American Journal of Arthritis

Research Article
Published: 29 Oct, 2021

The Efficacy of Topical Curcumin 5% Gel for Knee Osteoarthritis

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Abstract

Introduction: Curcumin is an antioxidant and anti-inflammatory compound although its oral clinical use is limited by low bioavailability. Osteoarthritis (OA) is characterized as a painful, inflammatory arthritis of the cartilage and standard therapy like NSAIDs have increased risk of side effects. The primary objective was to determine the efficacy of topical Curcumin 5% gel in patients with osteoarthritis of the knee.

Materials and Methods: This was a one week, randomized, double-blinded, vehicle control, pilot study. Patients with bilateral OA of the knee were selected and were given two types of gels, Curcumin 5% gel and control agent (Aloe Vera gel). They were asked to apply one gel on each knee twice daily for one week. The primary efficacy outcome was change from baseline to week one in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. Secondary outcome included WOMAC subscales, patient Global Assessment and numeric rating pain score.

Results: Significant reduction in WOMAC pain scores from baseline were observed in topical Curcumin 5% gel -2.47 compared to the control -0.70 for OA of the knee at week one, with the p-value being 0.03. No side effects were seen.

Conclusion: Administration of topical Curcumin 5% gel 2 ml twice daily resulted in significantly greater improvement in pain reduction at week one versus control. Topical Curcumin 5% gel is an effective and safe alternative to treat osteoarthritis knee pain.

Keywords: Curcumin; Topical; Gel; Osteoarthritis; Knee Pain; Turmeric

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Received Date: *27 Sep 2021*
Accepted Date: *22 Oct 2021*
Published Date: *29 Oct 2021*

Citation:
Rao SG, Bantval P, Chiniga R. The Efficacy of Topical Curcumin 5% Gel for Knee Osteoarthritis. Am J Arthritis. 2021; 5(1): 1021.

Introduction

Turmeric is a plant of the ginger family which is found in South Asia and has been in use for many years as a dye, flavoring and a medicinal herb [1]. Curcumin (chemically called diferuloylmethane), the active component was first isolated as "yellow coloring matter" from Curcuma long a by Vogel and Pelletier in 1815 [2]. Curcumin has a variety of therapeutic properties including antioxidant, analgesic, anti-inflammatory, antimicrobial, antidiabetic, anticancer, and antiallergic, as well as hepatoprotective, cardioprotective, neuroprotective, and nephroprotective activities [3]. Inhibition of phosphorylase kinase activity by Curcumin results in modulation of the inflammatory response because of down regulation of transcription factors (NF-kB, AP-1), cytokines (TNF-α), adhesion molecules and a variety of protein kinases [4].

Osteoarthritis (OA) is the most common joint disorder in the United States with the knee joints most affected [5]. OA of the knee accounted for 83% of the total OA burden [6]. The estimated lifetime risk of OA of the knee is 13.8%, ranging from 9.6% for non-obese males to 23.9% for obese females. About 9.3% of the US population will be diagnosed with symptomatic knee OA by the age of 60 [7]. OA of the knee is characterized as a painful, inflammatory arthritis and is the leading cause of lower extremity disability [6,8,9]. Research indicates that the impact of arthritis on disability is greater on physical functional limitations than on more complex social and role activities [10]. Although, non-pharmacologic interventions such as exercises and weight loss are the backbone of knee OA, the benefits of exercise were not sustained in the long term, which is largely related to the decreasing adherence rates to the exercise program over time [11]. The demand for arthritis pain control has resulted in the widespread use of treatments such as pharmacological, surgical, complementary

and conservative treatments [12]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [13], acetaminophen and steroids and are among the commonly used medications in osteoarthritis. However, long-term use is found to be associated with wide range of side-effects such as gastrointestinal, cardiovascular, and renal toxicity with oral NSAIDs although reduced toxicity with topical NSAIDs [14,15]. Furthermore, liver toxicity with acetaminophen and risks of tendon rupture may be seen with intra-articular steroid injections [16]. Age-related impairments in liver and kidney functions also increase the risk of experiencing serious drug side effects and interactions among older adults [17]. Despite the many options available, some patients may continue to experience inadequate symptom control and both clinicians and patients may be dissatisfied with the options [18]. Dissatisfaction with treatment was the most common reason reported by GPs for patients on an NSAID to re-present, with 73% citing either breakthrough pain or incomplete pain relief with current painkillers which drive many of them to seek self-treatment with complementary medications such as herbs and other alternative remedies.

The efficacy of Curcumin is shown to be similar to that of ibuprofen for the treatment of knee OA [19]. Curcumin has also been shown to inhibit inflammatory substances such as cyclooxygenase-2 [20]. A randomized open label parallel arm study investigating the safety and efficacy of Curcumin *vs.* diclofenac in knee osteoarthritis showed that patients receiving Curcumin had similar improvement in severity of pain compared with diclofenac, and at day 28, a weight-lowering effect ($P<0.01$) and anti-ulcer effect ($P<0.01$) of Curcumin were observed [21]. Systematic review and meta-analysis of randomized clinical trials has highlighted the efficacy of turmeric extract (about 1000 mg/day of Curcumin) in the treatment of osteoarthritis [22]. As an example, a trial including 70 adults with painful knee OA with ultrasound-confirmed effusion synovitis randomly assigned patients to receive Curcuma long a capsules (CL1000 mg daily) or placebo [23]. At week 12 the study showed that CL was more effective than placebo for knee pain but did not affect knee effusion-synovitis or cartilage composition. Oral Curcumin use is limited by its low bioavailability and is a major concern as; it hinders its therapeutic efficacy because the unconjugated Curcumin molecule, which is hydrophobic, is poorly absorbed by the gastrointestinal tract [24]. Instability of the Curcumin due to its low absorption in the gastrointestinal system, have resulted in the studies using the oral Curcumin are unreliable. Comprehensive review by Nelson et al. [25], reported that in 2015, noted that despite over 120 clinical trials of Curcumin done, with majority related to oral Curcumin, no double-blinded, placebo-controlled trial has been reported successful. Rarely negative side effects to turmeric may occur in people allergic to ginger and a case of jaundice has been reported [26]. Another study reported seven of twenty-four subjects receiving doses between 1000 mg to 12,000 mg were followed for 72 h and experienced nausea, diarrhea, headache, and rash [27]. Most studies showed the effect of Curcumin on knee pain used the oral forms, however very few studies are available on the effect of its topical forms. Some studies have reported that topical use of Curcumin results in greater bioavailability [28]. Topical Curcumin can be formulated to be better absorbed through the skin. Topical Curcumin is found to be beneficial in several conditions such as burns, scars, skin injuries and psoriasis [29]. A single blinded study by Gemmell et al. [30] reported the successful topical application of an ointment containing turmeric and some other herbs for relieving pain and stiffness associated with OA of the hand and knee in a small samples size of 17 patients. There were some drawbacks, the study lacked blinding of the observers and the sole efficacy of Curcumin was not assessed as the ointment contained several herbs such as brewer's yeast, comfrey, common fallow laurel, English oak, fenugreek, kelp, Solomon's seal, turmeric winter cherry, glycerol, castor oil, coconut oil, menthol, and capsaicin. Another study published in October 2020 aimed to investigate the effect of Curcumin ointment on the severity of knee pain in older adults with OA concluded that the absolute difference of 1.133 at the end of the 6 weeks study in the intervention group achieved a minimal clinically important difference [31].

Despite these findings, Curcumin has been difficult to use topically due to its characteristic odor and bright yellow color as the naturally occurring yellow pigment stains the surfaces yellow. But there is increasing research studying colorless turmeric extract to reduce the appearance of fine lines, wrinkles, and clinical studies have shown its ability to improve scarring in acneiform conditions, surgical wounds [29]. A colorless hydrogenated product derived from the yellow curcuminoids is Tetrahydrocurcuminoids (THC) [32]. The superior antioxidant property of THC, combined with the lack of yellow color, render this product useful in achromatic food and cosmetic applications that currently employ conventional synthetic antioxidants. Substantial beneficial effects could be achieved with lower level of this active metabolite as compared to the parent component [33]. A study showed that supplementation of THCs (C3 reduct manufactured from Sami labs) 100 mg twice daily for 21 days reduced the pain and prevented the progression of the disease in patients suffering from canker sore and gingivitis without adverse side effects [34]. Studies with THCs have reported higher bioavailability and physiological stability than Curcumin and are easily absorbed through the gastrointestinal tract [35]. THC offer protection to the skin and could be included in as functional antioxidants in topical preparations [36]. Studies on absorption of 3 topical formulations; gel (Iprogel) or hydrophilic ointment or an emulsion cream and the relative drug bioavailability has been shown with topical NSAIDs. Analysis of the plasma drug concentrations of percutaneous 5% ibuprofen showed the highest drug concentration in blood, reached in the shortest period with gel formulation, whereas that from the hydrophilic ointment showed the lowest drug concentration, and at the slowest rate [37]. Studies with gel-based applications such as Voltaren gel application increased skin hydration by 13.1%; cooling effect was experienced by 94% subjects, while 74% felt that their skin became softer [38].

In this 1- week study we to investigate the efficacy and safety of topical Curcumin 5% gel in patients with OA of the knee.

Materials and Methods

This was a one-week, randomized double-blind vehicle-controlled pilot study. Patients between the ages of 40 to 85 years, with radiographic confirmation of bilateral knee osteoarthritis (as determined by the physician) were enrolled for this study. Patients had failed at least 2 oral forms of medications, which included oral NSAIDs and or acetaminophen. Patients were required to have moderate pain (numeric Rating Scale (NRS) >4/10, Scale 0 to 10, where 0 is no pain and 10 being highest) in both knees despite being on a stable form of therapy. All patients remained on their background therapy.

The study was performed at a rheumatology research clinic. Enrollment period began January 15th, 2020 and ended February 3rd, 2020.

Characteristics	N= 17
Age, Yrs , Mean± SD	67±9
Sex % Male Female	 35 65
BMI kg/m ²	28± 7

Figure 1: Patient characteristics.

Patient characteristics noted included age, sex, weight, height, examination of right and left knee joint.

Treatment

Patients were asked to use topical Curcumin 5% gel (5% tetrahydrocurcuminoid+ Aloe Vera gel) in one knee and the vehicle control (Aloe Vera gel) in the other knee twice a day for 1 week. The joints were randomly assigned as 1 and 2 (n=17 for experimental and control). The treating physician and also the patients were not aware of codes. The first application of the drug (2 pumps = 2 ml) was supervised in the clinic, with subsequent applications self-administered at home.

The preparations were well matched for color, smell, and consistency. Neither the examiner nor patient could distinguish the preparations.

Study medication compliance was assessed based by the patient completing daily time sheet during each application.

Study was approved by IRB Pearl Pathway Protocol ID 20-ACRC-101 and informed consent was received from all patients.

Curcumin gel and control preparation

Topical 5% Curcumin gel was prepared by mixing Tetrahydrocurcuminoid (50 mg/mL) purchased from Sabinsa Corp NJ, USA. Vehicle agent used was Aloe Vera gel; other inactive ingredients were Mint fragrance, Pro vitamin B and Polysorbate [20].

Control gel was prepared with Aloe Vera gel, inactive ingredients and 1 drop of food coloring to match the color of 5% Curcumin gel. The products were packed into a 50 ml Air-tight hand pump.

Efficacy assessments

The primary efficacy outcome was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK 3.1) pain subscale from baseline to week 1 for topical Curcumin 5% gel and change in the WOMAC pain score compared to vehicle control at week 1.

Secondary outcome measures included WOMAC physical function, stiffness subscales and Patient Global Assessment (PGA).

The WOMAC is composed of 24 items over 3 subscales (5 for pain, 2 for stiffness and 17 for physical function).WOMAC test questions are scored on a scale of 0 to 4, which correspond to: None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4). WOMAC has been recommended as one of the highest-performing outcome measures for knee and hip osteoarthritis, in terms of reliability, validity, responsiveness and interpretability [39]. There was no significant difference between the experimental and control group in the baseline WOMAC scores. To assess compliance, patients were instructed in the daily time sheet to rate their knee pain intensity daily for both knees using the NRS (0 to 10) in the morning and evening.

Safety and tolerability assessments

Treatment associated adverse events were assessed immediately after the first application of the study drug and 1 week. In addition, patients reported the number rescue medication taken daily.

Statistical analysis

Mean and standard deviations were calculated using excels, and ANOVA models were used for data analysis which compared the change from the baseline between topical Curcumin 5% and control.

Results

Total of 17 patients were enrolled for the study, all completed the study. Of these, 65% were female and 35% were males (Figure 1). The mean age was 67 years ±9 years, and the mean BMI was 28 ±7.

There was a statistically significant reduction in WOMAC pain score from baseline to week one (p-value 0.03) (Figure 2) were observed for topical Curcumin 5% gel (-2.47) over the control (-0.70) (Figure 3). Statistically significant improvement in WOMAC pain scores (p-value 0.019) (Figure 4) from baseline 10.0 ± 3.14 to week one 7.5 ± 2.7 were observed for Curcumin 5% gel. No significant improvement with active treatment over the control was observed for WOMAC physical function scores (p-value 0.32) (Figure 5), joint stiffness scores (p-value 0.16) (Figure 2).

No significant difference between Curcumin 5% gel and vehicle control were observed in the PGA scores (p-value 0.11) (Figure 2).

Safety and tolerability

No side effects were observed using topical Curcumin 5% gel. No rescue medications were used. All patients completed the study. Patients complied with the guidelines for the study which were confirmed by reviewing the daily time sheet.

Discussion

This 1- week, randomized double blinded, vehicle-controlled study evaluated the efficacy and safety of the Topical Curcumin 5% gel in the symptomatic treatment of OA of the knee. Administration of topical Curcumin 5% gel showed significant efficacy in pain reduction for osteoarthritis knee pain. The findings demonstrated that for primary endpoint i.e. from baseline to week 1 pain score, patients reported significant greater reductions in WOMAC pain score with topical 5% Curcumin gel *vs.* control (-2.47 *vs.* -0.7; p-value 0.03). Also, significant reductions in WOMAC pain score with topical Curcumin 5% gel when compared to vehicle control at week 1 scores (10.0 ± 3.14 *vs.* 7.5 ± 2.7; p-value 0.019). No statistical significance was demonstrated in knee stiffness, physical function or patient global assessment. However, the active treatment group had a higher change compared with control (-3.6 *vs.* -2.5). Studies using oral Curcumin supplements showed that it takes at least 6 weeks to demonstrate the change in physical function and stiffness [40]. Since this was a 1-week study there was insufficient time to expect benefit in stiffness and physical function. Background therapy was continued and could

OUTCOME	Topical 5% Curcumin gel N= 17 Mean± SD	Control N= 17 Mean± SD	p-value
WOMAC- pain score (0-20) Baseline Week 1 Change from baseline	 10.0±3.1 7.5±2.7 2.4±1.9	 9.4±4.1 8.6±3.4 0.7±2.4	**0.031**
WOMAC- physical function (0-68) Baseline Week 1 Change from baseline	 34.8±11.2 31.2±11.6 3.6±4.0	 36.2±12.7 33.9±12.4 2.4±5.7	0.49
WOMAC- stiffness (0-8) Baseline Week 1 Change from baseline	 4.4±1.2 3.9±1.2 0.5±0.9	 4.6±1.7 4.5±1.7 0.05±1.0	0.16
PGA (0-10) Baseline Week 1 Change from baseline	 6.0±1.6 5.8±2.1 0.4±1.6	 5.3±1.9 5.8±2.2 -0.5±1.8	0.11

Figure 2: Displays the baseline mean, week 1 mean and change from baseline mean for WOMAC pain score, stiffness, physical function, and patient global assessment, in both Topical 5% Curcumin gel and control.

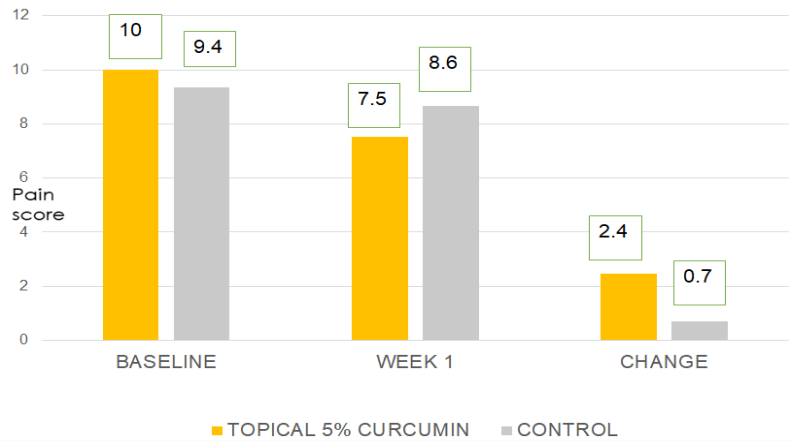

Figure 3: Displays WOMAC pain score comparing the changes between topical 5% Curcumin gel to the control.

be considered as a confounding factor. Most importantly no local or systemic reaction was seen.

A most recent study with 5% Curcumin ointment published by Jamali et al. [31] used a Visual Analog Scale, to measure the severity of knee pain at the beginning of the study, at the end of the fourth and sixth week. The repeated-measures analysis showed that over time, the Curcumin significantly decreased the mean pain intensity in the intervention group (P=0.001). Here we used WOMAC scale. The WOMAC Index has been used extensively in clinical trials and has generally been shown to exhibit greater or comparable responsiveness to change than other tests [37]. This varies, however, for different subscales and types of interventions. Some studies report inadequate factorial validity in the pain and physical function subscales of the WOMAC. Thus, the physical function subscale might be limited in its ability to detect change if the association between pain and function is weak.

In another small study of topical application of an ointment containing turmeric and many other herbs in knee and hand arthritis pain where 17 patients used the ointment for 42 days and found it beneficial in the improvement of joint pain and stiffness [28]. Despite the many options available, topical Curcumin is an option and is found to improve joint pain related to OA.

A key limitation of this trial is the small sample size due to the short period of enrollment. A larger and longer study was planned however canceled because of concern for the emerging Coronavirus and uncertainties with the methods of transmission at that time. Given the limited of studies on the effect of topical administration of Curcumin on joint pain, it is recommended to repeat the same study on larger samples with placebo control, for knee osteoarthritis and pain relief in other joints such as hands. Also, increasing the duration of treatment and frequent follow-ups can clarify whether the analgesic effect can be sustaining, and which may ultimately improve physical function. This is a very promising area of research, due to Curcumin's low cost, high tolerability, and the general public's interest in natural treatments. Furthermore, there is a need for ongoing high-quality clinical research, as well as development of new treatment modalities for the most common form of arthritis.

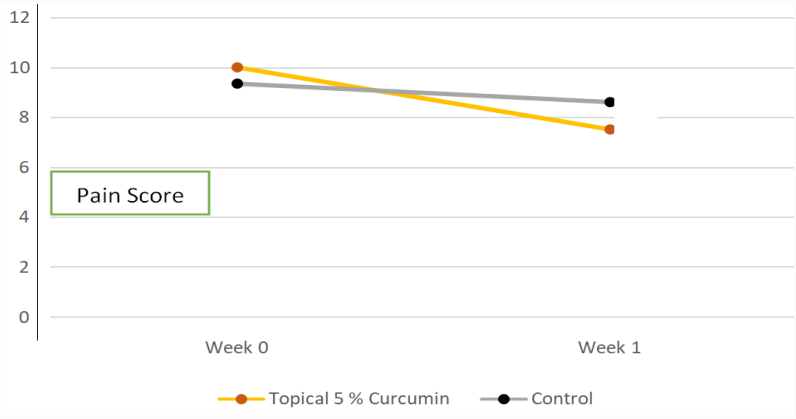

Figure 4: WOMAC pain score Topical Curcumin 5% gel week 0 to week 1 (p=0.01), and Control baseline to week one.

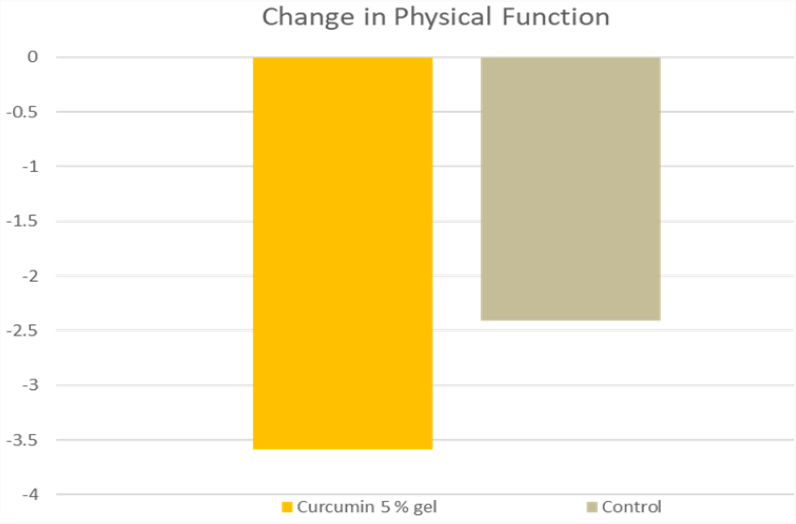

Figure 5: WOMAC change in physical function score Topical Curcumin 5% gel *vs.* control.

Conclusion

The present study showed topical administration of Curcumin 5% gel was safe and effective in reducing knee pain in patients with knee osteoarthritis by week 1. Therefore, we recommend the use of topical Curcumin 5% gel as an alternative treatment for knee pain related to osteoarthritis. Additionally, topical administration of Curcumin is also beneficial for patients who have limited disease, difficulty swallowing oral medications such as the elderly, comorbidities, or who are otherwise intolerant to oral medications. Thus, there is a need for safe and topical therapies to help relieve pain, improve function and aid in managing joint pain. Subsequently, this will improve the physical function and facilitate daily activities thus impacting the overall health of the population affected by osteoarthritis.

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