




Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved Satisfaction Immediately After Arthroscopic Rotator Cuff Repair

A Placebo-Controlled, Double-Blinded, Randomized Trial

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Background: Despite the widespread use and sales of cannabidiol (CBD) products in the United States, there is a paucity of literature to evaluate its effectiveness, safety, or ideal route of administration for postoperative pain.

Purpose: To evaluate the potential analgesic effects of buccally absorbed CBD in patients who have undergone arthroscopic rotator cuff repair (ARCR).

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: This was a US Food and Drug Administration-sanctioned, multicenter, placebo-controlled, randomized, double-blinded trial conducted in patients undergoing ARCR. Patients aged from 18 to 75 years undergoing ARCR were prospectively enrolled and randomized to the control and experimental groups. The experimental group received an oral, buccally absorbed tablet containing 25 mg of CBD 3 times a day if <80 kg, or 50 mg of CBD 3 times a day if >80 kg, for 14 days postoperatively, while the control group received an identical placebo. Patients were followed up on days 1, 2, 7, and 14, and visual analog scale (VAS) for pain scores, opioid consumption, and satisfaction with pain control were recorded. Additionally, liver function tests were conducted on days 7 and 14 to assess safety, and nausea was monitored. $P < .05$ was considered to be statistically significant.

Results: Overall, 100 patients were recruited, with 1 patient being excluded, for a total of 99 patients. There were no significant differences in patient demographics between the 2 groups. On day 1, the VAS pain score was significantly lower in the CBD group than in the control group (4.4 ± 3.1 vs 5.7 ± 3.2 , respectively; $P = .04$), although this difference was no longer present on day 2 (4.7 ± 2.8 vs 5.3 ± 2.6 , respectively; $P = .32$). On both days 1 and 2, patient satisfaction with pain control was significantly higher in the CBD group than in the control group (day 1: 7.0 ± 3.0 vs 5.6 ± 3.7 , respectively [$P = .04$]; day 2: 7.3 ± 2.5 vs 6.0 ± 3.3 , respectively [$P = .03$]). The quantity of opioids consumed was low in both groups, and there were no statistically significant differences in opioid consumption ($P > .05$). On days 7 and 14, there were no statistically significant differences in VAS scores, opioid consumption, or patient satisfaction with pain control between the CBD and control groups ($P > .05$ for all). There were no significant differences in liver function test results postoperatively ($P > .05$).

Conclusion: Buccally absorbed CBD demonstrated an acceptable safety profile and showed significant promise in the reduction of pain in the immediate perioperative period after ARCR compared with the control. Further studies are currently ongoing to confirm dosing and effectiveness in other orthopaedic conditions.

Registration: NCT04672252 (ClinicalTrials.gov identifier).

Keywords: cannabidiol; CBD; shoulder arthroscopic surgery; rotator cuff repair; postoperative pain

patients, multimodal management strategies have become increasingly important.¹ It is also estimated that 40% to 50% of all patients undergoing ARCR are on preoperative opioids.²⁷ As a result of the increasing volume of outpatient shoulder arthroscopic procedures performed, alternative multimodal pain management solutions should be explored because of potential benefits including a reduction in adverse events.^{6,9,26}

The endocannabinoid system (ECS) is a neuromodulatory system that has recently emerged as a therapeutic target in pain management, as it is involved with regulating the inflammatory response to injuries as well as modulating pain.¹⁵ The ECS is composed of the CB1 and CB2 cannabinoid receptors, endogenous cannabinoid ligands known as endocannabinoids, and enzymes responsible for the synthesis and degradation of these molecules. Cannabidiol (CBD), which targets the ECS, has become a subject of growing interest since the US Congress passed the 2018 Farm Bill, which legalized industrial hemp (*Cannabis sativa* plants containing <0.3% tetrahydrocannabinol [THC] content) and its derivative cannabinoids, including CBD.¹⁷ CBD is a nonpsychotropic cannabinoid that has been reported to exhibit a range of therapeutic properties.¹³ It is well tolerated in humans, has the potential for a small risk profile, and has safe co-administration with opioid analgesics.^{1,2}

Despite the widespread use and sales of CBD products in the United States, there is a paucity of literature to evaluate its effectiveness or safety. With current trends to optimize multimodal pain management strategies after ARCR, and to mitigate the risks of treating postoperative pain with prolonged opioid use, we sought to evaluate the effects of CBD on postoperative pain and satisfaction after ARCR. Therefore, the purpose of this study was to evaluate the potential analgesic effects of buccally absorbed CBD in patients undergoing ARCR. The hypothesis was that patients receiving postoperative CBD would have improved postoperative pain scores and satisfaction and decreased opioid use compared with patients receiving a placebo (control).

METHODS

Study Design

This was a US Food and Drug Administration (FDA)–sanctioned (IND #147249), multicenter, controlled, randomized, prospective clinical trial. Institutional review

board approval (s19-01293) was obtained from both institutions involved in the study. Patient informed consent was obtained before study enrollment. Patients were enrolled and treated during the time period from December 2020 to December 2021.

All opioid-naïve patients aged between 18 and 75 years undergoing ARCR (in addition to open subpectoral biceps tenodesis, subacromial decompression, both, or neither) were eligible for inclusion in the study. Exclusion criteria can be found in Table 1. All patients entering the study were administered the Columbia Suicide Severity Rating Scale to ensure that no patient had previous or current suicidal ideation (see Appendix, available in the online version of this article), in accordance with FDA recommendations for clinical trials involving drugs with central nervous system activity. Any patients with elevated liver enzyme levels in the preoperative period were also excluded. Urine drug screening was performed on all patients to ensure that patients were opioid naïve and not currently using marijuana. All participants were required to refrain from the use of THC or other cannabis-related products for the duration of the study. Those who were not able to comply were excluded from the final data analysis. Premenopausal female patients had to have been currently practicing 2 effective types of birth control, which are defined as those, alone or in combination, that result in a low failure rate (<1% per year) when used consistently and correctly. Information recorded preoperatively included age, sex, height, weight, body mass index, and American Society of Anesthesiologists classification.

Randomization and Study Intervention

Patients were randomized preoperatively by researchers who were not involved in the study via the validated web-based Research Randomizer to receive either CBD or an identically tasting and appearing placebo.²⁵ Patients and the treating physician (M.J.A., A.S.R., K.K., L.M.J., G.G.-L.) were blinded to randomization. Patients were instructed to take 25 or 50 mg (patients >80 kg received 50 mg) of buccally absorbed CBD (Oravexx; Orcosa) based on body weight per the manufacturer's recommendation 3 times a day for 14 days. Enrollees were educated on the proper administration of the medication before surgery. Patients were instructed to take a morning, afternoon, and evening dose, with an equal amount of elapsed time between each dose, but were not given specific hour and

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TABLE 1
Exclusion Criteria^a

Legally incompetent or mentally impaired patient (eg, minors, Alzheimer disease, dementia)
<18 years of age
>75 years of age
Any patient considered a vulnerable participant: pregnant women or fetuses, children, cognitively impaired adults, prisoners
History of cannabis abuse or dependence
History of coagulation abnormalities and thromboembolic disease or current abnormal coagulation test values
History of stroke or acute coronary syndrome within 3 months before surgery
Abnormal coagulation profile
Renal failure (serum creatinine >250 μmol/L [2.83 mg/dL]) or liver cirrhosis
History of hypersensitivity to Percocet
Preoperative opioid management for any reason
Patients meeting the DSM-5 for major psychiatric illnesses (eg, bipolar disorder)
Diagnosis of major depression, psychosis, or substance abuse disorder
Current or previous suicidal ideation
Breastfeeding female patients
Clinically significant illness, including cardiovascular disorders
Clinically significant abnormal laboratory values
Abnormal liver function test results
Major neurological disorders (eg, dementia, Parkinson disease, cognitive impairments, epilepsy, history of traumatic brain/head injuries, or seizures)
Moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairments
Use of moderate or strong inhibitors of CYP3A4 and CYP2C19 concomitantly
Use of strong CYP3A4 and CYP2C19 inducers concomitantly
Use of substrates of UTG1A9, UTGB17, CYP2A1, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 concomitantly

^aDSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

minute times at which to take the doses. All patients received Percocet (oxycodone/acetaminophen; Endo Pharmaceuticals) 5-mg/325-mg tablets and were instructed to take them as needed, 1 to 2 tablets every 4 to 6 hours, and to wean from narcotics as soon as possible. Patients were instructed to continue taking CBD/placebo throughout the entire 14-day follow-up period.

A data safety monitoring board was created for the trial, and while no stopping rules were established, per the lead investigator's (M.J.A.) discretion, the trial was to be stopped if significant side effects were seen in the CBD group that threatened the safety of the patients or caused perioperative complications, including but not limited to severe nausea or vomiting, mental status changes, bleeding, or increases in the infection rate.

Surgical Technique

Surgery was performed with the patient in either the beach-chair or lateral decubitus position, based on surgeon preference. Interscalene blocks were given preoperatively

by the anesthesia team, who were also blinded to patient enrollment. The standardization of block medication (bupivacaine vs ropivacaine) was not necessarily performed for 4 reasons: the anesthesiologist had specific preferences, randomization would negate any effects of using differing blocks, pain control was measured in the evening on postoperative day 1 and not on postoperative day 0 when any difference in blocks would be maximized, and no indwelling catheters were used. Additionally, patients were allowed to receive other pain medications on postoperative day 0 while in the recovery suite, as the medications administered were only for short-term pain relief.

Surgical time, number of anchors, and concomitant procedures were recorded. Additionally, all patients undergoing biceps tenodesis underwent it in the form of open subpectoral biceps tenodesis to maintain homogeneity between groups. Patients wore a sling postoperatively for a period of time chosen by the operating physician, with none being instructed to discontinue the sling before the 2-week follow-up. Patients were allowed to perform simple elbow, wrist, and hand range of motion exercises as soon as tolerated, as well as Codman or pendulum exercises as tolerated, after the first postoperative visit.

Outcome Measures

The primary outcome of the study was to detect any difference in the visual analog scale (VAS) for pain score at multiple time points after ARCR. Secondary outcomes included postoperative patient satisfaction, opioid use, and potential complications, including changes in liver function test results and nausea or other adverse outcomes. All postoperative complications (surgical or potentially related to CBD) were recorded, and liver function test results were obtained at 2 time points and compared with preoperatively. Additionally, patients were screened for any psychiatric manifestations of suicidality. Patients were instructed in their postoperative pain management log to note the amount of Percocet taken, patient satisfaction, nausea level, and VAS score. Pain control, patient satisfaction, and nausea were measured at 6 hours and on days 1, 2, 7, and 14. Opioid consumption was documented on days 1 to 7 on a daily basis and then additively from days 8 to 14. Patients were instructed to mark "yes" or "no" for CBD use each time they took the medication for the full 14-day period in a patient log provided at the start of the study and reviewed by study coordinators (E.T.H., K.V.) at the end of each patient's participation period to ensure compliance with the study protocol. Additional secondary analyses included any differences in outcomes when accounting for differences in the therapeutic dose. Patients were followed up in the office postoperatively at 1 and 2 weeks.

Statistical Analysis

Our power analysis was based on the literature on postoperative pain control after shoulder arthroscopic surgery. Calculations were performed using VAS scores of 3 and 1.6 for the control and CBD groups, respectively, with an

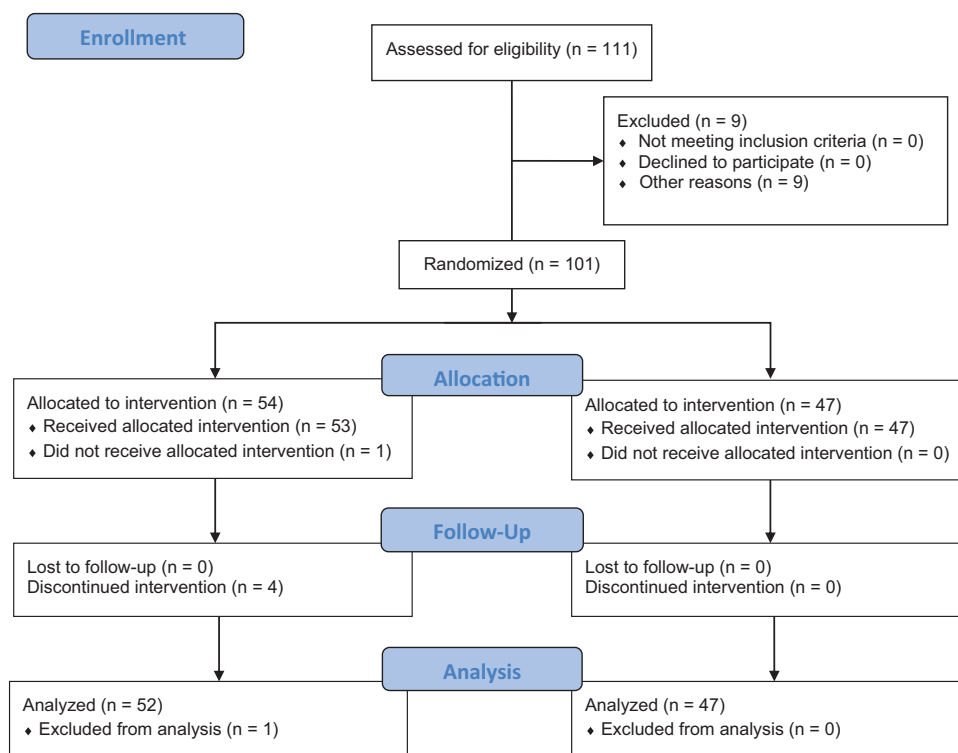


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

SD of 2. To achieve 80% power to reject the null hypothesis of equal means when the population mean difference between the control and CBD groups is $\mu_1 - \mu_2 = 3.0 - 1.6 = 1.4$, with an SD for both groups of 2.0 at a significance level (alpha) of .05 using a 2-sided, 2-sample equal variance t test, a sample size of 39 would be required in each group.²⁴ Thus, to allow for a 10% dropout rate at 14-day follow-up, 100 patients would be required to enroll. For all continuous and categorical variables, descriptive statistics were calculated. Continuous variables were reported as the weighted mean and estimated standard deviation, whereas categorical variables were reported as frequencies with percentages. Categorical variables were analyzed using the Fisher exact test or chi-square test. The independent or paired t test for normally distributed variables, or the nonparametric Wilcoxon signed-rank test, was performed to compare continuous variables. Subgroup analysis comparing patients receiving 50 mg of CBD versus 25 mg of CBD versus placebo medication was conducted using the Fisher exact test or chi-square test for categorical variables and analysis of variance or the Kruskal-Wallis H test for continuous variables. Post hoc Tukey testing was performed comparing all possible pairs of subgroup means to determine between which subgroups the differences were significant. These tests were necessary, as without post hoc testing, analysis of variance or the Kruskal-Wallis test is only able to determine that there is a difference between groups; however, they do not elucidate specifically where these differences lie. $P < .05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

Overall, 100 patients were enrolled in this study across the 2 investigating centers, with 47 patients randomized to the control group and 53 placed in the experimental group (Figure 1). One patient was excluded from the analysis, as he or she used marijuana postoperatively, leading to the final count of 52 patients in the experimental group. There were no significant differences in age, sex, body mass index, concomitant procedures including biceps tenodesis and subacromial decompression, and number of anchors used intraoperatively between the 2 groups (Table 2).

Postoperative Pain and Satisfaction

On day 1, the VAS pain score was significantly lower in the CBD group than in the control group (4.4 ± 3.1 vs 5.7 ± 3.2 , respectively; $P = .04$). On both days 1 and 2, patient satisfaction with pain control was significantly higher in the CBD group than in the control group (day 1: 7.0 ± 3.0 vs 5.6 ± 3.7 , respectively [$P = .04$]; day 2: 7.3 ± 2.5 vs 6.0 ± 3.3 , respectively [$P = .03$]). For the remainder of the study, the CBD group outperformed the control group at all time points for pain and patient satisfaction; however, the results did not meet statistical significance (Table 3).

TABLE 2
Patient Characteristics^a

Variable	CBD (n = 52)	Control (n = 47)
Age, y	58.2 ± 8.8	57.1 ± 10.1
Female sex	21 (40.4)	17 (36.2)
Body mass index	29.1 ± 5.0	28.2 ± 7.1
Biceps tenodesis	13 (25.0)	10 (21.3)
Subacromial decompression	15 (28.8)	23 (48.9)
Both biceps tenodesis and subacromial decompression	17 (32.7)	13 (27.7)
No. of anchors used	3.0 ± 1.6	3.3 ± 1.4

^aData are shown as mean ± SD or n (%). CBD, cannabidiol.

Opioid Consumption and Nausea

There were no statistically significant differences in opioid consumption ($P > .05$), which was relatively low in both groups, and no significant difference in nausea (Table 4).

Subgroup Analysis of Postoperative Pain, Satisfaction, Opioid Use, and Nausea

On subgroup analysis, it was noted that 23 patients received 25 mg of CBD and 29 patients received 50 mg of CBD. There were no significant differences between the subgroups in age, sex, or concomitant procedures including biceps tenodesis and subacromial decompression.

There were significant differences between the 3 subgroups in the VAS score on day 1 (CBD 50 mg: 3.9 ± 3.2 ; CBD 25 mg: 5.1 ± 2.9 ; control: 5.7 ± 3.2 ; $P = .04$), with an almost 2-point lower score in the CBD 50-mg subgroup compared to placebo. There were also significant differences in satisfaction on day 1 (CBD 50 mg: 8.0 ± 2.5 ; CBD 25 mg: 5.7 ± 3.2 ; control: 5.6 ± 3.7 ; $P = .005$) and day 2 (CBD 50 mg: 7.9 ± 2.1 ; CBD 25 mg: 6.5 ± 2.8 ; control: 6.0 ± 3.3 ; $P = .02$). The CBD 50-mg subgroup consistently outperformed the CBD 25-mg and control subgroups, trending toward statistical significance at several time points, especially for the VAS score (Table 5). Regarding opioid use, the 50-mg subgroup outperformed the control and 25-mg subgroups at all time points but the differences did not meet statistical significance (Table 6).

Post Hoc Analysis

Post hoc Tukey testing of subgroups showed that patients receiving 50 mg of CBD had significantly lower VAS scores on day 1 compared with controls (3.9 ± 3.2 vs 5.7 ± 3.2 , respectively; $P = .03$). Patients receiving 50 mg of CBD also reported increased satisfaction on day 1 (8.0 ± 2.5 vs 5.6 ± 3.7 , respectively; $P = .006$) and day 2 (7.9 ± 2.1 vs 6.0 ± 3.3 , respectively; $P = .02$) compared with controls. The subgroup receiving 25 mg of CBD did not differ significantly compared with the subgroup receiving 50 mg of CBD or the control subgroup ($P > .05$) except for satisfaction on day 1. On days 7 and 14, there were no statistically

TABLE 3
Pain and Patient Satisfaction^a

Variable	CBD	Control	P Value
Day 1			
VAS score	4.4 ± 3.1	5.7 ± 3.2	.04
Satisfaction	7.0 ± 3.0	5.6 ± 3.7	.04
Day 2			
VAS score	4.7 ± 2.8	5.3 ± 2.6	.32
Satisfaction	7.3 ± 2.5	6.0 ± 3.3	.03
Day 7			
VAS score	2.5 ± 1.9	3.2 ± 2.7	.15
Satisfaction	8.0 ± 2.6	7.9 ± 2.7	.78
Day 14			
VAS score	1.6 ± 1.4	2.3 ± 2.4	.11
Satisfaction	8.7 ± 2.3	8.5 ± 2.4	.71

^aData are shown as mean ± SD. CBD, cannabidiol; VAS, visual analog scale.TABLE 4
Opioid Consumption and Nausea Levels^a

Variable	CBD	Control	P Value
Opioid MME			
Day 1	15.2 ± 12.0	19.7 ± 13.6	.08
Day 2	10.3 ± 18.7	16.7 ± 36.6	.29
Day 7	59.3 ± 53.2	67.3 ± 55.2	.47
Day 14	8.0 ± 19.3	10.3 ± 22.7	.61
Nausea ^b			
Day 2	2.1 ± 2.6	2.5 ± 3.1	.51
Day 7	0.2 ± 1.1	0.6 ± 2.1	.23
Day 14	0.1 ± 0.4	0.5 ± 1.7	.15

^aData are shown as mean ± SD. CBD, cannabidiol; MME, morphine milligram equivalent.^bRated on a scale from 0 (no nausea) to 10 (extreme nausea).TABLE 5
Subgroup Analysis of Pain and Patient Satisfaction^a

Variable	CBD 25 mg	CBD 50 mg	Control	P Value
Day 1				
VAS score	5.1 ± 2.9	3.9 ± 3.2	5.7 ± 3.2	.04
Satisfaction	5.7 ± 3.2	8.0 ± 2.5	5.6 ± 3.7	.005
Day 2				
VAS score	4.7 ± 2.7	4.7 ± 3.0	5.3 ± 2.6	.61
Satisfaction	6.5 ± 2.8	7.9 ± 2.1	6.0 ± 3.3	.02
Day 7				
VAS score	3.1 ± 2.1	2.1 ± 1.7	3.2 ± 2.7	.13
Satisfaction	7.4 ± 2.7	8.6 ± 2.4	7.9 ± 2.7	.34
Day 14				
VAS score	2.0 ± 1.4	1.1 ± 1.3	2.3 ± 2.4	.10
Satisfaction	8.3 ± 2.2	9.1 ± 2.4	8.5 ± 2.4	.58

^aData are shown as mean ± SD. CBD, cannabidiol; VAS, visual analog scale.

significant differences in the VAS score, opioid consumption, or patient satisfaction with pain control ($P > .05$ for

TABLE 6
Subgroup Analysis of Opioid Consumption
and Nausea Levels^a

Variable	CBD 25 mg	CBD 50 mg	Control	P Value
Opioid MME				
Day 1	15.4 ± 10.0	15.0 ± 13.6	19.7 ± 13.6	.23
Day 2	10.2 ± 14.1	10.3 ± 21.9	16.4 ± 36.6	.58
Day 7	51.4 ± 47.4	65.4 ± 57.5	67.3 ± 55.2	.53
Day 14	10.8 ± 25.6	5.5 ± 10.8	10.3 ± 22.7	.63
Nausea ^b				
Day 2	1.0 ± 1.6	2.9 ± 3.0	2.5 ± 3.1	.05
Day 7	0.1 ± 0.5	0.3 ± 1.4	0.6 ± 2.1	.46
Day 14	0.1 ± 0.5	0.1 ± 0.4	0.5 ± 1.7	.36

^aData are shown as mean ± SD. CBD, cannabidiol; MME, morphine milligram equivalent.

^bRated on a scale from 0 (no nausea) to 10 (extreme nausea).

all). Although post hoc Tukey testing demonstrated a statistically significant difference in nausea levels on day 2 between the subgroups receiving 25 mg of CBD and 50 mg of CBD (1.0 ± 1.6 vs 2.9 ± 3.0 , respectively; $P = .04$), the difference required no clinical intervention or management of nausea for all but 1 patient, and there were no other significant differences in nausea levels (Table 7).

Adverse Events

Overall, 4 patients in the control group and 4 patients in the CBD group had elevated alanine transaminase levels at 7 days, which normalized at 14 days postoperatively. No other elevation in liver enzyme levels was seen, and there were no significant differences in postoperative liver function test results ($P > .05$). There were 5 suspected adverse events in the CBD group that could not confidently be attributed to CBD, especially as tablet absorption occurs buccally directly into the bloodstream and not through the gastrointestinal system. Two patients experienced a rash on postoperative day 2, 1 patient experienced nausea on postoperative day 2, 1 patient experienced abdominal pain, and 1 patient experienced rectal bleeding and elected to drop out of the study because of abdominal pain (although this was highly unlikely to be caused by the intervention medication, as the medication is not processed in the gastrointestinal tract). There were no significant differences in suspected adverse events between the CBD group and control group ($n = 5$ [9.6%] and $n = 0$ [0.0%], respectively; $P = .09$) or between the CBD 25-mg, CBD 50-mg, and control subgroups ($n = 2$ [8.7%], $n = 3$ [10.3%], and $n = 0$ [0.0%], respectively; $P = .09$).

DISCUSSION

The most important finding from this study was that buccally absorbed CBD was shown to be safe and effective in reducing pain and improving patient satisfaction in the immediate perioperative period after ARCR when compared with the control. These findings support our

TABLE 7
Post Hoc Tukey Testing^a

Variable	Adjusted P Value
VAS score on day 1	
CBD 50 mg–CBD 25 mg	.33
Control–CBD 25 mg	.71
Control–CBD 50 mg	.03
Satisfaction on day 1	
CBD 50 mg–CBD 25 mg	.03
Control–CBD 25 mg	.99
Control–CBD 50 mg	.006
Satisfaction on day 2	
CBD 50 mg–CBD 25 mg	.17
Control–CBD 25 mg	.78
Control–CBD 50 mg	.02
Nausea on day 2	
CBD 50 mg–CBD 25 mg	.04
Control–CBD 25 mg	.11
Control–CBD 50 mg	.78

^aPost hoc testing was conducted on variables that demonstrated significant differences between subgroups on analysis of variance or the Kruskal-Wallis test. CBD, cannabidiol; VAS, visual analog scale.

hypothesis. Although the results did not meet statistical significance for the later time points, the CBD group consistently outperformed the control group at all time points. Furthermore, those given a higher dose of CBD had statistically significant lower levels of postoperative pain and higher satisfaction; it is possible that a higher dose corresponded to improved outcomes, warranting further study. Additionally, there were no harmful side effects associated with the use of buccally absorbed CBD.

However, there exists a lack of clinical trials in this area, and thus, an evaluation of safety was also a significant concern of this study. Commercially available CBD is plagued by a lack of regulation as well as the potential for contamination by potentially hazardous chemicals.² Basic science studies have shown that CBD may be associated with elevated levels of hepatic transaminases, although our study found no significant change in liver function test results that could be exclusively attributed to CBD. Surgical trauma and acetaminophen use can both also mildly elevate liver function test results.^{5,10} Although CBD may be beneficial for nausea, the current study found minimal postoperative nausea and no difference between the CBD and control groups.¹⁹ Finally, CBD was not shown in our study to increase the risk of suicidal ideation and behavior, but this was assessed in accordance with FDA recommendations for clinical trials involving drugs with central nervous system activity.

Despite a very large shift toward the commercial use of CBD, legalization of marijuana, and growth of a multibillion dollar industry, there remains scant evidence supporting its use in the scientific literature, particularly in orthopaedic surgery and the role of CBD in managing pain. Chin et al⁴ recently reported in a survey of members of the Orthopaedic Trauma Association that 88% of trauma surgeons did not believe that they were knowledgeable in

the mechanism of CBD. However, 73% of the survey respondents believed that CBD has a role to play in the treatment of postoperative pain. Additionally, 83% of the respondents did not feel that they would be stigmatized if they recommended CBD to their patients, with 85% believing that there are no known effects on fracture healing and most saying that they would recommend CBD if it were medically and recreationally legal. Although some may worry about the possible effects of CBD on healing, the literature has shown that exposure to cannabinoids can potentially improve wound healing and can enhance the regenerative capacity of 2 major sources of stem cells: adipose and bone marrow derived.¹⁶ However, the clinical significance of this regenerative aspect of CBD remains unclear, although it is important to note that it does not have a negative effect, at least which may be contributed to cannabis if smoked.^{7,18,22}

The interest level of patients may also be quite significant when discussing the possibility of CBD as an adjunct for pain control. A recent survey study of patients with basal joint osteoarthritis found that almost 70% would be interested in trialing an oral-based CBD product, with 80% of patients interested in a topical treatment. However, Premkumar et al²⁰ reported that very few resources regarding CBD for knee or hip arthritis were available, the quality was poor, and few were sponsored by physicians or professional organizations, with the majority being overtly sales oriented.

The current study found that CBD resulted in improved pain and satisfaction in the first 2 days postoperatively when pain was at its most severe in the acute postoperative phase. Additionally, the difference nearly equaled the minimal clinically important difference of 1.4.²⁴ With higher doses, the minimal clinically important difference for the VAS was easily surpassed on the first postoperative day. The VAS score trended toward statistical significance at multiple time points. As postoperative pain lessened, the difference stopped being statistically significant; however, the CBD group still outperformed the control group and trended toward statistical significance at multiple time points. As the study was designed to detect a VAS score change of 1.4, the study was likely underpowered to significantly detect smaller statistical changes between the 2 groups.²⁴ Thus, it appears that the effect was greatest when the pain was most severe. However, it should be noted that the CBD group also had significantly higher patient satisfaction as a result of improved pain levels in the first few days. Further, with post hoc testing, by showing the true differences between the CBD 50-mg and control subgroups and not between the CBD 25-mg and control subgroups, our findings suggest that the 50-mg dose resulted in significant improvements in pain and satisfaction compared with other doses and should be utilized, as it may be superior to the 25-mg dose without significant adverse effects. These distinctions have important potential clinical implications.

Improved patient satisfaction is becoming an increasingly important variable, as patient-centered outcomes and pay-for-performance programs have become more common, particularly for inpatient services. Under the

Affordable Care Act, the Centers for Medicare and Medicaid Services have greatly expanded inpatient fee-for-value programs. The Hospital Value-Based Purchasing Program rewards hospitals that perform well on quality of care measures or, conversely, punishes those with poor scores. This is based on 4 quality domains: patient- and caregiver-centered experience, safety, clinical care outcomes/process, and efficiency and cost reduction.⁸ Although ARCR is almost exclusively an outpatient procedure, the potential for CBD use in other fields of orthopaedic surgery (inpatient fracture care, spine surgery, hip and knee reconstruction) holds tremendous promise,^{12,21} as mitigating postsurgical or chronic pain may improve the patient experience, improve clinical care outcomes, and reduce costs with more expeditious hospital discharges.

Additionally, there was no significant difference in opioid consumption between the 2 groups. While the goal of the current study was not to replace opioids with CBD, the lack of statistical significance is possibly because of the small cohort and the overall low level of opioids consumed, which may be attributable to institutional opioid stewardship and greater patient education.^{1,3,23} However, given the clinically relevant results, CBD may become another implement in the postoperative multimodal analgesia armamentarium after ARCR.⁹ Also, there is a lack of evidence on the use of oral medications after ARCR, with the majority of evidence being focused on gabapentinoids and a recent systematic review finding only 7 studies that have evaluated oral medications after ARCR.⁹

Further research is still required on the role of CBD as a postoperative medication as well as the optimal dosing and route of administration. A previous study by Lichtman et al¹⁴ found no superiority in 2 double-blind studies in regard to pain control when using systemically absorbed Sativex oral mucosal spray for chronic pain control in patients with advanced-stage cancer who were unresponsive to opioid analgesics but showed benefits at multiple interim time points, thereby demonstrating potential utility in patients with early intolerance to opioids. Similar to Lichtman et al, we elected to use a buccally absorbed tablet as opposed to oils or pills that are absorbed in the gastrointestinal system, as buccal absorption provides theoretical immediate release into the bloodstream, which could play a role in pain modulation. Additionally, the current study found that a higher dose of CBD resulted in significantly lower pain levels than a low dose of CBD, and as a result of the safety profile found in the current study, a further evaluation is warranted to see if higher doses are safe in patients <80 kg. Given that Epidiolex, an FDA-approved CBD formulation absorbed in the gastrointestinal system, utilizes dosages that far exceed those used in the present study, further research is necessary to evaluate the dose-response curve and efficacy using this route of administration. However, the current findings suggest that buccally absorbed CBD shows significant promise for immediate postoperative pain control. Alongside its optimization for ARCR, the use of CBD should be evaluated for other sources of orthopaedic pain, whether postoperative, acute, or chronic.

Limitations

There are a few limitations in the current study. First, this study included several orthopaedic surgeons, which may introduce bias into the study. However, their methods of ARCR were similar, and patients underwent a standardized postoperative rehabilitation protocol regardless of whether they underwent a concomitant procedure. Concomitant procedures and the size of the rotator cuff tear may have affected postoperative pain levels; however, these were controlled across the 2 groups. Finally, the study was primarily focused on immediate postoperative pain and was powered to evaluate this, and it was not powered to detect a difference at later stages when the pain became milder, but CBD still outperformed the control at each time point. Additionally, although differences in the preoperative interscalene nerve blocks could have potentially confounded results, randomization of the study intervention makes this less of a significant concern. Finally, the study was powered to detect an absolute difference regardless of timing.


CONCLUSION

Compared with placebo, buccally absorbed CBD for pain control after ARCR demonstrated no significant adverse events and resulted in a significant reduction in pain on postoperative day 1, increased patient satisfaction on postoperative days 1 and 2, and no significant differences in opioid consumption.

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REFERENCES

- Alaia MJ. Editorial commentary: Uncle Sam wants YOU! (to stop the opioid crisis). *Arthroscopy*. 2020;36(3):832-833.
- Argueta DA, Ventura CM, Kiven S, Sagi V, Gupta K. A balanced approach for cannabidiol use in chronic pain. *Front Pharmacol*. 2020;11:561.
- Bloom DA, Baron SL, Luthringer TA, et al. Preoperative opioid education has no effect on opioid use in patients undergoing arthroscopic rotator cuff repair: a prospective, randomized clinical trial. *J Am Acad Orthop Surg*. 2021;29(19):e961-e968.
- Chin G, Etiz BAF, Nelson AM, Lim PK, Scolaro JA. Knowledge and opinion on cannabinoids among orthopaedic traumatologists. *J Am Acad Orthop Surg Glob Res Rev*. 2021;5(4):e21.00047.
- Deiana S, Watanabe A, Yamasaki Y, et al. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarin (CBDV), delta(9)-tetrahydrocannabinol (THC) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and

- CBD action on obsessive-compulsive behaviour. *Psychopharmacology (Berl)*. 2012;219(3):859-873.
- Fader L, Scharf Z, DeGeorge BR Jr. Assessment of medical cannabis in patients with osteoarthritis of the thumb basal joint. *J Hand Surg Am*. Published online December 7, 2021. doi: 10.1016/j.jhsa.2021.10.018
- Fan N, Yuan S, Du P, et al. The effects of smoking on clinical and structural outcomes after rotator cuff repair: a systematic review and meta-analysis. *J Shoulder Elbow Surg*. 2022;31(3):656-667.
- Hong YR, Nguyen O, Yadav S, et al. Early performance of Hospital Value-Based Purchasing Program in Medicare: a systematic review. *Med Care*. 2020;58(8):734-743.
- Hurley ET, Maye AB, Thompson K, et al. Pain control after shoulder arthroscopy: a systematic review of randomized controlled trials with a network meta-analysis. *Am J Sports Med*. 2021;49(8):2262-2271.
- Iffland K, Grotenhermen F. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. *Cannabis Cannabinoid Res*. 2017;2(1):139-154.
- Jain NB, Higgins LD, Losina E, et al. Epidemiology of musculoskeletal upper extremity ambulatory surgery in the United States. *BMC Musculoskelet Disord*. 2014;15:4.
- Kogan NM, Melamed E, Wasserman E, et al. Cannabidiol, a major non-psychoactive cannabis constituent enhances fracture healing and stimulates lysyl hydroxylase activity in osteoblasts. *J Bone Miner Res*. 2015;30(10):1905-1913.
- Li J, Carvajal R, Bruner L, Kaminski NE. The current understanding of the benefits, safety, and regulation of cannabidiol in consumer products. *Food Chem Toxicol*. 2021;157:112600.
- Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage*. 2018;55(2):179-188.e1.
- Lu HC, Mackie K. An introduction to the endogenous cannabinoid system. *Biol Psychiatry*. 2016;79(7):516-525.
- Miller H, De Leo N, Badach J, et al. Role of marijuana components on the regenerative ability of stem cells. *Cell Biochem Funct*. 2021;39(3):432-441.
- Mozaffarian D, Griffin T, Mande J. The 2018 Farm Bill: implications and opportunities for public health. *JAMA*. 2019;321(9):835-836.
- Park JH, Oh KS, Kim TM, et al. Effect of smoking on healing failure after rotator cuff repair. *Am J Sports Med*. 2018;46(12):2960-2968.
- Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. *Br J Pharmacol*. 2011;163(7):1411-1422.
- Premkumar A, Almeida BA, Lopez J, et al. The quality of online resources available to patients regarding cannabidiol for symptomatic relief of hip or knee arthritis is poor. *J Am Acad Orthop Surg Glob Res Rev*. 2021;5(1):1-7.
- Raphael-Mizrahi B, Gabet Y. The cannabinoids effect on bone formation and bone healing. *Curr Osteoporos Rep*. 2020;18(5):433-438.
- Santiago-Torres J, Flanagan DC, Butler RB, Bishop JY. The effect of smoking on rotator cuff and glenoid labrum surgery: a systematic review. *Am J Sports Med*. 2015;43(3):745-751.
- Syed UAM, Aleem AW, Wowkanec C, et al. Neer Award 2018. The effect of preoperative education on opioid consumption in patients undergoing arthroscopic rotator cuff repair: a prospective, randomized clinical trial. *J Shoulder Elbow Surg*. 2018;27(6):962-967.
- Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. *J Shoulder Elbow Surg*. 2009;18(6):927-932.
- Urbanak GC, Plous S. Research Randomizer, Version 4.0. Accessed June 22, 2013. <http://www.randomizer.org/>
- Warrender WJ, Syed UAM, Hammoud S, et al. Pain management after outpatient shoulder arthroscopy: a systematic review of randomized controlled trials. *Am J Sports Med*. 2017;45(7):1676-1686.
- Westermann RW, Anthony CA, Bedard N, et al. Opioid consumption after rotator cuff repair. *Arthroscopy*. 2017;33(8):1467-1472.