Buccally Absorbed Cannabidiol Shows Promise in Treating Pain and Improving Satisfaction Immediately Following Arthroscopic Rotator Cuff Repair: A Placebo-Controlled, Double-Blinded, Randomized Trial

ABSTRACT

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.

PURPOSE: The purpose of this study is to evaluate the potential analgesic effects of buccally absorbed CBD in patients that have undergone arthroscopic rotator cuff repair (ARCR).

STUDY DESIGN: Level 1 Randomized Controlled Trial

METHODS: This is an FDA sanctioned, multi-center, placebo-controlled, randomized, double-blinded trial conducted in patients undergoing ARCR. Patients from 18 to 75 years of age undergoing ARCR were prospectively enrolled and randomized to the control and experimental groups. The experimental group received an oral, buccally absorbed tablet containing 25mg of CBD (Oravexx™, Orcosa Inc., USA) TID if < 80kg and 50mg of CBD TID if > 80kg for 14 days post-operatively, while the control group received an identical placebo. Patients were followed-up on Day 1, 2, 7, and 14, and Visual Analog Scale (VAS) for pain, opioid consumption, and satisfaction with pain control were recorded. Additionally, liver function tests (LFT) were done on Days 7 and 14 to assess safety, and nausea was monitored. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS: Overall, 100 patients were recruited with one patient being excluded for a total of 99 patients. There were no significant differences in patient demographics between the two groups. On Day 1, VAS pain score was significantly lower in those receiving CBD (4.4 ±3.1, 5.7 ±3.2, p = 0.039). On both Day 1 and Day 2, patient satisfaction with pain control was significantly higher

in the CBD group (Day 1: 7.0 ±3.0, 5.6 ±3.7, p = 0.040 | Day 2: 7.3 ±2.5, 6.0 ±3.3, p = 0.028). Quantities of opioids consumed were low in both cohorts, and there were no statistically significant differences in opioid consumption (p > 0.05). Additionally, patients receiving 50 mg of CBD reported even lower VAS scores at day 1 (CBD 50 mg: 3.9 ±3.2, Control: 5.7 ±3.2, p = 0.034) compared to the control group, which exceeds VAS MCID for shoulder arthroscopy (1.4). Patients receiving 50 mg also reported higher satisfaction with pain control on Days 1 (CBD 50 mg: 8.0 ± 2.5, Control: 5.6 ±3.7, p = 0.0060) and Day 2 (CBD 50 mg: 7.9 ±2.1, Control: 6.0 ±3.3, p = 0.014). On Day 7 and Day 14, there were no statistically significant differences in VAS score, opioid consumption, or patient satisfaction with pain control between the CBD and control group (p > 0.05 for all). There were no significant differences in LFTs post-operatively (p > 0.05).

CONCLUSION: Buccally absorbed CBD demonstrates an acceptable safety profile and shows significant promise in reduction of pain in the immediate peri-operative period following ARCR compared to the control. Further studies are currently ongoing to confirm dosing and effectiveness in other orthopedic pathologies.

LEVEL OF EVIDENCE: Level I

KEY TERMS: cannabidiol, CBD, shoulder arthroscopy, rotator cuff repair, postoperative pain

WHAT IS KNOWN ABOUT THE SUBJECT: Cannabidiol (CBD), which targets the ECS, has become a subject of growing interest since the United States Congress passed the 2018 Farm Bill, which legalized industrial hemp (Cannabis Sativa plants containing <0.3% THC content) and its derivative cannabinoids, including CBD. CBD is a non-psychotropic cannabinoid that has been reported to exhibit a range of therapeutic properties. It is well tolerated in humans, has potential for a small risk profile, and has safe co-administration with opioid analgesics. Despite the widespread use and sales of cannabidiol products in the United States, there is a paucity of literature to evaluate its effectiveness or safety and there exists minimal level one evidence, to

our knowledge, prospectively evaluating its use in an orthopedic population.

WHAT THIS STUDY ADDS TO EXISTING KNOWLEDGE: Buccally absorbed CBD demonstrates an acceptable safety profile and shows significant promise in reduction of pain in the immediate peri-operative period following ARCR compared to controls. This is, to our knowledge, one of the first level one studies evaluating the use of CBD in orthopedic surgery, and, specifically, sports medicine. We anticipate that further studies will be sparked by this data, to confirm dosing and effectiveness in other orthopedic pathologies.

INTRODUCTION

Arthroscopic rotator cuff repair (ARCR) is one of the most commonly performed orthopedic procedures, with over 500,000 procedures performed every year.[11] However, postoperative pain is a common complaint, and due to the increasing attention to opioid abuse amongst orthopedic patients, multi-modal management strategies have become increasingly important.[1] It is also estimated that 40-50 percent of all patients undergoing ARCR are on pre-operative opioids.[27] As a result of the increasing volume of outpatient shoulder arthroscopy performed, alternative pain management solutions have become of increased importance.[6,9,26]

The Endocannabinoid System (ECS) is a neuromodulatory system that has recently emerged as a therapeutic focus. As it is involved with regulating the inflammatory response to injury, as well as modulating pain, it has become a pharmacological target in pain management.[15] The ECS is comprised of the CB1 and CB2 cannabinoid receptors, endogenous cannabinoid ligands known as endocannabinoids, as well as the 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 United States Congress passed the 2018 Farm Bill, which legalized industrial hemp (Cannabis Sativa plants containing <0.3% THC content) and its derivative cannabinoids, including CBD.[17] CBD is a non-psychotropic cannabinoid that has been reported to exhibit a range of therapeutic properties.[13] It is well tolerated in humans, has potential for a small risk profile, and has safe co-administration with opioid analgesics. [1,2]

Despite the widespread use and sales of cannabidiol products in the United States, there is a paucity of literature to evaluate its effectiveness or safety. With current trends to optimize multi-modal pain management strategies after ARCR, and to mitigate 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 post-operative cannabidiol would have improved post-operative pain scores and satisfaction and decreased opioid use compared to patients receiving the control.

METHODS

Study Design

This is an FDA sanctioned (IND # 147249) multi-center, controlled, randomized, prospective clinical trial. IRB approval (s19-01293) was obtained from both institutions involved in the study. Patient informed consent was obtained prior to study enrollment. Patients were enrolled and treated during the time period 12/2020 – 12/2022.

All opioid-naïve patients between the ages of 18 and 75 undergoing ARCR (plus or minus biceps tenodesis) were eligible for inclusion in the study. Exclusion criteria can be found in Table 1**.** All patients entering the study were given the Columbia-Suicide Severity Rating Scale (C-SSRS) to ensure no patient had a history of prior or current suicidal ideations (Appendix A), in accordance with FDA recommendations for clinical trials involving drugs with CNS activity. Any patients with elevated liver enzymes in the pre-operative period were also excluded. Urine drug screens were obtained on all patients to ensure patients were opioid naïve and not currently using marijuana. All subjects 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. Pre-menopausal female patients had to have been currently practicing effective forms of two types of birth control, which are defined as those, alone or in combination, that result in a low failure rate (less than 1% per year) when used consistently and correctly. Information recorded pre-operatively included age, sex, height, weight, BMI, and American Society of Anesthesiology (ASA) classification.

Table 1. Exclusion Criteria

Legally incompetent or mentally impaired (e.g., minors, Alzheimer's subjects, dementia, etc.)
Younger than 18 years of age
Older than 75 years of age
Any patient considered a vulnerable subject: 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 syndromes within 3 months before surgery
Abnormal coagulation profile
Renal failure (serum creatinine > 250 μmol/L [2.83 mg/dL]) or liver cirrhosis
Patients with a history of hypersensitivity to Percocet
Patients that have been on pre-operative opioid management for any reason
Patients meeting the DSM-V for major psychiatric illness, such as bipolar disorder
Patients diagnosed with major depression, psychosis, or substance abuse disorder
Patients with current or a history of suicidal ideation
Breastfeeding females
Patients with clinically significant illness, including cardiovascular disorders
Clinically significant lab abnormalities
Abnormal LFTs
Patients with major neurological disorders, such as dementia, Parkinson's disease, cognitive impairment, epilepsy, history of traumatic brain/head injury, or seizures
Patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C).
Patients taking moderate or strong inhibitors of CYP3A4 and CYP2C19 concomitantly
Patients taking strong CYP3A4 and CYP2C19 inducers concomitantly
Patients taking substrates of UTG1A9, UTGB17, CYP2A1, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 concomitantly

Randomization and Study Intervention

Patients were randomized pre-operatively by the respective institutional pharmacies to

receive either cannabidiol or an identical tasting and appearing placebo. Patients and the treating physician were blinded to the randomization. Patients were instructed to take 25 or 50mg (patients over 80kg received 50mg) of buccally absorbed cannabidiol (Oravexx™, Orcosa, Inc., USA) based on body weight per initial manufacturer recommendation, three times a day, for fourteen days. Enrollees were educated on proper administration of the medications prior to surgery. All patients received Percocet (oxycodone/acetaminophen) 5/325mg tabs and were instructed to take them as needed, 1-2 tabs every 4-6 hours, and instructed to wean from narcotics as soon as possible. Patients were instructed to continue CBD/placebo throughout the entire 14-day follow-up period.

Surgical Technique

Surgeries were performed in either the beach chair or the lateral decubitus position, based on surgeon preference. Interscalene blocks were given pre-operatively by the anesthesia team, who were also blinded to the patient enrollment. 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 were placed in a sling post-operatively for a period of time chosen by the operating physician, with none being instructed to discontinue the sling prior to the two-week follow-up. Patients were allowed to perform simple elbow, wrist and hand range of motion as soon as tolerated, and Codman or pendulum exercises as tolerated after the first post-operative visit.

Outcome Measures

The primary outcome of the study was to detect any difference in the VAS at multiple time points after ARCR. Secondary outcomes included postoperative patient satisfaction, opioid use, and all potential complications including change in liver function tests, nausea, or other adverse outcomes. All postoperative complications (surgical or CBD-potentially related) were recorded and liver function tests were obtained at two time points and compared to pre-operative.

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, days 1, 2, 7, and 14. Opioid consumption was documented at days 1-7 on a daily basis and then additively from days 8-14. Patients were instructed to mark the CBD use each time they took the medication, to ensure compliance for the full 14-day period. Additional secondary analyses included any differences in outcomes when accounting for differences in therapeutic dose.

A patient log was administered to each patient to ensure compliance with the study protocol. Patients were followed-up in the office post-operatively at 1- and 2- weeks.

Statistical Analysis

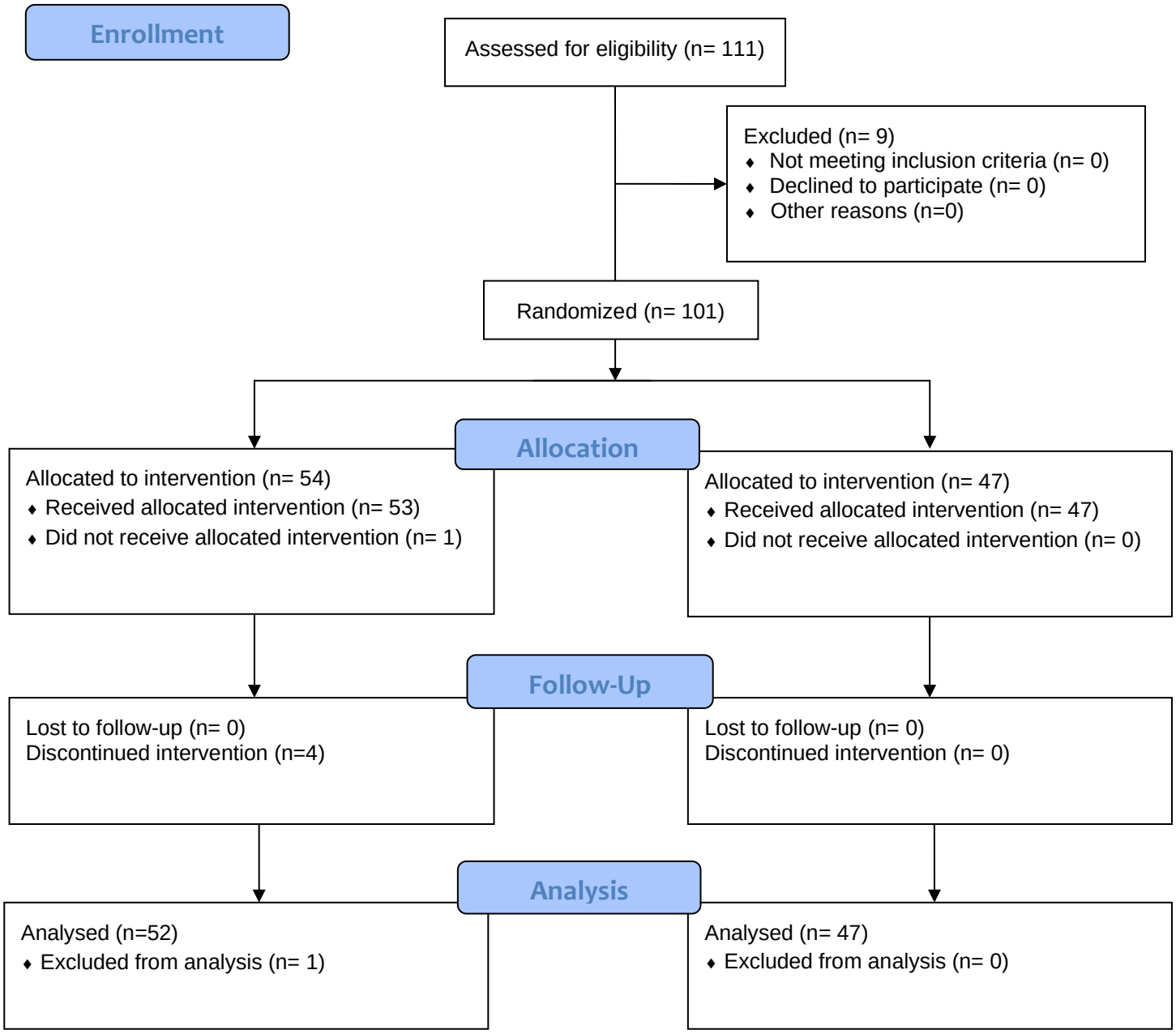
Our power analysis was based on the literature on post-operative pain control following shoulder arthroscopy. Calculations were performed using VAS of 3 and 1.6 for the control and CBD respectively, with an SD of 2. In order to achieve 80% power to reject the null hypothesis of equal means when the population mean difference between Control and CBD is $\mu 1 - \mu 2 = 3.0 - 1.6 = 1.4$ with a standard deviation for both groups of 2.0 at a significance level (alpha) of 0.05 using a two-sided two-sample equal-variance t-test, group sample sizes of 39 would be required in each group. Thus, to allow for a 10% drop-out 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 weighted mean and estimated standard deviation, whereas categorical variables were reported as frequencies with percentages. Categorical variables were analyzed using Fisher's exact 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 50mg of CBD versus 25mg

of CBD versus control medications was conducted using Fisher's exact or chi-square tests for categorical variables and analysis of variance or Kruskal-Wallis H testing for continuous variables. Posthoc Tukey testing was performed comparing all possible pairs of subgroup means to determine exactly between which subgroups the differences were significant. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Patient Characteristics (Table 2)

Overall, 100 patients were enrolled in this study across the two investigating centers, and 47 patients were placed in the control group while 53 were placed in the experimental group (Figure 1).



One patient was excluded from the analysis as they used marijuana postoperatively, leading to the final count of 52 patients in the experimental group. There were no significant differences in age, sex, BMI, concomitant procedures including biceps tenodesis and subacromial decompression, and the number of anchors used intraoperatively between the two groups.

Table 2: Patient Characteristics

Variable	**CBD**	**Placebo**	**P Value**
N	52	47	
Age (yrs.)	58.2 ± 8.78	57.1 ± 10.1	0.56
Female Sex	21.0 ± 40.4	17 ± 36.2	0.82
BMI	29.1 ± 5.0	28.2 ± 7.1	0.45
Biceps tenodesis (BT)	13 (27.7)	10 (19.2)	0.451
Subacromial Decompression (SD)	15 (31.9)	23 (44.2)	0.293
Both (BT+SD)	17 (36.2)	13 (25.0)	0.323
Anchors used	3.0 ± 1.6	3.28 ± 1.40	0.52

Data are shown as mean ± standard deviation and No. of patients (%)

Postoperative Pain and Satisfaction (Table 3)

On Day 1, VAS pain score was significantly lower in those receiving CBD (4.4 ±3.1, 5.7 ±3.2, p = 0.039) and was nearly equivalent to MCID as defined by a difference of 1.4. On both Day 1 and Day 2, patient satisfaction with pain control was significantly higher in the CBD group (Day 1: 7.0 ±3.0, 5.6 ±3.7, p=0.040 | Day 2: 7.3 ±2.5, 5.98 ±3.3, p = 0.028). For the remainder of the study, the experimental group outperformed the placebo group at all time points for pain, MME consumption, and patient satisfaction; however, the results did not meet statistical significance.

Table 3: Postoperative Pain and Patient Satisfaction

Variable	CBD	Placebo	P value
VAS Day 1	4.4 ± 3.1	5.7 ± 3.2	0.039
Satisfaction Day 1	7.0 ± 3.0	5.6 ± 3.7	0.040
VAS Day 2	4.7 ± 2.8	5.3 ± 2.6	0.32
Satisfaction Day 2	7.3 ± 2.5	6.0 ± 3.3	0.028
VAS Day 7	2.5 ± 1.9	3.23 ± 2.7	0.15
Satisfaction Day 7	8.0 ± 2.6	7.88 ± 2.7	0.78
VAS Day 14	1.6 ± 1.4	2.26 ± 2.4	0.11
Satisfaction Day 14	8.7 ± 2.3	8.51 ± 2.4	0.712

Data are shown as mean ± standard deviation and No. of patients (%)

Opioid Consumption and Nausea Levels (Table 4)

There were no statistically significant differences in opioid consumption ($p < 0.05$), which was relatively small in both groups, with no significant difference in nausea.

Table 4: Opioid Consumption and Nausea Levels

Variable	CBD	Placebo	P value
MME Day 1	15.2 ± 12.0	19.7 ± 13.6	0.084
MME Day 2	10.3 ± 18.7	16.7 ± 36.6	0.29
MME Day 7	59.3 ± 53.2	67.3 ± 55.2	0.47
MME Day 14	8.0 ± 19.3	10.3 ± 22.7	0.61
Nausea Day 2	2.1 ± 2.6	2.5 ± 3.1	0.51
Nausea Day 7	0.2 ± 1.1	0.6 ± 2.1	0.23
Nausea Day 14	0.1± 0.4	0.5 ± 1.7	0.15

MME = Major Morphine Equivalents. Rated on a scale of 0 (no nausea) to 10 (extreme nausea). Data are shown as mean ± standard deviation and No. of patients (%).

Subgroup Analysis of Postoperative Pain, Satisfaction, Opioid use, and Nausea (Table 5 & 6)

On subgroup analysis, it was noted that 23 patients received 25mg of CBD and 29 patients received 50mg 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 three subgroups in VAS pain score at Day 1 (CBD 50mg: 3.9 ±3.2, CBD 25: 5.1 ±2.9, Control: 5.7 ±3.2, p=0.044) with an almost 2-point VAS improvement in the 50 mg CBD group. There were also significant differences in satisfaction at Day 1 (CBD 50mg: 8.0 ±2.5, CBD 25: 5.7 ±3.2, Control: 5.6 ±3.7, p=0.0050), and satisfaction at Day 2 (CBD 50mg: 7.9 ±2.1, CBD 25: 6.5 ±2.8, Control: 6.0 ±3.3, p = 0.018). The CBD 50mg group consistently outperformed the 25mg and placebo group, trending towards statistical significance at several time points, especially for VAS. Regarding MME use, the 50 mg subgroup outperformed the placebo and 25 mg groups at all time points, however did not meet statistical significance.

Table 5: Subgroup Analysis of Postoperative Pain and Patient Satisfaction

Variable	**CBD 25 mg**	**CBD 50 mg**	**Placebo**	**P value**
VAS Day 1	5.1 ± 2.9	3.9 ± 3.2	5.7 ± 3.2	0.044
Satisfaction Day 1	5.7 ± 3.2	8.0 ± 2.5	5.6 ± 3.7	0.005
VAS Day 2	4.7 ± 2.7	4.7 ± 3.0	5.3 ± 2.6	0.61
Satisfaction Day 2	6.5 ± 2.8	7.9 ± 2.1	6.0 ± 3.3	0.018
VAS Day 7	3.1 ± 2.1	2.1 ± 1.7	3.2 ± 2.7	0.13
Satisfaction Day 7	7.4 ± 2.7	8.6 ± 2.4	7.9 ± 2.7	0.34
VAS Day 14	2.0 ± 1.4	1.1 ± 1.3	2.3 ± 2.4	0.099

Satisfaction Day 14	8.3 ± 2.2	9.1 ± 2.4	8.5 ± 2.4	0.58

Data are shown as mean ± standard deviation and No. of patients (%).

Table 6: Subgroup Analysis Opioid Consumption and Nausea Levels

Variable	**CBD 25 mg**	**CBD 50 mg**	**Placebo**	**P value**
MME Day 1	15.4 ± 10.0	15.0 ± 13.6	19.7 ± 13.6	0.23
MME Day 2	10.2 ± 14.1	10.3 ± 21.9	16.4 ± 36.6	0.58
MME Day 7	51.4 ± 47.4	65.4 ± 57.5	67.3 ± 55.2	0.53
MME Day 14	10.8 ± 25.6	5.5 ± 10.8	10.3 ± 22.7	0.63
Nausea Day 2	1.0 ± 1.6	2.9 ± 3.0	2.5 ± 3.1	0.045
Nausea Day 7	0.1 ± 0.5	0.3 ± 1.4	0.6 ± 2.1	0.46
Nausea Day 14	0.1 ± 0.5	0.1 ± 0.4	0.5 ± 1.7	0.36

MME = Major Morphine Equivalents. Rated on a scale of 0 (no nausea) to 10 (extreme nausea). Data are shown as mean ± standard deviation and No. of patients (%)

Posthoc Analysis (Table 7)

Posthoc Tukey testing of subgroups showed that compared to the control group, patients receiving 50mg of CBD had significantly lower VAS pain scores on Day 1 ($p=0.034$), which also met VAS MCID for shoulder arthroscopy (1.4). Patients receiving 50mg CBD also report increased satisfaction on Day 1 and Day 2 ($p=0.0058$, $p=0.014$). The group receiving 25mg of CBD did not differ significantly compared to the group receiving 50mg or the control group ($p < 0.05$). On Day 7 and Day 14, there were no statistically significant differences in VAS score, opioid consumption, or patient satisfaction with pain control ($p>0.05$ for all). Although posthoc Tukey testing demonstrated a significant difference in nausea levels on Day 2 between the group receiving 25mg of CBD and 50mg of CBD ($p=0.043$), the difference was not clinically significant, and there

were no other significant differences in nausea.

Table 7. Posthoc Tukey Testing

VAS Day 1	**Adjusted P Value**
CBD 50-CBD 25	0.33
Control-CBD 25	0.71
Control-CBD 50	0.034
Satisfaction Day 1	
CBD 50-CBD 25	0.031
Control-CBD 25	0.99
Control-CBD 50	0.0060
Satisfaction Day 2	
CBD 50-CBD 25	0.17
Control-CBD 25	0.78
Control-CBD 50	0.014
Nausea Day 2	
CBD 50-CBD 25	0.043
Control-CBD 25	0.11
Control-CBD 50	0.78

Posthoc testing was conducted on variables that demonstrated significant differences between subgroups on ANOVA or Kruskal-Wallis testing.

Adverse Events

Overall, 4 patients in the placebo group and 4 patients in the CBD group had elevated ALT values at 7 days which normalized at 14 days postoperatively. No other liver enzyme elevations were seen, and there were no significant differences in postoperative LFTs ($p>0.05$). There were five suspected adverse events in patients in the CBD group that could not confidently be attributed

to CBD, especially as tablet absorption occurs buccally directly into the bloodstream, not through the GI system. Two patients experienced a rash on postoperative day two. One patient experienced nausea on postoperative day two. One patient experienced abdominal pain. Another patient experienced rectal bleeding and elected to drop out of the study due to abdominal pain, although highly unlikely to be due to intervention medication. There were no significant differences in suspected adverse events between the CBD 25 mg, CBD 50 mg, and control in subgroup analysis (2 (8.7%), 3 (10.3%), 0 (0%), p=0.089).

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 peri-operative period following ARCR. Although the results did not meet statistical significance for the later time points, the CBD group consistently outperformed the placebo group at all time points. Furthermore, those given a higher dose of CBD had statistically significant, lower levels of post-operative pain and higher satisfaction, suggesting that higher doses likely correspond to improved outcomes and warrant further studies. Additionally, there were no major side effects associated with the use of buccally absorbed CBD.

CBD has become a subject of growing interest since Congress passed the 2018 Farm Bill, which legalized Industrial Hemp (Cannabis Sativa plants containing <0.3% THC content) and its derivative cannabinoids, including CBD.[17] However, there exists a lack of clinical trials in this area and thus evaluation of safety was also a significant concern of the study. Commercially available CBD is plagued with 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 hepatic transaminases, although our study found no significant elevations in LFTs that could be exclusively attributed to CBD. Surgical trauma and acetaminophen use, can both also mildly elevate LFTs.[5,10] Although CBD may be beneficial for nausea, the current study found minimal post-operative nausea and no difference between the CBD and the control group.[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 CNS activity.

Despite a very large shift towards commercial use of cannabidiol and legalization of marijuana and growth of a multi-billion-dollar industry, there remains scant evidence supporting its use in the scientific literature, particularly in orthopedic surgery and the role of CBD in managing pain. Chin et al.[4] recently reported in a survey of members of the Orthopaedic Trauma Association that 88% of trauma surgeons did not believe they were knowledgeable in the mechanism of CBD. However, 73% of the survey respondents believed CBD has a role to play in the treatment of post-operative pain. Additionally, 83% of the respondents did not feel that they would be stigmatized if they recommended CBD to their patients, with 85% also believing that there are no known effects on fracture healing, with 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, literature has shown that priming with cannabinoids can potentially improve wound healing and can enhance the regenerative capacity of two major sources of stem cells, adipose- and bone marrow-derived.[16] In addition, studies have found that CBD has the potential to enhance fracture healing and stimulate lysyl hydroxylase in osteoblasts, with anti-inflammatory properties.[12,21,25] 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 impact 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 patients with basal joint osteoarthritis found that almost 70% would be interested in trialing an oral-based cannabidiol product, with 80% of patients interested in a topical treatment. However, Premkumar et al.[20]

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 CBD resulted in improved postoperative pain and satisfaction in the first two days post-operatively when pain is at its most severe in the acute post-operative phase. Additionally, the difference nearly equaled the minimal clinically important difference (MCID) cut-off of 1.4.[24] With higher doses, the MCID for VAS was easily surpassed on the first post-operative day and trended towards statistical significance at multiple time points. As post-operative pain lessened, the difference stopped being statistically significant, however the CBD group still outperformed the control group and trended towards statistical significance at multiple time points. As the study was designed to detect a VAS change of 1.4, the study was likely underpowered to significantly detect smaller statistical changes.[24] Thus, it appears the effect was greatest when the pain was most severe. However, it should be noted that CBD also had significantly higher patient satisfaction as a result of the improved pain levels in the first few days, highlighting the importance of this to patients.

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 (HVBP) rewards hospitals that perform well on quality of care measures, or, conversely, punishes those with poor scores. This is based on four 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 orthopedic surgery (inpatient fracture care, spine surgery, hip and knee reconstruction) holds tremendous promise, as mitigating post-surgical or chronic pain may improve the patient experience, improve clinical care outcomes, and reduce cost with more expeditious hospital discharges.

Additionally, there were no significant difference in opioid consumption between the two groups. While the goal of the current study was not to replace opioids with CBD, the lack of statistical significance is possibly due to a 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 following ARCR.[9] Additionally, there is a lack of evidence on the use of oral medications following ARCR, with the majority of evidence being focused on gabapentinoids and a recent systematic review finding only 7 studies that evaluated oral medications following ARCR.[9]

Further research is still required on the role of CBD as a post-operative medication, as well as the optimal dosing and route of administration. A previous study by Fallon et al.[14] found no superiority in two double-blind studies in regard to pain control when using Sativex through an oral mucosal spray. We elected to use a buccally absorbed tablet as opposed oils or pills that are absorbed in the gastrointestinal system, which may account for the effectiveness seen in the current study. Buccal absorption provides a 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 those with a low dose of CBD, and as a result of the safety profile found in the current study, it warrants further evaluation if higher doses are safe in patients < 80kg. Given that Epidiolex, an FDA-approved CBD formulation absorbed in the gastrointestinal system, utilizes dosages that far exceed those utilized 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 optimization for ARCR, the use of CBD should be evaluated for other sources of orthopedic pain, whether postoperative, acute or chronic.

Limitations

There are a few limitations in the current study. Firstly, this study included several orthopedic surgeons, which may introduce bias into the study. However, their methods of ARCR were similar, and patients underwent a standardized post-operative rehabilitation protocol regardless of whether or not 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 two groups. Finally, the study was primarily focused on immediate post-operative pain and was powered to evaluate this, and it was not powered to detect a difference at later stages as the pain became milder but CBD still outperformed the control at each time point. Additionally, although variability in the pre-operative nerve interscalene blocks could have potentially confounded results, the randomization of the study intervention makes this less of a significant concern.

CONCLUSION

Buccally absorbed CBD demonstrates an acceptable safety profile and shows significant promise in reduction of pain in the immediate peri-operative period following ARCR compared to controls.

REFERENCES

1. Alaia MJ. Editorial Commentary: Uncle Sam Wants YOU! (to Stop the Opioid Crisis). *Arthroscopy.* 2020;36(3):832-833.
2. Argueta DA, Ventura CM, Kiven S, Sagi V, Gupta K. A Balanced Approach for Cannabidiol Use in Chronic Pain. *Front Pharmacol.* 2020;11:561.
3. 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. *The Journal of the American Academy of Orthopaedic Surgeons.* 2021;29(19):e961-e968.
4. 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).
5. Deiana S, Watanabe A, Yamasaki Y, et al. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Delta(9)-tetrahydrocannabivarin (THCV) 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.
6. Fader L, Scharf Z, DeGeorge BR, Jr. Assessment of Medical Cannabis in Patients With Osteoarthritis of the Thumb Basal Joint. *J Hand Surg Am.* 2021.
7. 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.* 2021.
8. 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.
9. 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.
10. 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.
11. 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.
12. Kogan NM, Melamed E, Wasserman E, et al. Cannabidiol, a Major Non-Psychotropic Cannabis Constituent Enhances Fracture Healing and Stimulates Lysyl Hydroxylase Activity in Osteoblasts. *J Bone Miner Res.* 2015;30(10):1905-1913.
13. 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.
14. 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 e171.

15. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. *Biol Psychiatry.* 2016;79(7):516-525.
16. 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.
17. Mozaffarian D, Griffin T, Mande J. The 2018 Farm Bill-Implications and Opportunities for Public Health. *JAMA.* 2019;321(9):835-836.
18. 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.
19. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. *Br J Pharmacol.* 2011;163(7):1411-1422.
20. 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.
21. Raphael-Mizrahi B, Gabet Y. The Cannabinoids Effect on Bone Formation and Bone Healing. *Curr Osteoporos Rep.* 2020;18(5):433-438.
22. Santiago-Torres J, Flanigan 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.
23. Syed UAM, Aleem AW, Wowkanech 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.
24. 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.
25. Trivedi MK, Mondal S, Gangwar M, Jana S. Anti-inflammatory potential of cannabidiol (CBD) on combination of caecal slurry, LPS, and E. coli-induced systemic inflammatory response syndrome (SIRS) in Sprague Dawley Rats. *Inflammopharmacology.* 2022.
26. 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.
27. Westermann RW, Anthony CA, Bedard N, et al. Opioid Consumption After Rotator Cuff Repair. *Arthroscopy.* 2017;33(8):1467-1472.