Original Article

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Efficacy of curcuminoids on postoperative pain control after third molar surgery: multicenter double-blind randomized control trial

Kullaya Boonwatcharachai[1], **Settakorn Pongpanich**[1], Prisana Pripatnanont[1], Kwunchit Oungbho[2] Sanguan Lerkiatbundit[3], Vasin Pitakmahamongkol[4], Apisara Rodklai[5]

[1] *Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Prince of Songkla University, Songkhla, Thailand*
[2] *Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla, Thailand*
[3] *Department of Social Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla, Thailand*
[4] *Dental Clinic, Songkhla Hospital, Songkhla, Thailand*
[5] *Dental Clinic, Satun Hospital, Satun, Thailand*

Objective: To compare the efficacy of turmeric extract (curcuminoids) to ibuprofen on postoperative pain control after lower third molar surgery.

Materials and Methods: Eighty-six patients requiring lower third-molar surgery with moderate difficulty from three centers were randomly assigned to two groups: one receiving 500 mg of curcuminoids and the other 400 mg of ibuprofen three times daily for three days. Pain intensity was assessed using a visual analog scale (VAS) at 1, 2, 6, 12, 24, 48, 72 hours, and 7 days after surgery. If necessary, the rescue analgesic drug was paracetamol 325 mg with tramadol 37.5 mg. Statistical analyses were conducted using independent t-tests and the Chi-square test.

Results: There were 43 patients in the curcuminoids group and 43 in the ibuprofen group. One participant in the ibuprofen group withdrew from the study due to severe postoperative pain with alveolar osteitis. The baseline characteristics did not statistically differ between the two groups. At 6 hours post-operation, the mean pain intensity score of the curcuminoids group (5.33±2.71) reached its highest peak, which was statistically significantly higher (p<0.05) than that of the ibuprofen group (2.74±2.06). The highest peak in the ibuprofen group occurred at 2 hours post-operation, with a score of 2.96±2.60. The need for rescue analgesics was significantly higher in the curcuminoids group (32.6%) compared to the ibuprofen group (14.3%) (p<0.05).

Conclusions: The efficacy of pain control in the low dose of turmeric extract (curcuminoids) 1500 mg per day was lower than ibuprofen 1200 mg per day after lower third molar surgery with moderate difficulty levels. The low dose of curcuminoids could be used in tooth extraction and other minor oral surgery with mild pain or in the condition that NSAIDs are not indicated. The higher dose of curcuminoids can be used for proper pain control in further study.

Keywords: analgesic drugs, curcuminoids extract, ibuprofen, postoperative pain, third molar.

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Corresponding Author: Settakorn Pongpanich
Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Prince of Songkla University,
Hat Yai, Songkhla 90112, Thailand
Tel: +667 428 7596, +668 9733 0434, +668 5136 1135
E-mail: settakorn.p@psu.ac.th, k.boonwat@gmail.com
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Introduction

Pain is an unpleasant sensory and emotional experience caused by actual or potential tissue damage. Intensity, duration, and type of pain can vary, ranging from acute pain caused by injury or surgery to chronic pain that persists for a longer period [1]. Surgical trauma is an inflammatory process and leads to pain, edema, and trismus [2]. Lower third molar surgery, a common oral procedure, frequently causes mild to moderate pain and swelling in the surgical site [1], depending on the complexity and extent of the surgery, an individual's pain tolerance, and tooth conditions [2, 3]. Although Ibuprofen is the standard option for postoperative pain control, it induces gastrointestinal risks, particularly for patients with certain conditions or NSAID allergies [4].

Turmeric, scientifically known as Curcuma longa, is a perennial herbaceous plant, a part of the ginger family, which is a primary source of curcumin, a versatile bioactive compound [5, 6]. Turmeric contains curcuminoids, including curcumin, desmethoxycurcumin, and bisdemethoxycurcumin. Curcumin has been explored for its potential medicinal effects including anticancer, antidiabetic, anti-inflammatory, antimicrobial, antihypertensive, anti-psoriatic, and anti-scleroderma [7-10]. Curcumin suppresses inflammation by blocking the activation of nuclear factor (NF)-κB and regulating tumor necrosis factor α (TNF-α)[4]. Furthermore, curcumin affects Cyclooxygenases and Lipoxygenases by suppressing the synthesis of prostaglandins (PGs) [11, 12].

Curcumin has been studied for pain relief. It works through various mechanisms, such as modulating inflammatory pathways and inhibiting pain signaling molecules. An important trait of curcumin is its potential to reduce inflammation. Curcumin increases the concentrations of transforming growth factor-β (TGF-β), a suppressor of nociception [13]. Additionally, the benefit of curcumin, as a pain control alternative with fewer adverse effects, could be an option for patients with allergies or medical restrictions.

Curcuminoids have undergone extensive study for their pharmacological effects, encompassing anti-inflammatory, antioxidant, and potential pain-relieving properties [14-19]. The highest dose of 8,000 mg of curcumin per day for 3 months was used, as well as five other trials utilizing 1000–2,500 mg of curcumin per day. They concluded that curcumin was safe and had anti-inflammatory properties [20]. Moreover, taking 1000 mg of curcuminoids daily for 8–12 weeks can significantly diminish pain and inflammation symptoms, mirroring the effects of an ibuprofen dose of 800 mg/day [21] and diclofenac sodium dose of 100 mg/day [22, 23].

AntiOx is a product of curcuminoids 250 mg per capsule (active substance(s)) produced by the Government Pharmaceutical Organization (GPO)company, in Bangkok, Thailand. AntiOx has been labeled an indication of pain in osteoarthritis. There are three previous studies that utilized AntiOx for pain management. In the first study, AntiOx (curcuminoids 1000 mg/day) significantly reduced post-operative pain at the 24-hour and 72-hour follow-up after laparoscopic gynecologic surgery when compared to the analgesic group (the specific type of analgesic used in this study was not identified) [11]. The second and third previous studies focused on pain in osteoarthritis. One study compared AntiOx(curcuminoids 2000 mg/day for 6 weeks) to ibuprofen (800 mg/day for 6 weeks). The other study compared AntiOx (curcuminoids 1500 mg/day for 4 weeks) to ibuprofen (1200 mg/day for 4 weeks). in a multicenter design involving 8 hospitals. The results showed that AntiOx was effective in controlling pain in osteoarthritis patients, and there was no significant difference compared to ibuprofen [21, 24].

Lower third molar surgery is a common oral surgery procedure often associated with potential

complications, including pain [25]. Ibuprofen (approximately 1200 mg/day) has been used as the standard medication for pain control [1]. However, its usage can result in adverse effects on the digestive system, such as gastritis or gastrointestinal bleeding, particularly in patients with preexisting gastrointestinal issues. Moreover, for those taking other medications like warfarin or oral hypoglycemics, drug interaction may occur particularly in wound hemostasis. The ibuprofen would contraindicate in patients who are allergic. The prevalence of NSAID hypersensitivity has been reported to range between 0.6% and 5.7% in the general population. Curcumin exhibits analgesic effects like those of ibuprofen but with fewer side effects [4]. Curcuminoids could serve as an alternative treatment option for patients who cannot use ibuprofen due to allergies or underlying medical conditions.

Curcuminoids (AntiOx) at a dosage of 1500 mg per day have shown equivalent efficacy in pain control when compared to ibuprofen at a dosage of 1200 mg per day for osteoarthritis [24]. We utilized post-operative pain following third molar surgery as a model for our study, and there is no evidence regarding the effectiveness of AntiOx (curcuminoids 1500 mg/ days) in managing postoperative pain after lower third molar surgery. This study aimed to compare the efficacy of curcuminoid to ibuprofen in postoperative pain control following third molar surgery.

Materials and Methods

This study was a double-blinded, randomized, controlled clinical trial for lower third molar surgery at the Prince of Songkla University Oral and Maxillofacial Surgery dental clinic, Satun Hospital dental clinic, and Songkhla Hospital dental clinic. The study was approved by the Human Research Ethics Committee, Faculty of Dentistry, Prince of Songkla University (EC16412079), and was registered with the Thai Clinical Trial Registry (TCTR20220705002). All patients were informed of all research protocols before giving consent and participating in the study.

Patient selection

Healthy adults aged 18–29 and weighing 40–90 kg, who needed lower third molar surgery in both sites of the jaw were enrolled in the study. Pederson's difficulty index score of 5–6 from radiographic location and angulation was considered as a difficulty level for the study. Bone removal and tooth section were indicated. Patients were included if there was no infection, edema, or periodontal disease that existed before surgery. Patients with uncontrolled systemic disorders, allergies to local anesthetics, NSAIDs (like ibuprofen), curcuminoids, amoxicillin, tramadol, and paracetamol, smokers, and individuals using analgesics 24 hours to two weeks before surgery were excluded. Patients with severe asthma, gastrointestinal disorders like dyspepsia or peptic ulcers (PU), bile duct obstruction, hematologic, renal, or hepatic diseases, immunosuppressive disorders, neurological disorders affecting pain perception, and those taking anticoagulants or antiplatelet drugs, or pregnant or lactating women were also excluded. Patients who refused to participate or experienced severe side effects or complications during or after surgery, such as severe bleeding, inferior alveolar nerve injury, alveolar osteitis, postoperative infection, or allergic reaction to the test drug, were withdrawn. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Figure 1.

Sample size calculation

The sample size estimation was performed with G*Power 3.1.9.4 utilizing a two-sample mean comparison by using data of 12-hour pain intensity (Mean difference = 3.19 -2.48 = 0.71). from Gaetano Isola et al. (2018)[26]. The calculated sample size for each group was 39 patients plus

adding 10% more as reserved samples, resulting in a total number of 86.

Due to a large sample size, a multicenter approach was employed at 3 centers, the dental clinic at the Prince of Songkla University (Main center) with 43 patients, the dental clinic at the Songkhla (Kor-yo) Hospital with 20 patients, and the dental clinic at the Satun Hospital with 23 patients. The surgery was performed by one oral maxillofacial specialist in each hospital. Patients were divided into two groups using block randomization.

Drug preparation

The turmeric extract ((curcuminoid(AntiOx)), Government Pharmaceutical Organization(GPO), (Bangkok, and Thailand)) capsules 250 mg and Ibuprofen 200 mg were prepared in sets of 18 identical capsules per package by the pharmacologists. The patients were instructed to take 2 capsules of the drug 1 hour after surgery. Amoxicillin 500 mg (20 caps/package), and three rescue analgesic tablets were prescribed. The patients, dentists, and evaluators were blinded with medication used for each patient preventing research bias. A pharmacist outside the study stored confidential codes (Group A or B, signifying AntiOx (curcuminoids extracted 500 mg) or ibuprofen 400 mg) in envelopes for unbiased delivery (Figure 1).

Surgical procedures

Three experienced specialist dentists were calibrated with research techniques, data collection, and surgical protocol to ensure the correction of the outcomes before the beginning of the project's procedure. First, a local anesthesia (4% Articaine and epinephrine 1:100000) injection was administered on the surgical site,1.0ml for the inferior alveolar nerve (IAN) along with 0.7ml for the

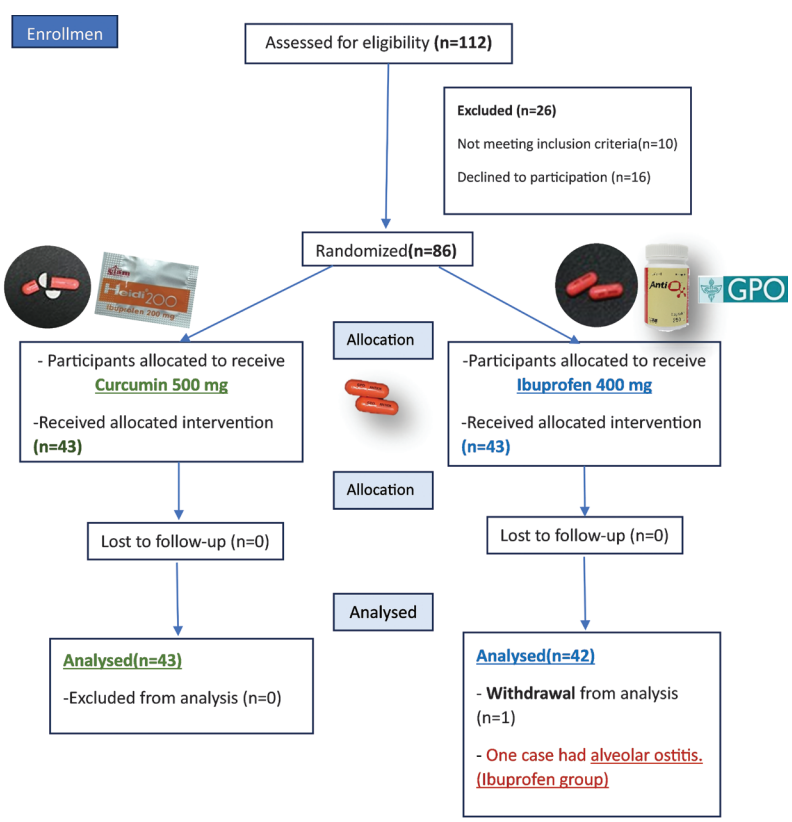

Figure 1 Illustrates the CONSORT (Consolidated Standards of Reporting Trials) flowchart.

lingual nerve, 1.0ml for the long buccal nerves. The envelope flap was reflected from the distobuccal aspect of the second molar, extending the flap to involve the distal papilla of the first molar. The distal and buccal bone around the impacted third molar was removed. After sectioning with a carbide rotary bur, the tooth was elevated and extracted. Curetted sockets had extensive saline irrigation. Black silk 3-0 sutures were used for wound closure and then the patient bit the gauze. The post-op instructions and drugs were given.

At 1, 2, 6, 12, 24, 48, 72 hours, and on the 7th day after surgery, pain levels and time for medication intake were recorded. The patients were instructed to take the first drug one hour after surgery and recorded as the first-time drug. Postoperative instructions included taking a liquid and cold diet for 24 hours, maintaining oral hygiene care, and contacting the surgeon if they experienced active bleeding, nausea, vomiting, headache, or infection. The rescue analgesic drug (Ultracet - Tramadol 37.5 mg + Paracetamol 325 mg per tablet) taken was recorded for the number and frequency of usage.

Outcome measurement.

The average pain intensity score was assessed by using a visual analog scale at 1, 2, 6, 12, 24, 48, 72 hours, and 7 days after surgery, serving as the primary outcome. The secondary outcome was the recorded time and quantity of rescue medicine intake.

Statistical Analysis

The data was reported as mean and standard deviation (SD). Statistical analysis was performed using IBM SPSS version 23 with a significance level of $p<0.05$. A t-test was used for normally distributed data otherwise the Mann-Whitney U test was used to compare the mean pain score, time, and rescue drug needs of the two groups. and the Chi-square test.

Results

Demographic data

A total of 43 patients were from Prince of Songkla University's dental clinic, 20 from Songkhla (Kor-yo) Hospital, and 23 from Satun Hospital. One patient from Prince of Songkla University's dental clinic was excluded due to post-operative alveolar osteitis. The curcuminoids (AntiOx group) had 43 patients and the (ibuprofen group) had 42 patients. There were 67 females (32 curcuminoids and 35 ibuprofen) and 18 males (11 curcuminoids and 7 ibuprofen). Table 1 displayed baseline characteristics such as gender, age, weight, height, and anxiety before the third molar surgery, difficulty index, root shape, and nerve-related of the impacted lower third molar. The two groups had no statistically significant differences.

Pain intensity

The postoperative pain scores using the Visual Analog Scale (VAS) at 1, 2, 6, 12, 24, 48, 72 hours, and 7 days after lower third molar extraction, between the group receiving curcuminoids 1500mg/day and the group receiving ibuprofen 1200 mg/day were presented in Table 2. At 6 hours, the curcuminoids group had a statistically significantly higher ($p<0.001$) peak pain score (5.33±2.71) than the ibuprofen group (2.74±2.06), The ibuprofen group exhibited a lower peak pain score (2.96±2.60) in the first 2 hours post-surgery compared to the curcuminoids group (3.76±2.97) with no statistical difference between groups. As time passed, individuals' pain scores correlated with the analgesic duration that reached the highest and then declined, 6 h in the curcuminoids group and 2 h in the ibuprofen group but at different pain levels. The pain scores of both groups declined after their highest point as shown in Table 2, Figure 2.

Table 1 The demographic data and baseline 3rd molar between the two groups, with the mean and SD of the difference

Characteristics	Curcuminoids (N=43)	Ibuprofen(N=42)	*p*-value
Gender, n			
Male	11(13%)	7(8%)	0.317
Female	32(38%)	35(41%)	
Age (Year) (Mean ± SD)	20.19±1.75	20.76±1.89	0.148
Weight(kg) (Mean ± SD)	57.30±11.28	55.60±9.76	0.458
Height(cm) (Mean ± SD)	163.98±8.54	162.69±8.34	0.485
Anxiety before surgery, n			
No	5(6%)	10(12%)	
Mild	29(34%)	19(23%)	0.879
Moderate	7(8%)	12(14%)	
Severe	2(2%)	1(1%)	
Difficulty index (Moderate)			
5 point	17(20%)	19(22%)	0.597
6 point	26(31%)	23(27%)	
Root shape			
Divergence	22(26%)	25(30%)	0.518
Convergence	16(19%)	12(14%)	
Curve root	5(6%)	5(6%)	
Nerve related			
Related	38(45%)	36(42.4%)	0.717
Non-related	5(6%)	6(7.1%)	

* Statistically significant at p<0.05

Table 2 Pain intensity between two groups, with the mean and SD of the difference

Time (Hours)	Pain intensity (cm) (Mean± SD)		*p*-value
	Curcuminoids (n=43)	Ibuprofen (n=42)	
1	2.40±2.80	2.74±2.63	0.572
2	3.76±2.97	2.96±2.60	0.190
6	5.33±2.71	2.74±2.06	0.000*
12	3.20±2.71	2.21±1.91	0.053
24	2.13±2.09	1.69±1.82	0.304
48	1.73±1.86	1.63±1.94	0.819
72	1.09±1.31	1.32±1.76	0.503
7 days	0.46±0.67	0.53±0.85	0.666

* Statistically significant at *p*<0.05 (between time and Mean VAS group drug)

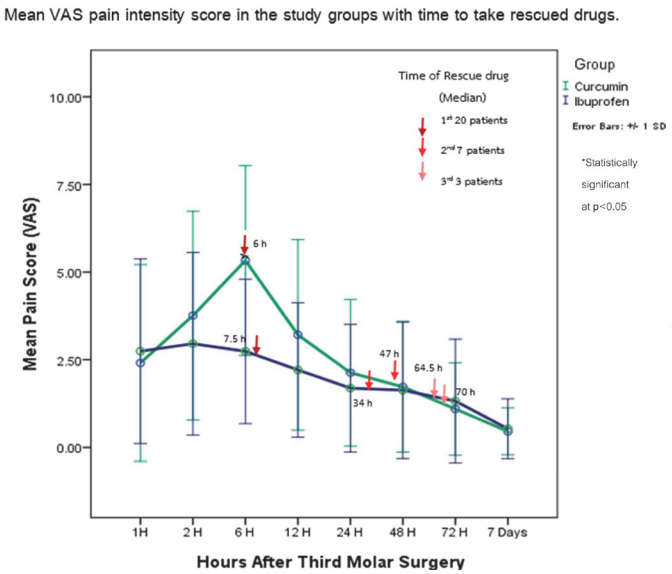

Figure 2 Line graph of mean VAS pain intensity score in the study groups with the time of taking rescue drugs. (*p<0.05)

Rescue medication

Rescue drugs were taken by 20 patients, 14 patients were from the curcumin group and 6 patients from the ibuprofen group which was statistically different between the groups. Of the patients who took 1 tablet of rescue drugs were 13 patients, 10 from the curcuminoid group, and 3 from the ibuprofen group, Additionally, a total of 4 patients took two tablets (3 from the curcuminoid group, 1 from the ibuprofen group), and another 3 patients took three tablets (1 from the curcuminoid group, 2 from the ibuprofen group). These results show no statistically significant differences within the groups (Table 3).

Table 3 The number of patients requiring and the time of taking rescue medication between groups.

Rescue Drugs (n, %) / Groups		Curcuminoids (n=43)	Ibuprofen (n=42)	Total (n=85)	*p*-valve
Not drug taken		29(67.4%)	36(85.7%)	65(76.5%)	
Drug taken	one tab	10(23.30%)	3(7.1%)	13(15.3%)	0.047*
	two tabs	3(7%)	1(2.4%)	4(4.7%)	
	three tabs	1(2.3%)	2(4.8%)	3(3.5%)	
	Total	14(32.6%)	6(14.3%)	20(23.5%)	
The time of taking rescue drugs (Mean± SD), (Median)					
Rescue drugs		Curcuminoids		Ibuprofen	*p*-valve**
		Mean± SD	Median	Mean± SD	Median
First		8.42±9.21	6(4-40)	7.16±4.16	7.5(2-12)	0.754
Second		47.25±17.72	46(36-65)	31.33±10.26	34(20-40)	0.228
Third		70	70	64.5±10.61	64.5(57-72)	0.745

* Statistically significant at p<0.05 (between using rescue drug and not using rescue drug)

** p<0.05 using the Mann-Whitney U test (Median)

Discussion

The purpose of this study was to compare the efficacy of turmeric extract (curcuminoids) 1500 mg/day to ibuprofen 1200 mg/day for controlling postoperative pain after lower third molar surgery. The extent of surgery in both groups and all centers was comparable in that the pain at the first hour was a rather similar level (curcuminoids 2.40±2.80 VAS, ibuprofen 2.74±2.63 VAS), and the time the patients took studied drugs was also not different (curcuminoids 1.74±0.97 h, ibuprofen 1.51±0.845 h). Postoperative pain following third molar surgery is transient and acute and reaches its peak (moderate interference with daily activities) 6-8 hours after surgery [27, 28]. In this study, the highest pain in the ibuprofen group was 2.96, indicating mild pain at 2 hours post-surgery. The ibuprofen could alleviate pain after the drug was taken right away but the curcuminoids group underwent a normal physiologic process that reached the highest pain at 6 hours as a moderate pain.

Ibuprofen took approximately 1 hour to control pain and showed less pain than the initial pain at 6 hours and continued to gradual pain relief until 12 hours. The curcuminoids group showed increased pain scores from 1 to 6 hours and higher than the ibuprofen group statistically significantly at 6 hours (5.33±2.71 VAS vs 2.74±2.06 VAS). However, the time for taking the sequential drugs in both groups was not different (curcuminoids 8.42±9.21 h, ibuprofen 7.16±4.16 h). Rescue medicine was required in (14 patients) more than (6 patients) significantly.

This study employed 1500 mg per day (500 mg 3 times a day) of curcuminoids which are low doses when compared to previous studies [20]. and demonstrated inadequate efficacy for our purposes. A prior study demonstrated that 2 g of curcumin provided more effective relief for acute pain than 500 mg of acetaminophen in individuals with osteoarthritis (OA) [29]. Previous studies confirmed that curcuminoids effectively managed pain similar to ibuprofen for osteoarthritis and alleviated postoperative pain after laparoscopic gynecologic surgery [30]. Therefore only 1500 mg of curcuminoids tended to be less effective than 500 mg of acetaminophen, and lower dose than 400 mg of ibuprofen. Osteoarthritis pain results from joint degeneration and bears a chronic nature, while postoperative pain is inflammatory and acute pain in nature [31]. Hence pain experienced in osteoarthritis is not equivalent to the pain level of postoperative recovery. Another factor is that the curcuminoids used in the study are not pure curcumin, which contributes to the pharmacological medical function for controlling pain and the dose was lower than the effective dose.

A previous study from Maulina, 2018, used pure curcumin extract 600 mg/day to control postoperative pain after third molar surgery and it was more effective than mefenamic acid 1500 mg/day. This study used curcuminoid 1500 mg/day (Anti Ox) which was approximately 1000 mg/day of pure curcumin. When comparing mefenamic to ibuprofen, Ibuprofen seems to be a more potent and widely used NSAID in the treatment of dental pain than mefenamic [32]. Therefore, curcuminoids in this study may have had lower potency than curcumin in Maulina's study. However, mefenamic and ibuprofen cannot be compared directly because the pharmacologic effects are not the same [16].

This study conducted 3 multicenter to gain more samples in a limited time. The procedure, research protocol, and data collection are not complicated, easy to understand, and follow to enable inclusiveness and comprehensiveness. However, multicenter research presents challenges, including uniform data collection and communication management. Pain perception was measured using the Visual Analog Scale

(VAS) on a ratio scale, providing meaningful measurement, facilitating analysis, and enabling accurate comparisons. These scales are crucial for thorough quantitative research.

This study focused on pain perception data only to ease data collection by multicenter evaluation which was the limitation of the study. Data concerning curcumin's inhibitory effects on inflammatory mechanisms like redness and swelling has not been collected and should be beneficial to the study. Additionally, increasing the dosage of curcuminoids to 2000–2500 mg per day could better control pain than the present dose. The modification in drug preparation to extract concentrated pure curcumin is another challenge. Furthermore, a comparison of 1500 mg curcuminoids (mild analgesics) could be explored for potentially effective management of mild pain, particularly in cases of soft tissue surgery or tooth extractions. Further studies have explored various curcuminoid doses for the management of post-operative pain.

Conclusions:

The efficacy of pain control in the low dose of turmeric extract (curcuminoids) 500 mg was lower than ibuprofen 400 mg after lower third molar surgery with moderate difficulty levels, The low dose of curcuminoids could be used in tooth extraction and other minor oral surgery with mild pain or in the condition that NSAIDs are not indicated. The higher dose of curcuminoids can be used for proper pain control in further study.

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