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# Effectiveness of Cannabis Oil as an Adjuvant Therapy in Patients with Severe Knee Osteoarthritis: A Randomized, Double-Blind Study

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**Purpose:** The removal of cannabis from Thailand's narcotic drug list presents both opportunities and challenges for medical use. The effectiveness of cannabis oil in treating severe knee osteoarthritis in patients awaiting total knee arthroplasty was evaluated in this study.
**Methods:** Thirty-two patients with severe knee osteoarthritis, unresponsive to conservative treatment, were enrolled and divided into two equal groups. The control and experimental groups received syrup and cannabis oil, respectively, at night for 30 days. Pain and quality of life (QOL) were assessed using the Numeric Rating Scale (NRS), and the Knee Injury and Osteoarthritis Outcome Score (KOOS), respectively. Liver and kidney functions were also assessed.
**Results:** The experimental group showed a significant reduction in NRS scores compared to the control group ($p = 0.00015$). Significant improvements were observed in KOOS subscales for pain, activities of daily living (ADL), and QOL ($p = 0.01$). However, the symptoms subscale improvement was not significant ($p = 0.14$). When comparing the KOOS subscales, no significant differences were observed between the groups ($p > 0.05$). Liver and kidney function remained stable in both groups. Despite these improvements, the changes did not reach a minimal clinically important difference (MCID), indicating limited clinical perceptibility to the patients.
**Conclusions:** Cannabis oil was associated with significant improvements in pain, ADL, and QOL in severe knee osteoarthritis. Although improvements did not meet MCID thresholds, observed benefits suggest potential for pain management. Larger controlled studies are recommended to confirm its clinical efficacy in pain management.

**Keywords:** cannabis, THC, CBD, knee osteoarthritis, KOOS, MCID

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Severe osteoarthritis (OA) significantly affects the activities of daily living of patients, rendering them unable to work, placing a burden on their families, and affecting their physical and mental well-being. Knee replacement surgery is an effective treatment that often enables patients to resume near-normal postoperative activities of living. According to data from the NHSO [(1)], >60,000 individuals require knee replacement surgery, but

only 20,000 undergo surgery annually. The waiting time for surgery in government hospitals is as long as 1-2 years. These patients suffer owing to extended waiting periods; therefore, exploring alternative therapies that alleviate pain and enhance function during this waiting period is imperative.

Cannabis is a promising alternative to be used as an adjunctive treatment for patients with OA waiting for surgery. It exhibits diverse therapeutic effects, including analgesic, anti-inflammatory, antioxidant, and anxiolytic properties[2,3]. These patients often experience pain, knee inflammation, stress, and anxiety[4]. Given its properties, cannabis can potentially manage these symptoms effectively. Lykins W.[5] explored the use of cannabis in the treatment of patients with knee OA and revealed that cannabidiol (CBD) can be used as an alternative treatment for knee OA that may provide symptomatic relief with minimal risk. In addition, Echeverria-Villalobos M.[6] revealed that cannabis did not affect knee replacement surgery when used at low doses and was discontinued before surgery.

Despite concerns regarding the long-term use of cannabis, particularly its potential adverse effects on the nervous and cardiovascular systems, as well as the risk of addiction, evidence suggests that these risks are mitigated by numerous factors, such as low dosage and frequency, older age at initiation, and the medical purpose[7,8]. In addition, a study by Lopez-Quintero,[9] revealed that the rate of drug dependence on cannabis is lower than that of cigarettes and alcohol. The cumulative probability of transitioning to dependence was estimated as 67.5%, 22.7%, 20.9%, and 8.9% for nicotine, alcohol, cocaine, and cannabis users, respectively. Therefore, if cannabis is used appropriately for medical purposes, the risk of addiction is low. Cannabis has emerged as a potential alternative treatment for patients with OA who are awaiting surgery, offering pain relief, and potentially improving quality of life (QOL) with a relatively low risk of addiction when used appropriately. The primary objective of this study was to evaluate the effectiveness of cannabis in relieving pain in patients with severe OA. Secondary objectives included assessing its impact on the QOL and monitoring any potential complications related to its use.

## METHODS

This randomized controlled trial compared the efficacy of cannabis oil versus placebo syrup in relieving pain, improving QOL, and monitoring complications in patients with severe knee OA. It was conducted between March and May 2022 in the northern region of Sukhothai, Thailand. Patients with severe knee OA, as classified using the Kellgren and Lawrence grading system, who had previously undergone conservative treatment with unsatisfactory results and were scheduled for total knee arthroplasty were enrolled in this study. The inclusion criteria included the presence of Kellgren and Lawrence type 4 OA, indicating severe knee OA with large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends. Patients were excluded if they were allergic to cannabis oil, required warfarin, had cirrhosis, grade 4 or higher chronic kidney disease, a history of heart disease or stroke, or schizophrenia or depression.

A total of 32 patients were enrolled in the study, with 16 randomized to each of the experimental (cannabis oil) and control groups (placebo syrup). Systematic random sampling was employed, with patients drawing one of eight lottery tickets numbered 1-8. Patients who drew odd and even numbers were assigned to the experimental and control groups, respectively. To maintain a double-blind protocol, only the pharmacist responsible for preparing the study medications was aware of the group assignments. The study medications were prepared in identical bottles to ensure blinding of both patients and healthcare providers. Physicians prescribed the study medications according to a predetermined schedule without knowing whether the patient was receiving cannabis oil or placebo syrup.

Patients in the experimental group were administered 1:1 Tetrahydrocannabinol (THC): CBD cannabis oil sublingually at bedtime. Cannabis oil was manufactured and provided by Chaophraya Abhaibhubejhr Hospital and contained 2.7% THC and 2.5% CBD, corresponding to

approximately 4.59 mg of THC and 4.25 mg of CBD per drop. The dosing regimen was based on recommendations from the study by Bhaskar et al.[10], which suggested initiating treatment with 2.5-5 mg of THC daily. Patients in the control group received one drop of placebo syrup made from coconut oil adjusted for color and flavor to mimic cannabis oil. All patients, regardless of group assignment, received the following concomitant medications to manage their knee OA symptoms: gabapentin (300 mg) one capsule at bedtime, a muscle relaxant (orphenadrine 35 mg with paracetamol 450 mg) one tablet three times daily, meloxicam (7.5 mg) once daily after breakfast, and omeprazole (40 mg) one capsule before breakfast.

The primary outcome measure was pain relief, assessed using a Numeric Rating Scale (NRS), whereas the secondary outcome was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS). Additionally, complications or side effects associated with the use of cannabis oil were monitored. KOOS assessments were conducted by a trained research nurse who was blinded to the treatment allocation. NRS scores and KOOS outcomes were evaluated at baseline and one month after treatment. To monitor potential side effects, blood tests for kidney and liver function were performed at the beginning and end of the study.

### *Research Tools*

KOOS[11,12] is a widely validated and extensively used questionnaire, developed in 1990. It is designed to assess patient perceptions of knee health across five distinct subscales: 1. Pain (KOOS Pain) 2. Other Symptoms (KOOS Symptoms) 3. Activities of Daily Living (ADL; KOOS ADL) 4. Function in Sport and Recreation (KOOS Sport) 5. Knee-related QOL (KOOS QOL). Each subscales is scored separately, enabling a detailed assessment of the specific aspects of knee function and the impact of OA on the life of patients. In this study, the KOOS Sport was excluded, as the study population may have been unsuitable for sports activities or unable to participate in such activities due to the severity of their condition. KOOS assessments were conducted at two time points: baseline (before the initiation of the intervention) and one month after treatment. The results from each subscale were analyzed separately, with comparisons made between the pre- and post-treatment scores to evaluate the effectiveness of the intervention.

General Characteristics Questionnaire: In addition to the KOOS, a general characteristics questionnaire was administered to obtain demographic and baseline health data from each participant, including sex, weight, height, body mass index (BMI), occupation, underlying diseases, and the frequency of painkiller use. Furthermore, kidney function and liver enzyme levels were monitored at baseline and end of the study to assess any potential renal adverse effects of the intervention on renal and hepatic function.

### *Data Analysis*

Trained research nurses systematically collected all data to ensure blinding throughout the study period. Statistical analysis was performed using STATA, with significance set at $p < 0.05$. Paired t-tests were used for within-group comparisons of pain and KOOS and independent t-tests were used for between-group comparisons. The incidence of complications was compared between groups using independent t-tests. The sample size was calculated based on the formula from Bernard (2000) in "Fundamentals of Biostatistics" (7th ed.)[13]. This involved calculating the change in the KOOS values between the control group that received the placebo and the group that received cannabis oil. The resulting sample size was 16 participants per group. The study was approved by the Human Research Ethics Committee of the hospital (IRB number: 07/2565), and all patients provided written informed consent before participation. The patients were informed of their right to withdraw from the study at any time without any impact on their future medical care.

## RESULTS

The general characteristics of the control and experimental groups were similar (Table 1). Participants were predominantly aged >60 years, with a higher proportion of females than males in

both groups. The average BMI for both groups fell within the range of class I obesity, and most participants required regular use of painkillers.

Following treatment, the NRS scores improved in both groups; however, only the experimental group demonstrated a statistically significant improvement (Table 2). When comparing outcomes between the groups, the experimental group exhibited a significantly greater reduction in NRS scores than the control group (Table 3), indicating the potential efficacy of cannabis oil in reducing pain.

Improvements in the KOOS were observed in both groups after treatment (Table 2). The KOOS values exhibited statistically significant improvements in the experimental group in the Pain, ADL, and QOL subscales, whereas the symptoms subscale did not show significant improvement. However, the control group did not exhibit statistically significant changes in any of the KOOS subscale scores. When comparing KOOS improvement between the groups, no statistically significant differences were observed (Table 3).

Blood tests for kidney (glomerular filtration rate) and liver functions (aspartate aminotransferase, alanine transaminase) were conducted at baseline and 30 days after treatment. No significant changes were observed in kidney or liver function in either group, indicating that cannabis oil use did not adversely affect these parameters (Table 2).

**Table 1** General characteristics of the participants.

| Characteristic | Control group (Receiving placebo) | Experimental group (Receiving cannabis) |
|---|---|---|
| Age (yr.) | 62.62 ± 5.99 (55-77) | 63.5 ± 5.25 (55-73) |
| Gender | | |
| Male | 1 | 3 |
| Female | 15 | 13 |
| Weight (kg.) | 69.19 ± 7.56 (55-83) | 62.28 ± 11.33 (48-80.5) |
| Height (cm.) | 156.25 ± 5.32 (148-165) | 156.50 ± 6.64 (150-171) |
| Body mass index | 28.30 ± 2.41 (24.14-31.63) | 25.29 ± 3.59 (19.22-28.84) |
| Occupation | | |
| None | 7 | 7 |
| Agriculturist | 7 | 7 |
| Laborer | 1 | 2 |
| Grocer | 1 | 0 |
| UD | | |
| no UD | 0 | 4 |
| DM alone | 0 | 1 |
| HT alone | 3 | 2 |
| DLP alone | 1 | 1 |
| DM + HT | 2 | 0 |
| DM + DLP | 0 | 0 |
| HT + DLP | 8 | 6 |
| DM + HT + DLP | 1 | 2 |
| Frequency of painkiller used | | |
| Every day | 11 | 9 |
| Every other day | 6 | 5 |
| Once a week | 0 | 2 |

Underlying disease, UD; Diabetes mellitus, DM; Hypertension, HT; Dyslipidemia, DLP

**Table 2** Variables before and after treatment.

| Parameter | Control Group | | Experimental Group | | P-value |
|---|---|---|---|---|---|
| | Before Rx | After Rx | Before Rx | After Rx | |
| Pain (NRS) | 8.06 ± 1.24 | 7.94 ± 1.29 | 8.35 ± 1.15 | 7.06 ± 1.48 | 0.43/0.00015 |
| KOOS pain | 34.02 ± 14.33 | 40.45 ± 17.36 | 31.94 ± 9.89 | 39.58 ± 11.89 | 0.1/0.01 |
| KOOS Symptoms | 37.28 ± 17.29 | 40.17 ± 18.65 | 34.40 ± 11.10 | 38.84 ± 7.59 | 0.51/0.14 |
| KOOS ADL | 33.99 ± 16.28 | 41.54 ± 22.00 | 31.88 ± 11.96 | 42.46 ± 14.67 | 0.16/0.14 |
| KOOS QOL | 19.92 ± 11.68 | 25.78 ± 12.26 | 17.57 ± 12.12 | 29.69 ± 12.39 | 0.1/0.01 |
| GFR (L/min) | 72.47 ± 17.10 | 69.16 ± 13.42 | 74.40 ± 24.03 | 76.51 ± 21.72 | 0.38/0.43 |
| AST (U/L) | 23.18 ± 4.29 | 25.91 ± 8.01 | 26.75 ± 8.48 | 29.36 ± 10.86 | 0.24/0.48 |
| ALT (U/L) | 25.56 ± 6.85 | 24.36 ± 12.01 | 35.88 ± 24.03 | 26.00 ± 14.22 | 0.32/0.28 |

Numeric Rating Scale, NRS; KOOS, Knee Injury and Osteoarthritis Outcome Score; Activities of daily living, ADL; Quality of life, QOL; GFR, Glomerular filtration rate; Aspartate aminotransferase, AST; Alanine aminotransferase, ALT

**Table 3** Comparison of outcomes between control and experimental groups.

| | Mean score improvement | | p-value |
|---|---|---|---|
| | Control group | Experimental group | |
| Pain score (NRS) | 0.125 + 0.15 | 1.31 + 0.34 | 0.003 |
| KOOS Pain | 5.38 + 3.72 | 7.63 + 2.91 | 0.64 |
| KOOS Symptoms | 2.90 + 4.29 | 4.44 + 2.88 | 0.77 |
| KOOS ADL | 7.56 + 5.08 | 10.58 + 3.48 | 0.63 |
| KOOS QOL | 5.85 + 3.44 | 12.11 + 2.99 | 0.18 |

Numeric Rating Scale, NRS; KOOS, Knee Injury and Osteoarthritis Outcome Score; Activities of daily living, ADL; Quality of life, QOL

## DISCUSSION

Cannabis oil demonstrated notable efficacy in reducing pain, as reflected in improved NRS and KOOS Pain scores, which is consistent with other research. Lykins W.[5] and Lovecchio et al.[14] revealed that CBD and cannabis use significantly reduced pain in patients with OA and spine-related conditions. Similarly, Yassin et al.[15] demonstrated that the addition of medical cannabis to analgesics improved pain management in patients with fibromyalgia and low back pain. However, these studies utilized higher doses of cannabis, which were associated with more pronounced effects and increased side effects[7,8,16]. In contrast, our study employed a conservative initial dose of cannabis oil to balance the therapeutic efficacy and minimize adverse effects.

The anti-inflammatory properties of CBD likely contributed to the improvements observed in the KOOS Pain and ADL scores. Previous studies by Atalay et al.[17] and Boehnke et al.[18] revealed similar anti-inflammatory effects, emphasizing the role of CBD in reducing inflammation in OA and fibromyalgia. These anti-inflammatory effects may have played a crucial role in the improvement in pain and functional outcomes observed in our study.

Anxiety exacerbates physical symptoms in patients with OA.[19] Sharpe L.[20] revealed that CBD can reduce anxiety and improve the QOL. This may explain the improvements in KOOS QOL observed in our study.

Our findings are consistent with those of Francis et al.[21], who demonstrated that medical cannabis significantly improved pain, interference, and QOL in patients with OA. Frane et al.[22] also revealed that CBD use was associated with a reduction in pain and arthritis symptoms.

Vannabouathong et al.[23] suggested that cannabis may be a cost-effective strategy for managing chronic knee pain, which supports our findings.

The NRS and KOOS assessments are based on distinct principles. The NRS primarily evaluates pain intensity, whereas the KOOS Pain assesses the frequency of pain and the specific movements that exacerbate it. This distinction implies that while the frequency of pain and movement-induced pain may not exhibit significant improvement, cannabis can still effectively reduce the overall pain intensity. The KOOS ADL focuses on the ability of the patient to perform daily activities, whereas the KOOS QOL reflects the perception of the patient of the challenges posed by knee OA in daily life. In the cannabis group, although the differences compared to the placebo group were not statistically significant, the patients demonstrated significant improvements when comparing pre- and post-treatment measures. This improvement is likely attributable to the anxiolytic effects of cannabis, which may have contributed to the enhanced KOOS ADL and QOL outcomes. The KOOS Symptoms, which evaluates joint stiffness, is less likely to be improved by pharmacological interventions in patients with severe OA. Consequently, the experimental and control groups showed no significant improvements in KOOS Symptoms.

The Minimal Clinically Important Difference (MCID) is essential to determine whether statistically significant results correspond to clinically meaningful improvements. Suzuki H.[24] and Eleswarapu AS.[25] suggested that a change of 2 on the Numerical Rating Scale is necessary for clinically relevant pain relief. In our study, the change of NRS was 0.125 and 1.31 in the control and experimental groups, respectively, both of which fell below this threshold. This suggests that although a statistically significant reduction in pain was observed with the use of cannabis oil, the improvements may not have been clinically perceptible to patients. Similarly, the MCID values for the KOOS subscales[26] (pain, symptoms, ADL, and QOL) were not met in either group, indicating that, while the KOOSs improved significantly in the cannabis group, these changes were likely below the threshold for meaningful patient-perceived improvements.

In our study, cannabis oil significantly improved pain intensity, measured using the NRS, and QOL, assessed using the KOOS, in patients with knee OA. However, these improvements did not reach the MCID, suggesting that although the changes were statistically significant, they may not have been perceptible or meaningful to patients. Although cannabis oil has potential as a component of OA management, its use should be considered with caution. Future research with optimized dosages, larger sample sizes, and longer follow-up periods is needed to evaluate its true clinical relevance. Factors such as inflammation, psychological effects, and individual patient variability warrant further exploration to optimize the therapeutic use of cannabis for the management of knee OA symptoms.

## CONCLUSIONS

Our study revealed that cannabis oil significantly reduced pain intensity and improved the QOL in patients with knee OA, as reflected by improvements in the NRS and KOOS scores. However, these changes did not reach the MCID, indicating that although the results were statistically significant, they may not have been perceived as meaningful by the patients. This suggests that, while cannabis oil shows potential as adjunctive therapy, further research with optimized dosages and larger sample sizes is needed to determine its clinical relevance in the management of OA.

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