Cannabis to Reduce Chronic Postsurgical Pain Following Total Knee Arthroplasty: A Pilot Randomized Controlled Trial

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Abstract

Background

Chronic postsurgical pain (CPSP) after total knee arthroplasty (TKA) affects 20% of patients and is associated with higher peri-operative pain. Cannabis products may be effective for reducing CPSP after TKA. We conducted a pilot trial to determine feasibility of a definitive trial assessing a 25:1 cannabidiol (CBD): tetrahydrocannabinol (THC) oral formulation of oil drops (MPL-001) versus placebo to reduce CPSP after TKA. The primary outcome is feasibility including recruitment, retention, and adherence. Clinical (secondary) outcomes were moderate-to-severe CPSP, opioid use, pain interference, physical and emotional function, return to functioning, sleep, and adverse events.

Methods

We conducted a multicentre parallel group randomized controlled trial of 37 patients scheduled for TKA who received up to 2.5 ml/day (125mg CBD/5mg THC) of MPL-001 or placebo 4 weeks before and 6 weeks after surgery. Participants could extend their study medication up to 12 weeks postoperatively. We followed participants for 26 weeks after surgery. MPL-001 has approximately 50mg/mL of CBD, 2mg/mL of THC, 0.1mg/mL cannabinol (CBN), 2.8mg/mL of cannabichromene (CBC), and 0.2mg/mL of cannabigerol (CBG), with small variations between lots.

Results

We randomized 19 participants to receive MPL-001 and 18 participants to receive placebo. 71% of participants took at least 75% of their allocated study medication preoperatively, and 48% took at least 75% of study medication postop. Most participants (28/36; 78%) who started the study medication were able to titrate up to and tolerate the maximum daily dose of 2.5mL (125mg CBD/5mg THC). Of the 37 participants randomized, 30 (81%) completed their 26-week follow-up visit. Participants' mean age was 66 (standard deviation [SD] 9.4), most were female (76%) and had never used cannabis (81%). At the 12-week follow-up, 41% in the placebo arm (7 of 17) reported moderate-to-severe CPSP, and 13% in the MPL-001 arm (2 of 15). At 26 weeks follow-up, 19% in the placebo arm (3 of 16) reported moderate-to-severe CPSP, and 14% in the MPL-001 arm (2 of 14). There were 18 treatment-related adverse events reported among 11 patients randomized to MPL-001, and 19 treatment-related adverse events reported among 12 patients randomized to placebo. The most common adverse events were gastrointestinal, typically nausea and diarrhea.

Conclusions

Modifications to our study protocol will be required to ensure feasibility of a definitive trial of cannabis versus placebo to reduce CPSP among TKA patients. For the definitive trial, we will expand participant recruitment to additional centres and switch from oil drops to capsules to increase adherence.

Trial Registration:

clinicaltrials.gov NCT03825965

BACKGROUND

Total knee arthroplasty (TKA) is performed to provide pain relief and functional improvement for patients with advanced knee osteoarthritis. Over 700,000 TKAs are performed in the United States each year [1]. However, chronic postsurgical pain (CPSP), defined as pain that develops after surgery and lasts at least three months in the absence of other identifiable causes [2], occurs in approximately 20% of TKA recipients [3, 4]. Higher preoperative and immediate postoperative pain, and pain catastrophizing, have shown large associations with the development of CPSP after TKA [4].

Opioids are a cornerstone of perioperative pain management; [5] however, opioids are associated with risks, including addiction, overdose, constipation, sedation, respiratory depression, nausea and vomiting [6]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often incorporated into multimodal pain management strategies following TKA, however, their use is limited by gastrointestinal, renal, and cardiovascular side effects [7]. The most recent systematic review of 110 randomized trials of pharmacotherapy to prevent chronic pain after surgery found no effective interventions, including ketamine, pregabalin, gabapentin or NSAIDs [8]. As a result, there is interest in alternative therapies that target perioperative pain while minimizing side effects.

The cannabis plant contains multiple bioactive compounds, including Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [9]. THC is primarily responsible for cannabis's psychoactive effects [10] and has been associated with sedation, dizziness, and impaired cognition [11]. In contrast, CBD is non-psychoactive [12] and has demonstrated anxiolytic, anti-inflammatory, and analgesic effects in both preclinical and clinical settings [13–15]. CBD may mitigate some of the undesirable central effects of THC when administered in combination [13, 16]. Cannabinoid-based therapies have shown potential benefits in chronic pain [11], nausea and vomiting [13], and sleep disturbance [14, 15]. However, existing evidence in surgical contexts is limited, and low to very low certainty evidence suggests that recreational use of cannabis (favoring THC dominant products) may increase risks of post-operative complications following total joint replacement [17]. A 2019 systematic review [18] identified only five randomized controlled trials investigating synthetic or plant-derived cannabinoids for pain in an orthopaedic context. Published trials report mixed results and are limited by small sample sizes and short follow-up durations [19–23]. None of these trials examined CBD-dominant formulations, and none have evaluated effects on CPSP after TKA. A more recent randomized controlled trial evaluated topical cannabis versus placebo on acute pain after TKA. The authors did not find a difference between groups, however this was a small

study (19–21 patients/group) with only two weeks of cannabis application and did not focus on chronic pain [24].

Objectives

We conducted a pilot trial to determine the feasibility of a definitive trial of cannabis for reducing the incidence of developing moderate-to-severe CPSP in TKA patients. Specific feasibility objectives were adequate participant enrollment, patient adherence to treatment, and participant follow-up.

METHODS

This is a pilot randomized controlled trial with a two-group parallel design and superiority framework. The protocol is published in Pilot and Feasibility Studies [25]. We chose to complete a pilot trial prior to a larger definitive trial as 43% of surgical trials are discontinued prematurely, often due to feasibility issues [26].

Study Setting

We conducted this study at two high-volume arthroplasty centres at university-affiliated hospitals in Hamilton Ontario (St. Joseph's Healthcare Hamilton) and Toronto Ontario (St. Michael's Hospital). Two fellowship-trained arthroplasty surgeons, with 14 and 24 years of experience in practice, contributed patients to the study.

Eligibility Criteria

Our inclusion criteria were: (1) adult patients (aged 18 or older) undergoing TKA, (2) cognitive ability and English-language skills required to complete outcome measures, and (3) signed informed consent. Exclusion criteria were: (1) severe cardio-respiratory disease, (2) substance use disorder, (3) allergy or intolerance to cannabis, cannabis derivatives, or other ingredients of the study drug, (4) patients who are pregnant, planning to be pregnant, or breastfeeding, (5) undergoing revision TKA, (6) undergoing simultaneous bilateral TKA, (7) presenting for their pre-surgical consultation < 4 weeks before surgery, (8) patients with a chronic pain condition other than osteoarthritis, (9) unwilling or unable to follow the study protocol, (10) enrolled in a study that does not permit co-enrollment, and (11) other reason to exclude the patient, as approved by the Methods Centre We did not require participants to be cannabis-naïve.

Screening and Recruitment

Participating surgeons identified potentially eligible patients during regularly scheduled preoperative clinic visits a minimum of four weeks before surgery. Research coordinators at each site screened

potential participants for eligibility and conducted the informed consent process.

Randomization and allocation concealment

We randomized participants 1:1 to receive either MPL-001 or placebo. An unblinded study team member (AD) generated the allocation sequence using Microsoft Excel. The allocation sequence was stratified by site and used blocking with varying block sizes of 2 and 4. Investigators did not know the block sizes until after the study was complete. Unblinded study team members (AD, AF) received the unblinded investigational product from the manufacturer and applied blinded labels according to the randomized sequence using sequential numbers. E.g. the bottle with the appropriate allocation to be used first was labelled 1, the bottle with the appropriate allocation to be used second was labeled 2, etc. This was repeated for the second site. Because the bottles were visually identical, identified only by the sequence number, allocation was concealed.

Treatment groups

MPL-001 (MediPharm Labs Corp., Barrie ON) is a 25:1 CBD:THC oral formulation in medium-chain triglyceride (MCT) oil containing 50 mg/mL CBD and 2 mg/mL THC. Control patients received MCT oil only. This formulation was chosen because, at the time of trial startup, it was the only product produced under Good Manufacturing Practices (GMP) with sufficient safety, quality, and stability data to submit a regulatory application to Health Canada. An international consensus panel has recommended a maximum of 40mg of CBD/day for management of chronic pain [27]. However, in practice, patients report a wide dose range of CBD for pain management [28]. In discussion with the manufacturer, and informed by their patient data, we elected to use a maximum tolerated dose of up to 125mg/day of CBD to provide assurances that our definitive trial will be able to show an effect if CBD can reduce the prevalence of chronic pain after knee replacement surgery.

The manufacturer's stability testing demonstrated that amounts of THC and CBD in MPL-001 remained consistent over 36 months, within 4–6% of values compared to time 0 at room temperature, with small variations between lots. Amounts of minor cannabinoids cannabinol (CBN), cannabichromene (CBC), and cannabigerol (CBG) remained within specifications at all stability testing timepoints, with some variation between lots due to natural variations in the plant material. Manufacturer-provided data for one of the two lots used in this trial showed the following concentrations of cannabinoids: 51.802 mg/mL of CBD, 2.022 mg/mL of THC, 0.106 mg/mL of CBN, 2.825 mg/mL of CBC, and 0.211 mg/mL of CBG.

Participants received their assigned study medication 4 weeks before surgery and were instructed to increase their dose over a 2-week titration period from 25 mg CBD and 1 mg THC (0.5 mL) per day up to 125 mg CBD and 5 mg THC (2.5 mL) per day, according to the schedule in Table 1. If participants did not tolerate a dose increase, they were instructed to return to their previous dose. Participants maintained their tolerated dosage for 2 weeks before surgery (for a total of 4 weeks use of study product before surgery) and at least 6 weeks post-surgery. Participants did not take their study medication on the day of

surgery or while in hospital due to local hospital restrictions on storage of cannabis on the wards. Participants received written and verbal dosing instructions and dosing syringes with a bottle adapter to assist with administration. Participants were instructed to draw up the appropriate amount of study drug in the syringe using the bottle adapter, dispense the liquid under their tongue, hold the liquid in their mouth for 30 to 60 seconds, and swallow the liquid. Participants were instructed to take the study drug with food twice per day; one dose in the morning and one dose in the evening before bed, ideally 12 hours apart.

Table 1
Dosing for the preoperative titration and maintenance phase

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Titration phase*							
Week 1	0.5 ml	0.5 ml	1 ml	1 ml	1 ml	1.5 ml	1.5 ml
Week 2	1.5 ml	2 ml	2 ml	2 ml	2.5 ml	2.5 ml	2.5 ml
Maintenance phase							
Week 3	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml
Week 4	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml
*If participants could not tolerate a dose increase, they were instructed to return to the previous dose.							
Each mL contains 50 mg CBD and 1mg THC.							

Optional medication extension

6 weeks after surgery, participants who were still experiencing pain were offered the option to continue with their study treatment (MPL-001 or placebo), up to 12 weeks post-surgery.

Concomitant care

All participants received standard perioperative care, surgical and anesthesia techniques, postoperative rehabilitation, and discharge pain medications according to local practice at the two study sites. Typically, discharge pain medications included hydromorphone (immediate-release opioid), hydromorph contin (controlled-release opioid), and acetaminophen as needed. Participants were asked not to consume any other cannabis products for therapeutic or recreational purposes during the study period, but we did not have a formal washout period.

Blinding

All participants, healthcare personnel, and study staff were blinded aside from the two designated unblinded study team members who labelled study products. The study product (MPL-001 or placebo) was packaged by the manufacturer, MediPharm Labs, in identical amber bottles. To maintain blinding, the manufacturer added peppermint and lemon extract to mask the cannabis scent and taste. The unblinded study team members were available in case emergency unblinding was required but were otherwise not involved in the trial.

Primary Outcome (Feasibility)

The goals of our pilot study were to determine the rate of enrollment, treatment adherence, and follow-up. Specifically, we aimed to determine our ability to enroll 40 participants in 26 weeks, to achieve ≥ 75% treatment adherence (75% of participants adhere to 75% of treatment doses), and to demonstrate participant retention of ≥ 85% at 26 weeks.

Secondary Outcomes and Measurement

We captured planned effectiveness outcomes for the definitive trial as secondary outcomes. These included moderate-to-severe CPSP, opioid use, pain intensity, pain interference, mental health, health-related quality of life, insomnia, return to function, and adverse events. Clinical outcomes were assessed at 2 weeks, 6 weeks, 12 weeks, and 26 weeks post-surgery.

Moderate-to-severe persistent post-surgical pain: We used a modified version of the World Health Organization (WHO)'s definition of CPSP [2] to include a minimum threshold of average pain severity in the previous week of ≥ 4 on a 0–10 numeric rating scale (0 = no pain, 10 = pain as bad as the patient can imagine). The WHO definition requires: (1) pain that develops or increases in intensity after a surgical procedure, (2) lasting for at least 3 months, and (3) not explained by an infection, malignancy, pre-existing pain condition, or an alternative cause.

Opioid use

Participants recorded their use of opioids in a daily medication log. We collected information about the number of days opioids were used, and the type and dose of opioids.

Safety

We documented all serious and non-serious adverse events. One of the two medical monitors (HS, HJ), an orthopaedic surgeon and a pain physician, blinded to treatment allocation, reviewed each AE and determined if they were likely to be related to the treatment.

Pain intensity and interference

We used the Brief Pain Inventory-Short Form (BPI-SF) [29] which includes four 0 to 10-point numeric rating scales (NRS) of pain intensity at its worst, least, and average in the past 24 hours, and pain right now. The BPI-SF also asks participants to rate the degree to which pain interferes with seven activities

on a 10-point scale. (0 = does not interfere, 10 = complete interference). We reported the mean of the seven subscale items.

Mental health

We used the Hospital Anxiety and Depression Scale (HADS) to measure depression and anxiety [30, 31]. Scores of 0–7 in each subscale are considered normal, with 8–10 borderline and ≥ 11 indicating clinically important anxiety or depression.

Health-related quality of life

We used the EuroQol Five Dimension (EQ-5D-5L) questionnaire to measure health-related quality-of-life (HRQL) [32]. The EQ-5D descriptive section consists of five domains (pain, mobility, usual activities, self-care, and mental health) with five response options each, from no problems to extreme problems. The EQ-5D visual analog scale (VAS) is a 0-100 scale of worst health imaginable to best health imaginable.

Return to function

We used the Return to Function questionnaire to assess participants' return to activities. This questionnaire, which has been used in previous orthopaedic trials [33] documents patients' return to work, household activities, and leisure activities with response options ranging from no return to activities to returned without restrictions. The questionnaire also includes a VAS asking about patient's level of functioning ranging from 0% to 100%. We calculated the EQ-5D-5L index values, which typically range from 0 (death) to 1 (full health) but it is also possible to have negative values (worse than death). To calculate index values, we used the Canadian time trade-off (TTO) value set established by Xie et al [34] and Stata software version 19.5.

Insomnia: We used the Insomnia Severity Index (ISI) to measure insomnia [35]. We used the thresholds established by Bastien et al to categorize insomnia severity [35]: 0–7 no clinically significant insomnia, 8–14 subthreshold insomnia, 15–21 moderate insomnia, and 22–28 severe insomnia.

Baseline Data and Participant Follow-up

We collected participant demographics, preoperative opioid use, range of motion, comorbidities, previous knee surgery, and baseline clinical outcomes at their preoperative visit. On the date of surgery, we collected surgical and perioperative characteristics. Within 48 hours after surgery, we collected immediate postoperative data such as pain medications, blood transfusions required, and discharge details, and asked participants about their pain. We completed follow-up visits at 2, 6 12, and 26 weeks after surgery. Participants completed a daily study medication log for as long as they took their study medication.

Success Criteria for Pilot Study Outcomes

Feasibility outcomes were selected to determine what modifications, if any, would be required before proceeding to a larger, definitive trial. We established thresholds of feasibility using a “traffic light” set of criteria, which are detailed in Table 2. Using this approach, a “green light” indicated moving forward as is with a definitive trial, a “yellow light” indicated proceeding with some protocol modifications, and a “red light” indicated the objective was not feasible without substantial modifications [36]. Success thresholds were informed by prior orthopaedic trauma pilot studies [37, 38].

Table 2
Pilot Trial Objectives and Progression Criteria Results

Criterion	**Result**	**Traffic Light Criteria**		
		Proceed	**Modifications required**	**Not feasible**
Enrollment: Length of time required to enroll 40 participants	57 weeks	< 26 weeks	Between 26–39 weeks	**> 39 weeks**
Adherence: Adherence to 75% of study medication doses	71% preop 48% postop	≥ 75% adherence	**65–74% adherence**	**< 65% adherence**
Retention: Participants who complete the 26 week follow-up visit	81.1%	≥ 85%	**75–84%**	< 75%

Sample Size

Our sample size target was 40 participants. Based on the feasibility success criterion for participant retention (i.e. achieving at least 85% follow-up at 26 weeks), if 39/40 participants achieved successful follow-up, the lower boundary of the 95% confidence interval would be above 85%. If fewer than 29/40 achieved complete follow-up the upper boundary of the confidence interval would be below 85% and we would consider the trial unfeasible without substantial modifications. If between 29 and 39 participants completed the 26 week follow-up, feasibility may be acceptable with modifications [39]. As this is a pilot trial, it was not powered to detect between-group differences.

Data Analyses

For this pilot trial, we focused on descriptive statistics rather than inferential statistics. We presented continuous variables as means with standard deviations (SDs) and 95% confidence intervals (95%CIs) when normally distributed (median and interquartile range when not), and categorical variables as frequencies, percentages and 95% CIs. We presented enrollment numbers by month, and duration of opioid use with a Kaplan-Meier curve. We used SPSS version 28.0.1.0 for the analyses.

RESULTS

Demographics

Of the 61 patients who were screened for eligibility, 37 met eligibility criteria, provided informed consent and were randomized, for an overall enrollment rate of 61%. Two additional patients were originally randomized to placebo but were ineligible for surgery and were excluded. Post-randomization exclusions are considered appropriate when patients do not meet pre-defined eligibility criteria, and the feature that rendered them ineligible for participation could have been known at the time of randomization [40]. (Fig. 1) The mean age of participants was 66 (SD 9.4) and most were female (28/37, 76%). Approximately half of participants were employed prior to their surgery (17/37, 46%), a minority had experience using cannabis recreationally (5/37, 14% current use; 2/37, 5% past use), and 16% (6/37) were prescribed opioids prior to surgery. (Table 3). Preoperatively, the mean BPI pain interference score for all participants was 6.0 (SD 2.2) on a 0–10 scale. One in four (9/37, 24%) met criteria for depression and 43% (16/37) for anxiety. Participants mean EQ-5D overall health score was 64.0 (SD 19.3) on a 0-100 scale, and half (19/37, 51%) met criteria for moderate to severe insomnia.

Table 3
Demographics and surgical characteristics

Variable	Placebo (n = 18)	MPL-001 (n = 19)	Total (n = 37)
Age Mean (SD)	64.6 (10.2)	67.8 (8.5)	66.3 (9.4)
Female (%)	12 (66.7)	16 (84.2)	28 (75.7)
BMI Mean (SD)	36.0 (7.2)	32.3 (6.6)	34.1 (7.1)
Employed prior to injury (%)	8 (44.4)	9 (47.4)	17 (45.9)
Never smoked (%)	12 (66.7)	13 (68.4)	25 (67.6)
Alcohol consumption (%)			
Never drank alcohol	5 (27.8)	6 (31.6)	11 (29.7)
Currently drinking alcohol	10 (55.6)	12 (63.2)	22 (59.5)
Previous use	3 (16.7)	1 (5.3)	4 (10.8)
Cannabis consumption (%)			
Never used rec. cannabis	14 (77.8)	16 (84.2)	30 (81.1)
Current rec. cannabis use	3 (16.7)	2 (10.5)	5 (13.5)
Previous use	1 (5.6)	1 (5.3)	2 (5.4)
Taking opioids preop – PRN (%)	3 (16.7)	3 (15.8)	6 (16.2)
Previous knee surgery (%)	2 (11.1)	4 (21.0)	6 (16.2)
Duration of surgery (min) Mean (SD)*	51.8 (10.9)	51.4 (7.5)	51.6 (9.2)
Regional/Spinal anesthesia (%)*	16 (94.1)	17 (100)	33 (97.1)
*n = 34 participants who had surgery; 17 Placebo, 17 MPL-001			

In-Hospital Care

Half of participants (16/33, 49%) were discharged on the day of surgery without staying overnight; 36% (12/33) stayed in the hospital for one night and 9% (3/33) stayed for two nights. One stayed 4 nights due to comorbidities and pain, and one stayed for 8 nights due to comorbidities. All but one participant had regional/spinal anesthesia. All participants received oral and/or intravenous opioids while in hospital.

Primary Outcome: Feasibility

Enrollment

Across two sites, we included 37 participants. Total study enrollment spanned 57 weeks, from May 2023 to June 2024, for an overall enrollment rate of 2.9 patients/month. To meet our predefined feasibility

target of 40-patients in 26 weeks, an enrollment rate of 6.7 patients/month was required. Notably, after an initial strong recruitment period where we enrolled 9 participants in the first month, we paused enrollment for 17 weeks due to logistical reasons. Excluding this pause, our overall enrollment rate was 4.2 patients/month. (Fig. 2)

Treatment Adherence

36 of 37 randomized participants started their study medication. One randomized participant withdrew immediately after randomization without taking any study doses. Two participants withdrew before surgery after starting the study drug. These three patients remained in the trial. Of the remaining 34 participants, the mean adherence preoperatively was 82% of doses (SD 25.7; 95% CI 73 to 91), with 71% (24/34; 95% CI 53 to 85) achieving our prespecified goal of at least 75% of doses taken. Of the 33 participants remaining in the trial at the immediate post-op visit, the mean adherence postoperatively was 59% (SD 38; 95% CI 46 to 73) of doses, with 48% (16/33; 95% CI 31 to 66) achieving our prespecified goal of at least 75% of doses taken. Five participants also chose to extend their treatment past 6 weeks with a range of 16–57 additional days of study medication use.

Tolerable Dose

Most participants (28/36; 78%) who started the study medication were able to titrate up to and tolerate the maximum 2.5 mL (125mg CBD/5mg THC) daily dose. Of the remaining 8 participants (3 in the placebo group and 5 in the CBD group), 2 reached 1 mL/day (50mg CBD/2mg THC), 3 reached 1.5 mL/day (75mg CBD/3mg THC), and 3 reached 2 mL/day (100mg CBD/4mg THC). Reasons given for not reaching the target dose or decreasing their dose included diarrhea, unpleasant taste, vomiting, nausea, and impaired concentration.

Follow-Up Completion

Of 37 participants, 30 (81%; 95% CI 65 to 92) completed their 26 week follow-up visit.

Secondary Outcomes: Clinical

CPSP

At 12 weeks postop, 9/32 (28%; 95% CI 14 to 47) participants reported CPSP; 41% in the placebo arm (7/17; 95% CI 18 to 67) and 13% in the cannabis arm (2/15; 95% CI 2 to 41). At 26 weeks postop, 5/30 (17%; 95% CI 6 to 35) participants reported CPSP; 19% in the placebo arm (3/16; 95% CI 4 to 46) and 14% in the cannabis arm (2/14; 95% CI 2 to 43). Of note, one of the patients in the cannabis arm that reported CPSP at both 12 and 26 weeks did not take any of their study drug during the trial.

Opioid use

All participants reported using opioids after discharge. The duration of postoperative opioid use ranged from 2 days to more than 26 weeks, with a median duration of 25 days (IQR 14 to 48). The median duration was 32 days (IQR 14 to 64) in the cannabis group and 16 days (IQR 12 to 37) in the placebo group. The Kaplan-Meier survival curve is shown in Fig. 3.

Adverse Events

In total, there were 66 AEs reported among 31 participants. In the cannabis arm, there were 18 treatment-related AEs in 11 patients, and in the placebo arm there were 19 treatment-related AEs in 12 patients. Gastrointestinal events comprised 39% of AEs (26 out of 66), with nausea and diarrhea being the most common. There was one serious AEs recorded (enteritis in the CBD arm), which was not related to the study drug. (Table 4). AEs that participants reported as reasons for stopping the study drug included throat irritation, diarrhea, vomiting due to unpleasant taste, nausea, headache, and impaired concentration, and two participants reported decreasing their dose due to diarrhea but did not stop the study drug.

Table 4
Adverse Event Details

AE	Placebo	MPL-001	Total
Knee-related AEs			
Knee stiffness	6	1	7
Superficial infection	0	1	1
Erythema	0	1	1
Gastrointestinal AEs			
Nausea/upset stomach	4	8	12
Diarrhea	4	4	8
Vomiting	1	0	1
Constipation	0	1	1
Enteritis	0	1*	1
Small bowel obstruction	1	0	1
Indigestion	1	0	1
Abdominal pain	0	1	1
Other AEs			
Headache	7	1	8
Fatigue	2	2	4
AE in non study joint	2	1	3
Back pain	2	0	2
Insomnia	2	0	2
Dry mouth	2	0	2
Drowsiness	0	1	1
Dizziness	1	1	2
Throat irritation	2	0	2
Impaired concentration	0	1	1
Mood changes	0	1	1
Feeling flush	1	0	1
* Classified as a serious AE			

AE	Placebo	MPL-001	Total
Mouth sores	0	1	1
Restless leg	0	1	1
* Classified as a serious AE			

Pain intensity and interference

At preop, patients reported their average pain in the past 24 hours was 5.9 (SD 1.6) in the cannabis arm and 5.9 (SD 2.2) in the placebo arm on a 0–10 numeric rating scale. At 26 weeks postop this improved to 3.5 (SD 1.5) in the cannabis arm and 2.6 (SD 2.0) in the placebo arm. For the pain interference subscale, at preop the mean pain interference was 5.9 (SD 1.9) in the cannabis arm and 6.0 (SD 2.6) in the placebo arm on a 0–10 numeric rating scale. At 26 weeks postop this improved to 2.1 (SD 2.3) in the cannabis arm and 2.1 (SD 2.4) in the placebo arm. (Table 5).

Table 5
BPI Pain Intensity and Pain Interference

Time/pain score/level	Placebo	MPL-001	Total
Preop (n = 37) Mean (SD)	6.7 (2.2)	7.3 (2.0)	7.0 (2.1)
Worst	4.6 (2.7)	3.8 (1.9)	4.2 (2.3)
Least	5.9 (2.2)	5.9 (1.6)	5.9 (1.9)
Average	5.6 (2.6)	4.8 (2.1)	5.2 (2.4)
Now	6.0 (2.6)	5.9 (1.9)	6.0 (2.2)
Interference			
2 weeks postop (n = 32) Mean (SD)	6.4 (1.7)	6.9 (1.6)	6.6 (1.7)
Worst	2.9 (1.9)	1.9 (1.5)	2.4 (1.7)
Least	4.8 (2.0)	4.5 (1.1)	4.7 (1.6)
Average	4.2 (2.3)	3.1 (2.3)	3.7 (2.3)
Now	4.4 (3.3)	6.8 (2.9)	5.5 (3.3)
Interference			
6 weeks postop (n = 32) Mean (SD)	6.3 (2.2)	4.3 (2.5)	5.3 (2.5)
Worst	2.2 (1.4)	1.6 (1.5)	1.9 (1.5)
Least	4.2 (1.9)	3.1 (2.0)	3.7 (2.0)
Average	3.4 (2.3)	1.8 (1.7)	2.6 (2.2)
Now	3.7 (2.1)	3.7 (2.9)	3.7 (2.5)
Interference			
12 weeks postop (n = 32) Mean (SD)	5.0 (2.2)	4.5 (2.5)	4.8 (2.3)
Worst	1.5 (1.5)	1.5 (1.8)	1.5 (1.7)
Least	3.3 (1.8)	3.0 (2.0)	3.2 (1.9)
Average	1.7 (1.7)	2.1 (2.0)	1.9 (1.9)
Now	2.9 (2.5)	2.9 (2.9)	2.9 (2.7)
Interference			
26 weeks postop (n = 30) Mean (SD)	4.1 (2.6)	4.9 (2.2)	4.4 (2.4)
Worst	1.6 (1.5)	0.9 (1.2)	1.2 (1.4)
Least	2.6 (2.0)	3.5 (1.5)	3.0 (1.8)
0–10 numeric rating scale			

Time/pain score/level	Placebo	MPL-001	Total
Average	1.3 (1.4)	2.5 (2.4)	1.8 (2.0)
Now	2.1 (2.4)	2.1 (2.3)	2.1 (2.3)
Interference			
0–10 numeric rating scale			

HADS

At preop, 32% of participants (6/19) in the cannabis arm and 17% (3/18) in the placebo arm met the criteria for borderline or clinically important depression. For anxiety this was 47% of participants (9/19) in the cannabis arm and 39% (7/18) in the placebo arm. At 26 weeks postop, 14% of participants (2/14) in the cannabis arm and 0% (0/16) in the placebo arm met the criteria for borderline or clinically important depression. For anxiety this was 14% of participants (2/14) in the cannabis arm and 19% (3/16) in the placebo arm. (Table 6).

Table 6
Anxiety and Depression

Time	Placebo	MPL-001	Total
Depression subscale, n (%) meeting criteria			
Preop (n = 37)	3 (16.7)	6 (31.6)	9 (24.3)
2 weeks postop (n = 32)	4 (23.5)	8 (53.5)	12 (37.5)
6 weeks postop (n = 32)	2 (11.8)	4 (26.7)	6 (18.8)
12 weeks postop (n = 32)	2 (11.8)	2 (13.3)	4 (12.5)
26 weeks postop (n = 30)	0 (0)	2 (14.2)	2 (6.7)
Anxiety subscale, n (%) meeting criteria			
Preop (n = 37)	7 (38.9)	9 (47.4)	16 (43.2)
2 weeks postop (n = 32)	4 (23.5)	1 (6.7)	5 (15.6)
6 weeks postop (n = 32)	3 (17.6)	4 (26.7)	7 (18,8)
12 weeks postop (n = 32)	3 (17.6)	1 (6.7)	4 (12.5)
26 weeks postop (n = 30)	3 (18.8)	2 (14.2)	5 (16.7)
Using a cutoff of ≥ 8			

EQ-5D

Participants' health-related quality of life improved over time on average. At preop, the mean overall health on a scale of 0-100 (100 is the best) was 59.4 (SD 19.2) in the cannabis arm and 68.9 (SD 19.2) in the placebo arm. At 26 weeks postop, mean overall health was 79.5 (SD 14.8) in the cannabis arm and 80.7 (11.7) in the placebo group. Index values were generally low preoperatively and increased substantially after surgery. The mean preop index value was 0.555 (SD 0.242) in the cannabis arm and 0.573 (SD 0.178) in the placebo arm. The mean index value at 26 weeks postoperatively was 0.780 (SD 0.138) in the cannabis arm and 0.797 (SD 0.097) in the placebo arm. (Table 7).

Table 7
EQ-5D

Time	Placebo	MPL-001	Total
Index values (maximum value 1.0)			
Preop (n = 37)	0.573 (0.178)	0.555 (0.242)	0.564 (0.211)
2 weeks postop (n = 32)	0.673 (0.163)	0.643 (0.123)	0.659 (0.144)
6 weeks postop (n = 32)	0.764 (0.109)	0.739 (0.112)	0.752 (0.110)
12 weeks postop (n = 32)	0.821 (0.083)	0.799 (0.084)	0.811 (0.083)
26 weeks postop (n = 30)	0.797 (0.097)	0.780 (0.138)	0.789 (0.116)
Visual analog scale (Scale of 0-100%)			
Preop (n = 37) Mean (SD)	68.9 (19.2)	59.4 (19.2)	64.0 (19.3)
2 weeks postop (n = 32) Mean (SD)	74.9 (12.8)	74.1 (16.8)	74.5 (14.3)
6 weeks postop (n = 32) Mean (SD)	77.7 (12.5)	74.0 (15.9)	75.9 (13.8)
12 weeks postop (n = 32) Mean (SD)	75.9 (14.2)	77.0 (13.2)	76.8 (13.1)
26 weeks postop (n = 30) Mean (SD)	80.7 (11.7)	79.5 (14.8)	80.1 (13.1)

Return to Function

Participants' return to function improved over time on average. At 2 weeks postop, the mean percentage of function regained was 57.1% (SD 20.6) in the cannabis arm and 61.9% (SD 17.7) in the placebo arm. At 26 weeks postop, the mean percentage of function regained was 75.0% (SD 18.7) in the cannabis arm and 78.3% (SD 21.9) in the placebo arm. Few participants regained function with no restrictions by 26 weeks postop in the leisure or home duties domain (leisure 6/30, home duties 12/30); however, 10 of the 12 (83%) participants who were working before their surgery returned to work with no limitations. (Table 8).

Table 8
Return to Function

Time	Placebo	MPL-001	Total
Returned to work with no limitations (%)			
2 weeks postop (n = 13)*	0	1 (16.7)	1 (7.7)
6 weeks postop (n = 14)*	0	0	0
12 weeks postop (n = 12)*	2 (28.6)	1 (20.0)	3 (25.0)
26 weeks postop (n = 12)*	5 (83.3)	5 (83.3)	10 (83.3)
Returned to leisure activities with no limitations (%)			
2 weeks postop (n = 32)	0	0	0
6 weeks postop (n = 32)	0	1 (6.7)	1 (3.1)
12 weeks postop (n = 32)	2 (11.8)	2 (13.3)	4 (12.5)
26 weeks postop (n = 30)	3 (18.8)	3 (21.4)	6 (20.0)
Returned to home duties with no limitations (%)			
2 weeks postop (n = 32)	0	0	0
6 weeks postop (n = 32)	0	2 (13.3)	2 (6.3)
12 weeks postop (n = 32)	5 (29.4)	4 (28.6)	9 (29.0)
26 weeks postop (n = 30)	5 (31.3)	7 (50.0)	12 (40.0)
Percentage of function regained (*Scale of 0-100%)*			
2 weeks postop (n = 32) Mean (SD)	61.9 (17.7)	57.1 (13.4)	60.5 (15.7)
6 weeks postop (n = 32) Mean (SD)	72.1 (17.3)	69.6 (23.7)	71.2 (19.6)
12 weeks postop (n = 32) Mean (SD)	80.6 (13.2)	71.4 (17.4)	75.6 (15.9)
26 weeks postop (n = 30) Mean (SD)	78.3 (21.9)	75.0 (18.7)	76.7 (20.2)
*Denominator does not include participants who were not working before surgery			
9: Insomnia Severity Index			

Insomnia Severity Index

Preoperatively, 9/19 (47%) participants in the cannabis arm and 10/18 (56%) participants in the placebo arm met criteria for moderate to severe insomnia. At 26 weeks postop, 2/14 (14%) participants in the cannabis arm and 3/16 (19%) participants in the placebo arm met criteria for moderate to severe insomnia. (**Table 9**).

DISCUSSION

Our pilot trial demonstrated that a definitive trial to establish the effectiveness of cannabis to reduce CPSP after TKA may be feasible with modifications to our protocol. First, participants' adherence was lower than anticipated and several withdrew from the trial (in both groups) due to AEs or no longer wanting to take the study medication. The oil-based formulation may have adversely affected adherence because of gastrointestinal adverse events and difficulty with administration. We plan to address this issue by switching to a capsule formulation that contains a smaller volume of oil. Second, our enrollment rate was below our feasibility threshold. We will address this by including additional recruiting sites in our definitive trial. Third, it was challenging to set up infrastructure and cannabis licensing to store cannabis products on site at hospitals and clinics due to strict Cannabis Act [41] regulations surrounding security, reporting, and destruction of cannabis products. We will explore using a centralized dispensing model to mitigate this issue.

Our pilot study provides preliminary safety data of administering oral cannabis to TKA patients at a dose of 125 mg CBD and 5 mg THC per day. None of our participants experienced any cannabis-related serious AEs. The AEs that are of potential concern with cannabis-based medications such as dizziness, impaired concentration, falls, and mood changes were rare and evenly distributed across the two groups. This is reasonable given that we administered a CBD-dominant product, and most harms associated with cannabis products are associated with THC content [42]. Previous systematic reviews have identified associations between cannabis use and increased risk of acute coronary syndrome, stroke and cardiovascular death [43], risk of infection, deep vein thrombosis and revision surgery after TKA [44], but these studies focused on recreational versus therapeutic use of cannabis. Further studies are required to elucidate long-term and infrequent risks of medical cannabis after surgery, particularly among older adults.

Strengths and limitations

The strengths of this pilot study include recruitment across 2 institutions and use of broad eligibility criteria to increase generalizability, a high rate of consent among patients eligible to participate, concealment of allocation, and blinding of all study participants and staff. Limitations include a small sample size that increases the risk of imbalance of prognostic factors between study groups, and a modest treatment adherence rate. Further, although our study products were visually identical, and masked for smell and taste, and we found equal distribution of adverse events between groups, we did not formally assess for blinding success [45].

CONCLUSIONS

Our pilot study identified key issues that require modification before conducting a definitive trial of cannabis versus placebo to reduce CPSP among TKA. We will address these issues by including

additional centres to expand participant recruitment, and switch from oil drops to a capsule formulation to improve participant adherence to the study treatment and follow-up.

Abbreviations

AE
adverse event
CBD
cannabidiol
CI
confidence interval
CIHR
Canadian Institutes of Health Research
CPSP
chronic postsurgical pain
CTO
Clinical Trials Ontario
GMP
Good Manufacturing Practices
ICH
GCP–International Council for Harmonisation Good Clinical Practices
IQR
interquartile range
MCT
medium chain triglyceride
NSAIDs
nonsteroidal anti–inflammatory drugs
SD
standard deviation
THC
Δ9–tetrahydrocannabinol
TKA
total knee arthroplasty

Declarations

Ethics and consent

We received ethics approval through Clinical Trials Ontario (CTO project #3701) which provided approval for both study sites, and the Hamilton Integrated Research Ethics Board was the research ethics board on record. We received a No Objection Letter from Health Canada to conduct this trial, given that our

investigational product (MPL-001) is not an approved medication in Canada. We prospectively registered our protocol on clinicaltrials.gov (NCT03825965). We conducted this study under the principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practices (ICH-GCP). All participants provided written informed consent prior to participating.

Competing interests:

The authors declare that they have no competing interests.

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Note

two participants in the placebo group had a total of 8 adverse events but were removed post-randomization for being ineligible for surgery. These participants' AEs are not listed in the above table. The AEs were: drowsiness, diarrhea, nausea (2 events), anemia, bradycardia (SAE), and headache (2 events)

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Author Contribution

JWB conceived and designed the study, acquired funding, supervised research staff, and wrote and revised the manuscript. BF contributed to protocol design, collected data, and edited the manuscript. KM contributed to study design and methodology, managed the project, managed and analyzed data, and wrote and revised the manuscript. IK managed and analyzed data and revised the manuscript. BS contributed to statistical methodology and data analysis and revised the manuscript. A. Atrey contributed to data collection and supervision and revised the manuscript. CTT collected data and revised the manuscript. A. Adili conceived and designed the study, acquired funding, supervised research staff, and revised the manuscript. All authors read and approved the final manuscript.

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request with appropriate data sharing agreements and ethical approval.

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Figures

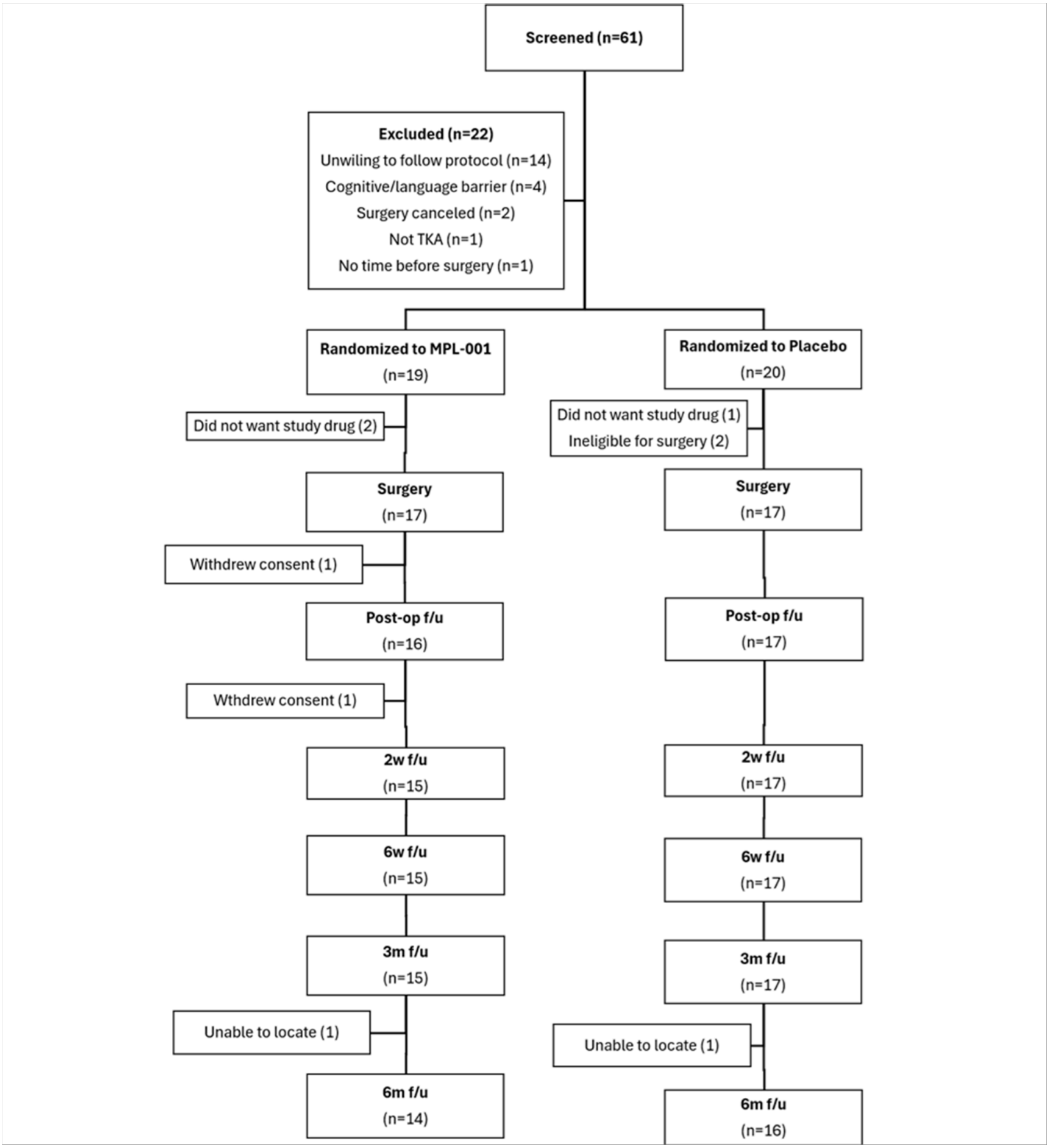

Figure 1

Study flow diagram

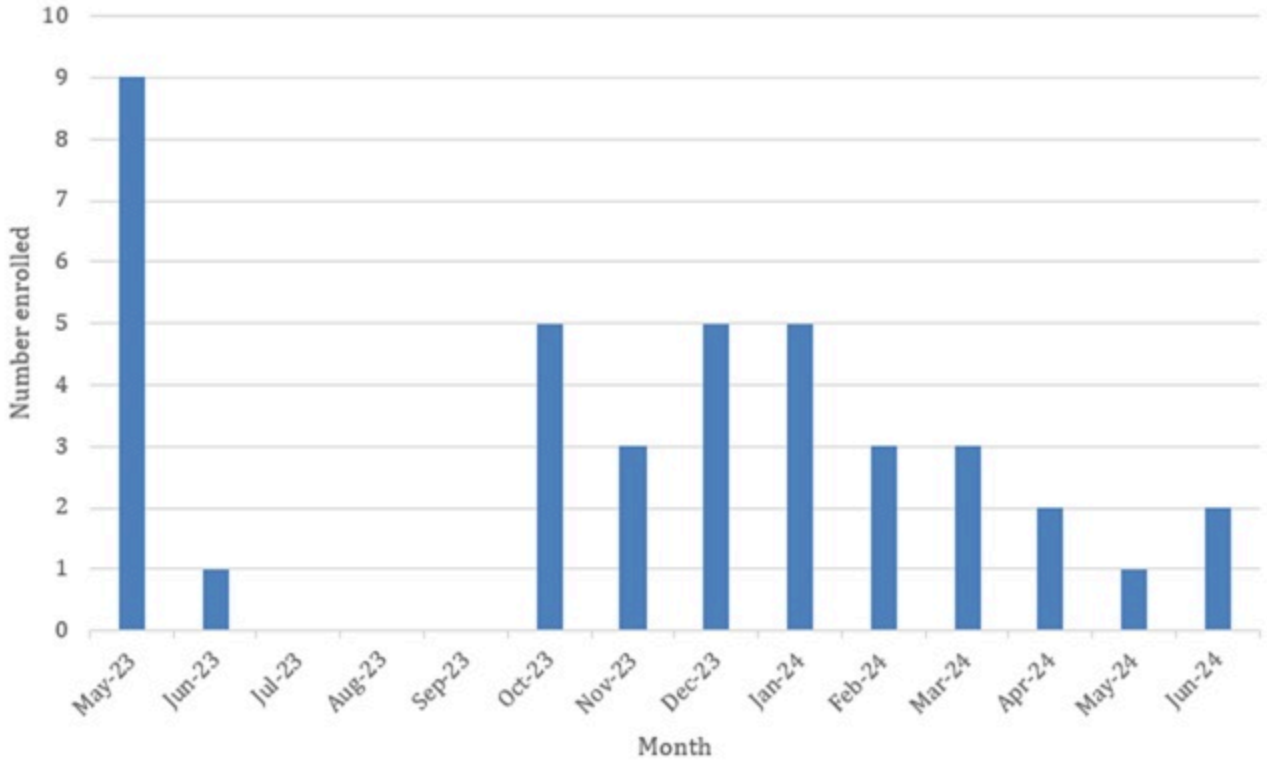

Figure 2

Enrollment per month

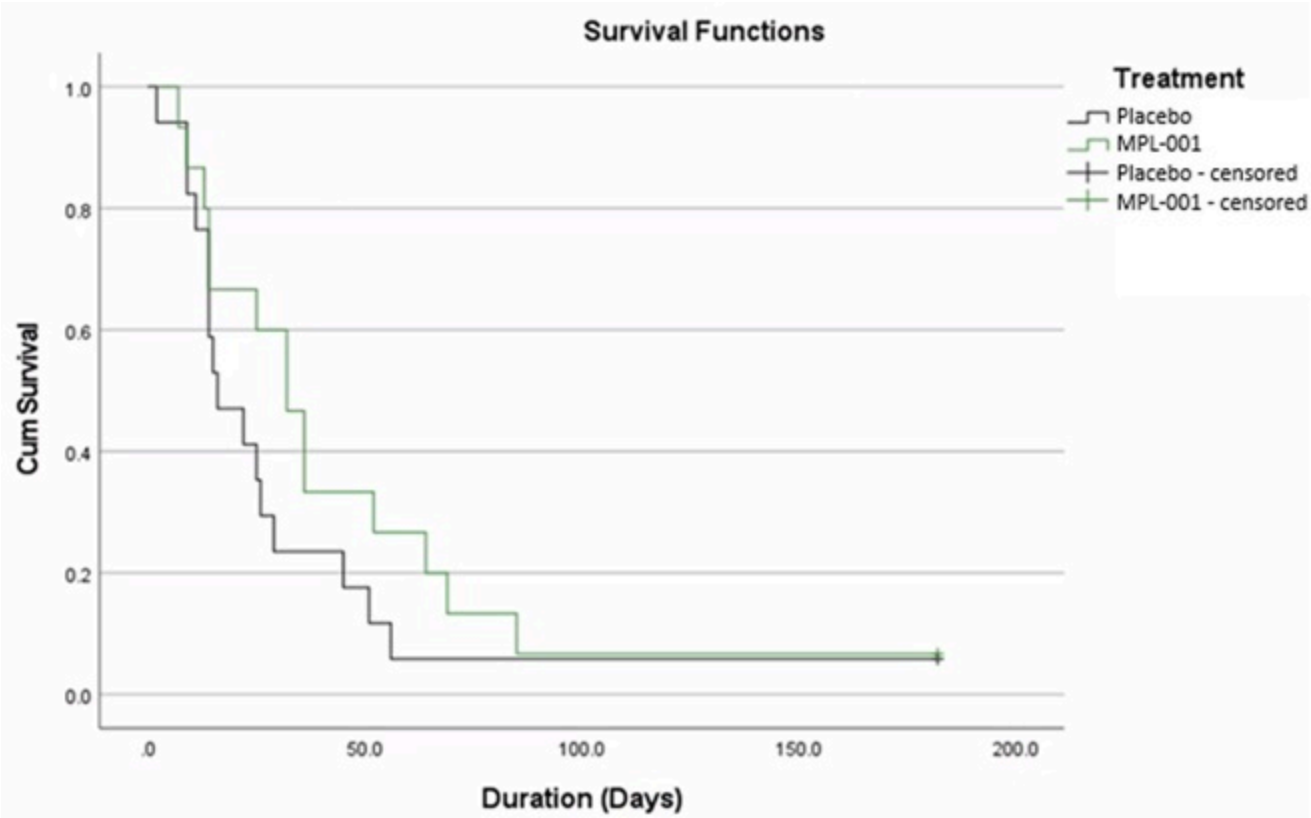

Figure 3

Kaplan-Meier survival curve for opioid duration