quantity over the past 4 weeks. Additionally, at baseline, 1 and 3-months follow-ups depression and anxiety symptoms will be assessed using the Beck's Depression Inventory-II (BDI-II) [92] and the Beck's Anxiety Inventory (BAI) (86). The BDI-II is a 21-item multiple-choice self-report questionnaire for measuring depression symptoms. The BAI is a 21-question multiple-choice self-report inventory used for measuring the severity of anxiety. Finally, symptoms of post-traumatic stress disorder will be assessed at the first visit and at 1-month follow-up using the PTSD Checklist for DSM-5 (PCL-5) questionnaire [93].

Data management

Data collected will be transcribed from the source documents into the electronic Case Report Form (eCRF) on the REDCap database hosted at CIUSSS du Nord-de-l'Île-de-Montréal [94] and quality controlled by a second qualified staff member. Data will be stored on a secure network with regular backups. An external, independent clinical monitor will conduct regular monitoring visits according to the monitoring plan, during which they will review and verify source data, informed consent forms, medical records, laboratory results, case report forms, medication dispensing logs and protocol deviations.

Statistical analyses

Sample size estimation

A 30% relative pain intensity reduction on the VAS (expected response of 50% or more in the CBD group and expected 20% in the placebo group) has been used extensively to reflect clinically significant pain relief in clinical trials. Based on a Fisher's exact test, a sample size of 225 participants (3 groups of 75) will be required to reach a power of 80% to detect a statistically significant difference in the proportion of patients who reaches 30% pain reduction between the CBD groups and placebo at 1-month post-injury, assuming a dropout rate of 20% and a significance level of 5%. These parameters are taken from a successful randomised, placebo-controlled clinical trial using Sativex© in treating 125 neuropathic pain patients [74].

Moreover, considering that the placebo group may ingest more opiates and that the anticipated inter-group effect at one month may be reduced to 20%, a total sample size of 225 subjects could be required to achieve 80% power, assuming a drop-out rate of 20% and a significance level of 5%.

Primary outcome

The primary outcome will be analyzed using an ANCOVA, with mTBI and orthopedic surgery as covariables and treatment (low and moderate CBD vs. placebo) as factor in the mean VAS pain score at the 1-month follow-up.

Secondary outcomes

For the secondary outcomes, a Kaplan Meier survival analysis with the log-rank test on VAS pain data collected during treatment will be used to assess CBD treatment success

rate relative to placebo at achieving 50% pain intensity reduction during treatment duration. The proportion of patients no longer experiencing significant pain symptoms at the 3-month follow-up (i.e., patients who did not convert to chronic pain) will be compared, as defined as VAS pain ≤ 30 between treatment with a chi-squared test. A mixed model for repeated measures with covariables mTBI and orthopedic surgery and treatment as factor will be used to assess between-group treatment effects on total opioids use at both 1 and 3-month follow-ups. The same approach will be used to assess between-group treatment effects at both 1- and 3-month follow-ups on secondary outcomes measures listed above.

Analyses will be performed on an intention-to-treat (ITT) dataset. The ITT dataset will include all participants randomized in the analysis, whether or not they have completed treatment in order to limit bias and reflect results under real treatment conditions.

Missing data will be reported and justified in the results. The multiple imputation method, which has been recognized in clinical studies involving experimental treatment, will be applied. Additionally, a sensitivity analysis will be performed to assess the impact of missing data on the results.

Discontinuation

Participants may withdraw from this research project at any time without giving reasons. Discontinuation of treatment does not imply withdrawal from the trial. The following reasons will be considered as grounds for patient withdrawal from the trial: withdrawal of consent by the participant, failure to pass the selection phase, meeting an exclusion

criterion, failure to participate in follow-up, termination of the trial by the investigator, major protocol deviation incompatible with trial participation, an adverse event or any other condition which, in the opinion of the investigator, would expose the participant to undue risk by continuing the treatment trial, any condition that the investigator considers medically necessary to withdraw the patient from the trial.

Adherence

During the baseline visit, a research team member will conduct an information session to discuss the significance of adhering to the guidelines related to doses, timing of drug administration, the procedure to be followed in case of a missed dose, and the importance of reporting any adverse event. Automatic SMS reminders will be sent to ensure completion of the digital VAS and medication diary. A high protocol adherence is expected given that cannabidiol has limited adverse side effects, and the administration is oral and non-invasive. A 10% loss to follow-up is expected based on a 3-month trial with the same patient characteristics[95]. For adherence purposes, patients will be instructed to return all treatment bottles, empty or not, to be monitored by the pharmacy staff. Each participant will receive financial compensation for costs incurred during their participation in this research study. Participants who withdraw or are withdrawn from the project prior to its completion will receive an amount proportional to the length of their participation.

Safety and serious adverse events

Risks of adverse effects are considered low given the demonstrated excellent safety profile of CBD [33, 35]. Somnolence, fatigue, drowsiness, gastro-intestinal issue, and decreased

appetite are the most probable adverse events associated with CBD in adult patients [34]. Participants will be instructed to advise the research team of any adverse events which will be thoroughly monitored and documented. Access to on-duty emergency physicians at HSCM will be provided during the entire treatment duration.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study.

Confidentiality

All data collected in our databases will be stored following a de-identification process. Participants will be identified by a unique identification code, and nominal data will be protected separately. Uncoded data will only be accessible to the principal investigator. No identifying data will be disclosed in any scientific communication or publication.

Ethics and dissemination

Ethical approval has been granted by the CIUSSS du Nord-de-l'Île-de-Montréal ethics board (#2025-2105 issued August 2024) and Health Canada (License, #LIC-NKA1EX2TUA-202-3 issued on March 26, 2024, and No Objection Letter, HC6-024-c275232 issued on May 30, 2024). This study adheres with the Declaration of Helsinki. The results will be published in a peer-reviewed journal and presented at local, national, and international conferences.

Author Contributions

DB, DW, FB, CA, GL, AP, DR, LDB conceived the study. DB and AAD will ensure coordination, recruitment and conduct of the protocol. DB and LDB wrote the manuscript. All authors contributed to the revisions of the manuscript. LDB is guarantor.

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Competing interests: None declared.

Figure 1. Study Schema. CBD, cannabidiol; mTBI, mild traumatic brain injury.

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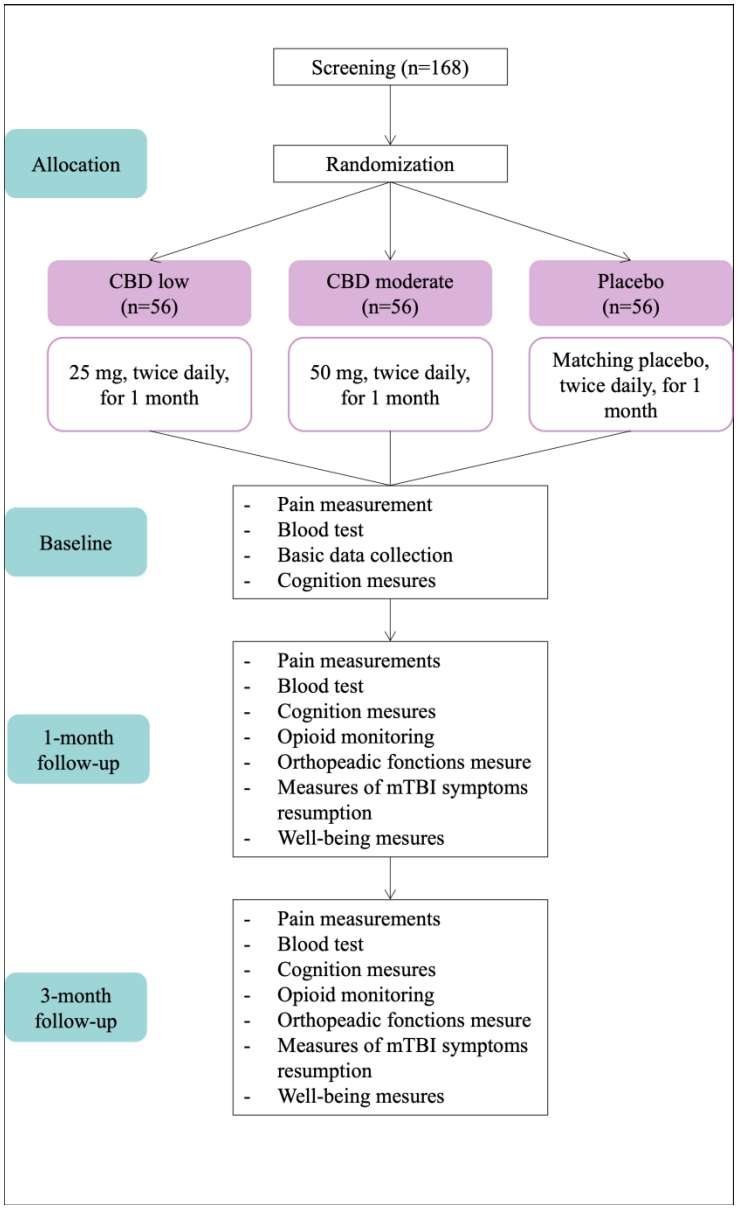

Figure 1 - Study schema

171x281mm (330 x 330 DPI)